VIRAL HEPATITIS

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PHAR 551: Pharmacotherapy I
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Background

- Most common cause for liver disease in world
- Acute Vs. Chronic
  - Duration: < 6 mo vs. > 6 mo
  - Type: A/E Vs. B/C/D
- Hep A and E are transmitted via fecal-oral route
- Hep B, C, D are transmitted parenterally
- Hep B, C, D are associated with chronic hepatitis
  - Cirrhosis, ESLD, HCC
- Hep D infection requires co-infection with Hep B

Hepatitis A

- Single-stranded, non-enveloped RNA virus, stable in environment for ≥ 1 mo
- Highest prevalence in underdeveloped regions
- Fecal-oral route of transmission
- Risk factors for infection include: infected household member, sexual contact, daycare centers, healthcare workers, IVDU, food service handlers, etc.
- Typically acute and self-limited, low mortality
- Confers lifelong immunity

Hepatitis A

- Incubation period ~ 28d
- Viremia and peak fecal shedding precedes clinical symptoms and elevation in LFTs
- First phase (~ 2 mo): non-specific GI symptoms, flu-like symptoms
- Second phase (~ 7-30 d): jaundice, scleral incterus, hepatomegaly
- Considered non-infectious 1 wk after jaundice onset

Hepatitis A

- IgM Anti-HAV→ Acute HAV infection (3 wks - 6 mo)
- IgG Anti-HAV→ Lifelong immunity (3 wks - lifelong)
- Mild elevation of LFTs (ALT, AST, Alk Phos) possible
- Diagnosis based on clinical criteria, IgM presence
- Treat with support therapy; most pts have spontaneous resolution within 6 mo
- Vaccination indicated for all children at 1 yr, and pts with risk factors who have not been vaccinated
- Use vaccine with caution in severely immunocompromised pts or those with chronic liver disease

Hepatitis A

- Vaccine immunity onset takes several weeks
- Immunity lasts ~ 8 yrs in adults and children
- Vaccine is inactivated, available for adults and pediatrics (≥ 12mo)
  - Not tested in pregnant women but thought to be safe
- Two doses, 6 months apart
- Should be given for pre-exposure prophylaxis if not previously vaccinated
  - If expected exposure in < 2 wks, give vaccine and IGIM
- Effective for post-exposure prophylaxis if given to pts ASAP and within 14d of exposure

Hepatitis A

- IG is another option for HAV protection
  - Antibodies from pooled human plasma
  - Provides passive, immediate protection
  - Ideal for when vaccine not indicated
  - Should separate from live vaccines
  - Used intramuscularly (IGIM) for pre-exposure and post-exposure prophylaxis for HAV
    - Pre-exposure: children < 12 mo at high risk, if vaccine C/I, exposure expected within 2 weeks
    - Post-exposure: > 40 y/o (preferred), chronic liver disease, immunocompromised, allergic to vaccine, should be given within 2 wks of exposure
    - Provides ~ 3 month protection

Hepatitis B

- Partially double-stranded DNA virus
- Most common in developing countries
- Transmitted sexually, parenterally, perinatally
- Infants born to positive mothers have 90% chance of developing chronic HBV infection
- In infected pts > 5 y/o, 5% develop chronic hep
- Risk factors: IVDU, sexual contact
- Can become chronic, associated with significant mortality 2/2 ESLD and cirrhosis

Hepatitis B

- HBsAg (surface)
  - Most abundant of surface antigens and is detectable at onset of symptoms
  - Detection > 6 mo indicates chronic infection
  - Development of antibodies to it (anti-HBsAG) confers lifelong immunity to the virus
  - Anti-HBsAg develops in 90% of infected adults
- HBcAg (core)
  - Responsible for immune-mediated liver cell death
  - IgM Anti-HBcAg → acute infection
  - IgG Anti-HBcAg → chronic infection or immunity

Hepatitis B

- HBeAg (envelope)
  - Indicates active replication
  - Anti-HBeAg development indicates resolving infection
- Presentation is typical (see HAV)
- Infection is self-limiting unless progresses to chronic
- HBsAg and high DNA titer usually indicate infection
  - IgM Anti-HBc indicates active infection
  - Detectable HBsAg and HBeAg and high serum titer > 6 mo indicate chronic infection

Hepatitis B

- Prevention of HBV infection
  - Vaccination- universal
  - Immunoglubulin post-exposure
  - Screening pregnant women
- HBIG
  - Pooled plasma with anti-HBsAg
  - Passive immunity for post-exposure prophylaxis
  - Prevents chronic hepatitis B infection
  - Intramuscular
  - Should be separated from live vaccines
- Vaccine mimics HBsAg to stimulate active immunity

Hepatitis B

- Intramuscular; series of 3 vaccines: 0, 1, 6 mo
- Can be given during pregnancy
- C/I in pts allergic to yeast
- Post-exposure prophylaxis
  - Vaccine prevents progression to chronic hepatitis
  - Booster shot if previously vaccinated
    - Best given within 24h of exposure
  - Vaccine + HBIG if no previous vaccination
- Perinatal exposure prophylaxis
  - Mother's HBsAg (+) → HBIG + vaccine
  - Mother's HBsAG (-) → vaccine (normal course)

Hepatitis B
Chronic Hepatitis

- Cure not possible
- Typically cycles of flares and remission that progressively causes liver damage
- HBeAg seroconversion
  - HBeAg is significant risk factor for cirrhosis and HCC
  - Development of anti-HBe and clearance of antigen is associated with low HBV DNA, lower rates of progression to cirrhosis and HCC, improved survival rates
  - Results in remission (inactive carrier status)
  - May occur spontaneously or due to treatment

Hepatitis B
Chronic Hepatitis

- Two types of chronic hepatitis
  - HBeAg (+): candidate for seroconversion
  - HBeAg (-): worse course and outcomes, no seroconversion
- Treatment determined by HBeAg status
  - HBeAg (+): seroconversion used as treatment endpoint
  - HBeAg (-): ALT and HBV DNA titer used as treatment endpoint

Hepatitis B
Chronic Hepatitis: Principles of Therapy

- Safety/efficacy/drug resistance should be considered
- First line: entecavir, tenofovir, peg-interferon
  - Profound DNA suppression
  - Minimal resistance
- Adefovir is 2nd line due to resistance issues
- Lamivudine: high rate of resistance, avoided
- If adequate response not achieved → add another antiretroviral or switch to more potent drug
- Generally HBeAg (-) pts are more likely to relapse and will require longer duration of therapy

Hepatitis B
Pharmacologic Therapy

- Interferon-α_{2b} and Pegylated-α_{2a} Interferon
  - Antiviral, antiproliferative, immunomodulatory
  - Indicated for HBeAg (+) and (-) chronic HBV treatment
  - Peg-interferon: longer half life (weekly vs. 3x/wk), similar efficacy. Given subcutaneously (SQ)
  - Seroconversion rate: 30-40% after one year of peg-interferon, often permanent, may occur after completion of therapy
  - Duration of treatment
    - HBeAg (+): 48 wks
    - HBeAg (-): > 48 wks, until HBV DNA undetectable
  - Should only be used in compensated liver disease
  - AEs: infection, flares, flu-like symptoms, hematologic toxicity, psych problems (irritability, depression)

Hepatitis B
Pharmacologic Therapy

- Entecavir
  - Guanosine nucleoside analog, suppresses HBV DNA polymerase
  - Indicated for HBeAg (+) and (-) chronic HBV treatment
  - Low resistance rates (1-2% after 5 yrs), more effective than adefovir or lamivudine in histologic improvements, HBV DNA reduction, and ALT normalization
  - Seroconversion is therapy-duration-dependent, up to 20% at 48 wks
  - No clear duration of treatment
  - Given orally on empty stomach, continued until remission is confirmed
  - AEs: lactic acidosis, severe hepatomegaly with steatosis, GI side effects

Hepatitis B
Pharmacologic Therapy

- Tenofovir
  - Acyclic adenine nucleotide reverse transcriptase inhibitor
  - Indicated for HBeAg (+) and (-) chronic HBV treatment, and for HIV treatment
  - Given orally on empty stomach
  - Similar seroconversion rate to other oral antivirals
  - AEs: lactic acidosis, severe hepatomegaly with steatosis, GI side effects

Hepatitis B
Pharmacologic Therapy

- Adefovir
  - Adenosine nucleotide analog that inhibits DNA polymerase
  - Indicated for HBeAg (+) and (-) chronic HBV > 12 yrs of age
  - Less effective than tenofovir and entecavir, higher resistance rates
  - Given orally
  - AEs:
    - Nephrotoxicity- SCr should be monitored baseline and every 3 mo on therapy
    - Severe hepatomegaly with steatosis, GI side effects

Hepatitis C

- Single-stranded RNA virus
- Similar risk factors to HBV; IVDU responsible for nearly 60% of HCV
- Diagnosed by testing for anti-HCV, HCV RNA
- Genotype determines duration of therapy and response
- Chronic HCV if anti-HCV and elevated RNA persist > 6 mo
- Chronic HCV is curable
- Over 70% of HCV turns chronic but remains asymptomatic in majority of pts
- Cirrhosis occurs in 15-20% in chronic HCV, after 20-40 yrs of infection

Hepatitis C

- No vaccine available for HCV
- Primary goal is sustained virologic response (SVR): aviremia x 24 wks post-therapy (cure)
- Peg-Interferon and Ribavirin
  - Given in combination- ribavirin increases interferon's SVR rate
  - AEs: Flu-like symptoms, psych symptoms (irritability, depression), hematologic complications
  - Ribavirin is teratogenic, pregnancy should be avoided for 6 mo after completing therapy

Hepatitis C

- Sofosbuvir (Sovaldi)
  - Direct-acting antiviral (DAA), inhibits RNA polymerase
  - Indicated for chronic HCV with concomitant ribvirin and with or without peg-interferon
  - SVR rates > 96% in genotype 4
  - Given orally, once daily
  - Monotherapy not recommended 2/2 drug resistance
  - Higher incidence of anemia and neutropenia than Peg-interferon and ribavirin combination
  - AEs: fatigue, HA, nausea, insomnia, anemia

Hepatitis C

- Other DAAs available: boceprevir, telaprevir
- Genotype 4: sofosbuvir + ribavirin + peg-interferon x 12 wks
- Successful therapy: virus become undetectable within 4-12 wks of therapy
- If undetectable status continues x 24 wks after completing therapy → SVR (cure)

Hepatitis D & E

- HDV
  - Requires HBV for replication
  - More severe complications compared with HBV alone
  - Confirmed by measuring HDV RNA levels in serum
  - Hep B vaccine can indirectly prevent HDV
  - No effective treatment or cure
  - Peg-interferon may reduce severity of disease in chronic HDV infection
- HEV
  - Self limiting with few complications, no vaccine