Hepatitis

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Chronic active hepatitis

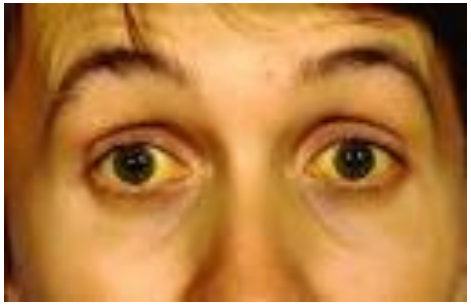
- **Viral Infections**
  - Hepatitis viruses (B, C, D)
  - Cytomegalovirus (CMV)
  - Epstein-Barr virus (EBV)
  - Rubella virus
- **Metabolic Disorders**
  - Alcoholic liver disease
  - Wilson disease
  - α 1-antitrypsin deficiency
  - Autoimmune hepatitis
- ***Drug-induced chronic active hepatitis***
  - Methyldopa
  - Nitrofurantoin
  - Isoniazid
  - Sulfonamides and Propylthiouracil (rarely)

Viral Hepatitis

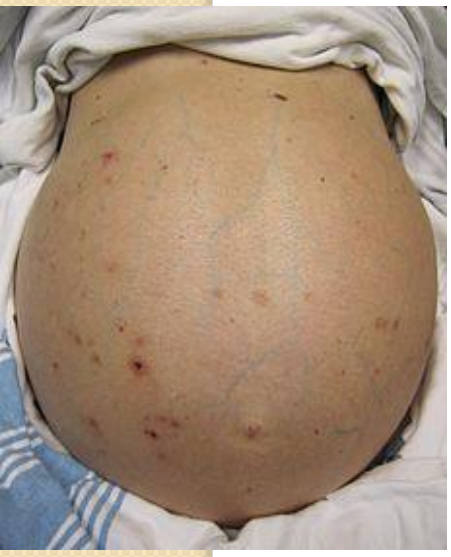
- **Types**
- **Causative agents**
  - Fecal-oral: HAV, HEV
  - Percutaneus transmission: HBV,HCV,HDV
- **Definitions of Acute and Chronic Hepatitis**
- **Chronic Hepatitis:**
  - The most common causes : HBV, HCV
  - Less frequently: drug-induced and autoimmune
  - Relatively rare : Metabolic disorders and HDV
  - Neither HAV nor HEV infections cause chronic hepatitis

Signs and symptoms

- Acute:
  - nonspecific flu-like symptoms (common to almost all acute viral infections)
  - malaise, muscle and joint aches, fever, nausea or vomiting , diarrhea and headache
  - More specific symptom : loss of appetite , dark urine, jaundice and abdominal discomfort, hepatomegaly, lymphadenopathy or splenomegaly



- Chronic:
  - nonspecific symptoms such as malaise, tiredness and weakness, and often leads to no symptoms at all
  - weight loss, easy bruising and bleeding tendencies, peripheral edema
  - Cirrhosis: Ascites, : esophageal varices, hepatic encephalopathy , Acne, abnormal menstruation , lung scarring , inflammation of the thyroid gland and kidneys



HEPATITIS A VIRUS

- Virology and Epidemiology
- Pathogenesis
- Clinical Manifestations
- Extrahepatic Manifestations
- Diagnosis and Serology
- Treatment
- Adjustment of Medication Doses
- Prevention of Hepatitis A
  - Pre-Exposure Prophylaxis
    - IMMUNOGLOBULIN
    - VACCINE
    - Efficacy, *Safety, and Duration of Response*
  - *POSTEXPOSUREPROPHYLAXIS*

HEPATITIS B VIRUS

- **Virology**
  - partially double-stranded DNA virus
  - a member of the Hepadnaviridae family
- **Epidemiology**
  - Approximately 5% of the world's population is infected with HBV
- **Transmission**
  - sexual contact
  - percutaneous or perinatal exposure
  - close person-to-person contact
  - only semen, saliva, and serum
  - Kissing or biting ???
- Although HBsAg is detectable in breast milk, breast-feeding is not believed to be a primary mode of HBV transmission

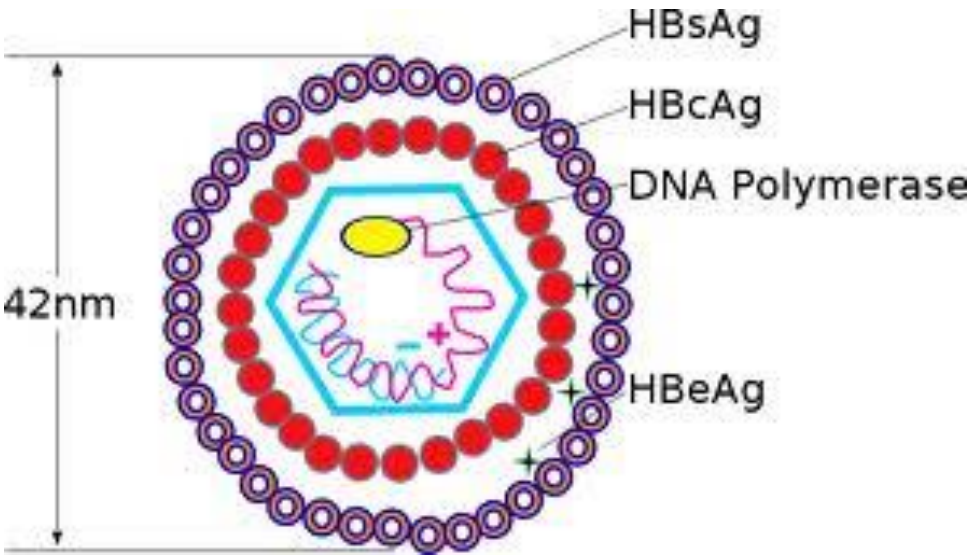
Diagnosis

- The presence of HBsAg in serum is diagnostic for HBV infection
- the presence of IgM anti-HBc in serum confirms a recent acute HBV infection
- the presence of HBV DNA in serum

Common Serologic Patterns of Hepatitis B Virus Infection

HBsAg	HBeAg	Anti-HBs	Anti-HBe	Anti-HBc	Interpretation
+	+	-	-	-	Incubation period
+	+	-	-	+ (IgM)	Acute HBV infection (typical case); chronic HBV carrier with high infectivity
-	-	+	-	+ (IgG)	Recovery from HBV infection
+	-	-	-	+ (IgG)	Chronic HBV carrier; chronic hepatitis B
-	-	+	-	-	Successful immunization with HBV vaccine

Anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B envelope antibody; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M.



Clinical Manifestations:

- ***ACUTE LIVER FAILURE:***
  - The most significant complication of acute HBV infection is ALF, widely defined as a coagulation abnormality (INR > 1.5) in a patient of less than 26 weeks duration
  - Hepatic encephalopathy, lethargy, confusion, coma, coagulopathy, hemodynamic instability, declining liver function, and acidosis
  - pulmonary complications (hypoxemia, aspiration, adult respiratory distress syndrome, and pulmonary edema)
  - Functional renal failure, also known as hepatorenal syndrome or acute tubular necrosis

TREATMENT

- The primary therapy for ALF is supportive care
- The last one: liver transplantation

- Prevention

Prevention of Hepatitis B

- Alterations in sexual behavior
- screening of high-risk patients or settings
- Vaccination
  - Dosing regimen
  - Efficacy:
    - an anti-HBs level of at least 10 milli-international units/mL is considered a protective antibody titer
    - age at vaccination and underlying immune function
    - Poor response : Immunocompromised patients: hemodialysis, HIV, or children receiving cytotoxic chemotherapy
    - Patients who smoke or are obese also have a reduced response

Vaccination

- The duration of vaccine-induced immunity: 6 to 12 years
- no need booster doses to immunocompetent persons after successful vaccination
- Immunocompromised patients :
  - booster dose when antibody levels are less than 10 milli-international units

Treatment of chronic HBV

- The goals of therapy: to achieve sustained suppression of HBV replication and remission of liver disease.

- Serum concentrations of aminotransferases can range from slightly abnormal to greatly elevated, with ALT concentrations generally greater than AST. Serum

- *DRUG THERAPY*
  - *Acute or chronic phase HBV hepatitis*
    - *Corticosteroids*
    - *HBIG*
    - *α- Interferon*
    - *NRT inhibitors*

INTERFERONS (IFNs)

- Previously, the most effective agents for treating chronic hepatitis B
- antiviral activity :
  - ability to abate viral entry into the host cells and modulate several steps of the viral replication cycle (e.g., viral uncoating, inhibition of messenger RNA, and protein synthesis)
  - IFN-α2b (Intron-A)
  - Pegylated IFN (PegIFN-α2a)
  - the only FDA-approved IFNs for the treatment of chronic HBV infection

Efficacy

- Conventional Interferon:
  - IFN-a is moderately effective in treating chronic hepatitis B in a small percentage
- Pegylated Interferon:
  - more convenient dosing and additional viral suppression
- PegIFN monotherapy or combination therapy more than lamivudine monotherapy had HBeAg conversion
- the addition of lamivudine to PegIFN did not improve post therapy response rates

Dosing Considerations

- Standard IFN doses of 2.5 to 10 million units can be administered subcutaneously (SC) daily or three times weekly
- The manufacturer of IFN-α2b recommends 30 to 35 million units/week
- administered SC or 1M as 5 million units/day or 10 million units three times weekly
- It is possible that more severe flulike symptoms and headache occur with thrice-weekly dosing when compared with daily administration.
- In contrast, severe bone marrow suppression tends to occur less often with thrice-weekly administration.

Dosing Considerations

- The recommended duration of therapy for patients who are HBeAg positive is for 16 to 24 weeks
- HBeAg negative HBV infection should be treated for at least 12 months and possibly for 24 months to enhance the rate of sustained response
- Peg IFN-α2α:
  - The only pegylated IFN approved for the treatment of HBV infection
  - 180 mcg SC weekly for 48 weeks

Adverse Effects

- standard and PegIFN-a therapy are similar and quite common
- The early side effects:
  - generally appear hours after administration
  - Resemble an influenza like syndrome with fever, chills, anorexia, nausea, myalgias, fatigue, and headache
  - Administration at bedtime may decrease the severity of early side effects.
  - Acetaminophen can be, *but should be limited to 2 g/day to minimize the* risk of hepatotoxicity

Adverse Effects

- The late side effects:
  - Usually are observed after 2 weeks of therapy and are more serious
  - *Worsening of the influenza like* syndrome
  - Alopecia
  - Bone marrow suppression
  - Bacterial infections
  - Thyroid dysfunction (both hypothyroidism and hyperthyroidism)
  - Psychiatric disturbances (emotional lability, irritability, depression, anxiety, delirium, and suicidal ideation)

NUCLEOSIDE / NUCLEOTIDE ANALOGS

- an alternative approach to treatment in patients with decompensated disease
- the FDA has approved antiviral agents for treatment of chronic hepatitis B infection
  - Lamivudine
  - Adefovir dipivoxil (+)
  - Entecavir(++)
  - Tenofovir disoproxil(+++)
  - Telbivudine (++)
- Emtricitabine and Clevudine that may be approved in the near future
- All Need to adjust dose in RF

Lamivudine

- the first nucleoside analog approved by the FDA
- 100 mg every day
- inhibits DNA synthesis
- *Lamivudine Resistancy:* after 6 months or more of continuous
- currently considered a second-line agent

Adefovir

- the oral prodrug of an acyclic nucleotide monophosphate analog
- adults with:
  - active viral replication or
  - persistent elevations in serum amino transferases (ALT or AST) or
  - histologically active disease
- Adverse effects:
  - abdominal pain, diarrhea, dyspepsia, headaches, and nausea
- Resistance to adefovir occurs at a much slower rate compared with lamivudine
- Dose :10 mg daily

Entecavir

- potent activity against HBV
- more potent than lamivudine and adefovir
- highly effective against lamivudine-resistant or refractory patients
- No resistance
- Dose:
  - Nucleoside naïve: 0.5 mg every day
  - Lamivudine refractory/resistant: 1.0 mg every day

Telbivudine

- Elevated creatinine kinase levels were more commonly seen in the patients treated with telbivudine, whereas elevated ALT and AST levels were more common in those treated with lamivudine
- Resistance rates were lower among the telbivudine group compared with the lamivudine group
- the rates of resistance are much greater than for entecavir
- Dose: 600 mg daily

Tenofovir

- A potent nucleotide analog
- Structurally similar, yet equipotent, but less nephrotoxic than adefovir
- well tolerated
- It has been reported to cause:
  - Fanconi syndrome
  - Renal insufficiency
  - Osteomalacia
- Dose: 300 mg every 24 hours

Combination therapy

- is superior to lamivudine monotherapy in reducing the rate of resistance
- combination therapy is not appropriate for entecavir and tenofovir associated with low resistance as monotherapy

HEPATITIS C VIRUS

- the most common cause of chronic NANB transfusion-associated hepatitis
- a single-stranded RNA virus related to the flaviviruses
- Age range: 20 to 39 years
- with a male predominance
- HCV genotype
  - genotype 1 and 4 may be more difficult to treat than genotypes 2 or 3 is that genotype 1 has a longer half-life (2.9 hours) than that of genotypes 2 or 3 (2.0 hours)

HCV

- Nonpercutaneous transmission:
  - transmission between sexual partners
  - from mother to child
  - less efficient compared with the percutaneous route
- Percutaneous transmission:
  - blood transfusion
  - Injection drug users (IDU)

HCV

- In nonimmunocompromised patients, the time between acute infection and manifestations of chronic liver disease is usually 20 to 30 years
- Coinfection with chronic HBV and HCV results in more severe liver disease than infection with either virus alone:
  - increased risk of liver cancer and fulminant hepatitis

HCV

- The incidence of HCV infection in HIV-infected patients is variable, with up to 100% infection reported in HIV-positive injection drug

- coinfection with HIV may have more severe hepatic injury and a worse outcome than those infected with HCV alone

HCV

- pregnancy is not contraindicated in HCV infected individuals
- Perinatal transmission from mother to baby occurs in less than 6%
- No evidence indicates that breast-feeding transmits HCV from mother to baby; therefore, it is considered safe
- Babies born to HCV-positive mothers should be tested for anti-HCV at 1 year

Prevention of Hepatitis C

- **PRE-EXPOSURE *PROPHYLAXIS***
  - No vaccines are effective against HCV

- **POSTEXPOSURE *PROPHYLAXIS***
  - Immunoglobulin is no longe recommended for postexposure prophylaxis of hepatitis C infection because it is not effective

Diagnosis

- serologic assays:
  - detect specific antibody to HCV (anti-HCV)
  - detect viral nucleic acid
- Biochemical markers:
  - Serum ALT
  - Is not sensitive marker
- Biopsy:
  - can determine the extent of liver injury caused by HCV

Treatment of Acute Hepatitis C

- PegIFN-a2b or IFN-a to minimize risk for developing chronic HCV infection
- Alcohol use (or HIV coinfection) can accelerate the progression of
- Chronic hepatitis develops approximately 80% of patients with acute hepatitis C infection

Treatment of Chronic Hepatitis C

- The current standard of care is:
  - combination of a PegIFN-a and ribavirin

- Two forms of PegIFN are FDA-approved for treatment of HCV infection.
  - PegIFN-α2b :
    - The linear (12-kDa PegIFN) was the first to be approved
  - PegIFN-α2a :
    - The 40-kDa PegIFN

Clinical trials

- monotherapy with PegIFNs is superior to conventional IFN alone.
- PegIFN-a2a plus ribavirin is superior to IFN-a2b plus ribavirin or PegIFN-a2a alone.

Algorithm for treatment of hepatitis C

1. Make the diagnosis based on aminotransferase elevations, anti-HCV and HCV RNA in serum, and chronic hepatitis shown by liver biopsy.

2. Assess for suitability of therapy and contraindications. Discuss side effects and possible treatment outcomes.

3. Test for HCV genotype.

4. Genotype 1: Test for HCV RNA level immediately before starting therapy (baseline level).

Genotype 1:

Start therapy with peginterferon-α2a in a dose of 180 mg weekly or peginterferon-α2b in a dose of 1.5 mg/kg weekly in combination with oral ribavirin in two divided doses of 1,000 mg daily if body weight is <75 kg (165 lb) or 1,200 mg daily if body weight is >75 kg.

Genotype 2 or 3:

Start therapy with peginterferon-α2a in a dose of 180 mcg weekly or with peginterferon-α2b in a dose of 1.5 mcg/kg weekly and oral ribavirin 800 mg daily in two divided doses.

Treatment duration

- Patients with genotypes 2 and 3 require only 24 weeks of therapy with 800 mg daily of ribavirin

- patients with genotype 1 (and potentially genotype 4) require 48 weeks of therapy and full doses of ribavirin (1,000-1,200 mg daily)

Pregnancy risk

- contraindicated in women who are pregnant
- by men whose female partners are pregnant
- negative pregnancy test should be obtained before therapy

Side effects

- INF:
  - Influenza like symptoms
  - hematologic abnormalities:
    - persistent cytopenias despite dose reductions, treatment with hematopoietic growth factors
  - Thyroid dysfunction
  - neuropsychiatric symptoms
    - Depression : ……SSRIs

- Ribavirin:
  - severe hemolysis (in renal insufficiency)
  - is not removed by hemodialysis
  - lactic acidosis (Rarely)

HEPATITIS D VIRUS

- a small, single-stranded circular RNA
- Vaccination for HBV significantly reduces the incidence of HDV
- The modes of transmission : similar to for HBV infection
- The goal of treatment is to eradicate HDV along with HBV
- Supportive care is the general strategy used to treat HDV infection
- antiviral therapy has been disappointing
- Liver transplantation:
  - the treatment of choice for patients with fulminant or end-stage liver disease after HDV infection

HEPATITIS E VIRUS

- a single-stranded polyadenylated RNA
- Transmission of HEV:
  - is via the fecal-oral route
  - the most common source: ingestion of fecally contaminated water
- HEV is a diagnosis of exclusion
- Fulminant hepatitis has also been associated with HEV infection, mostly in pregnancy
- No vaccines or postexposure prophylaxis treatments are currently available to prevent HEV infection

Viral hepatitis

- Any question?