Hepatitis Hieroglyphics

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Disclosures

- No relevant commercial relationships to disclose.

Learning Objectives

- At the conclusion of this session, participants should be able to:
  - Compare and contrast the presentation and prevention strategies for hepatitis B and C
  - Analyze and interpret lab values to diagnose stages of hepatitis B and hepatitis C
  - Explain the newest treatment options and their side effects for hepatitis B and C
  - Discuss the long-term complications of untreated hepatitis B and hepatitis C

Hepatitis

- Hepatitis A virus
- Hepatitis B virus
- Hepatitis C virus
- Hepatitis D virus
- Hepatitis E virus
- Drug induced, autoimmune
  - Acute versus Chronic

Mini Immunology Terminology Review

- Antibody
- Antigen
- Immunoglobulin G (IgG)
- Immunoglobulin M (IgM)

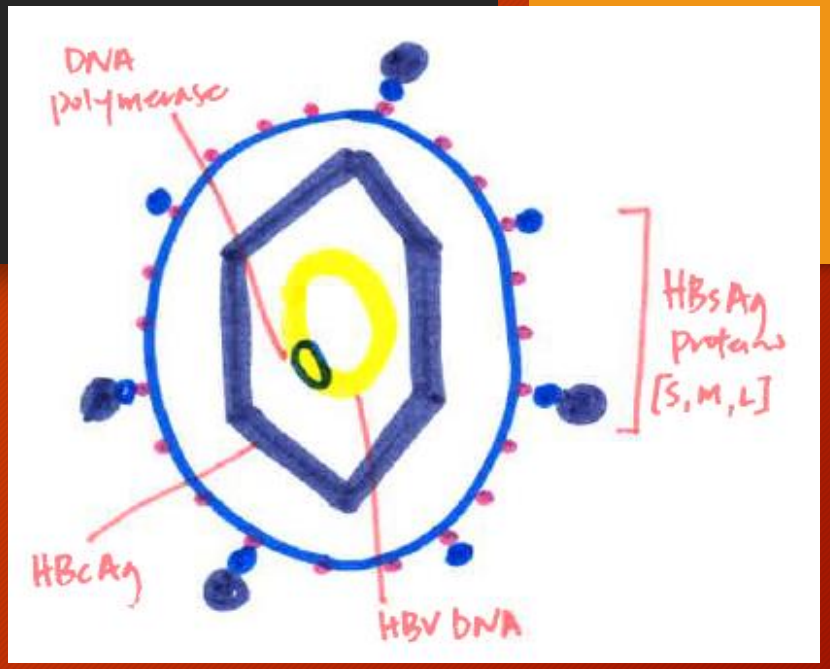
Acute Hepatitis Symptoms

- Prodromal Phase:
  - Nausea/vomiting
  - Anorexia
  - Fatigue
  - Malaise
  - Arthralgias
  - Low-grade fever
  - Myalgias
- Clinical Jaundice:
  - Dark urine
  - Acholic stools
  - Yellow skin/eyes
  - Weight loss
  - Hepatomegaly and RUQ discomfort
  - Splenomegaly
  - Cervical adenopathy
- Recovery Phase:
  - Hepatomegaly
  - Resolving LFTs

Acute Hepatitis Laboratory Findings

- Elevated AST
- Elevated ALT
- Normal to elevated total bilirubin
- Normal to elevated alkaline Phosphatase
- Immunoglobulins

Hepatitis B

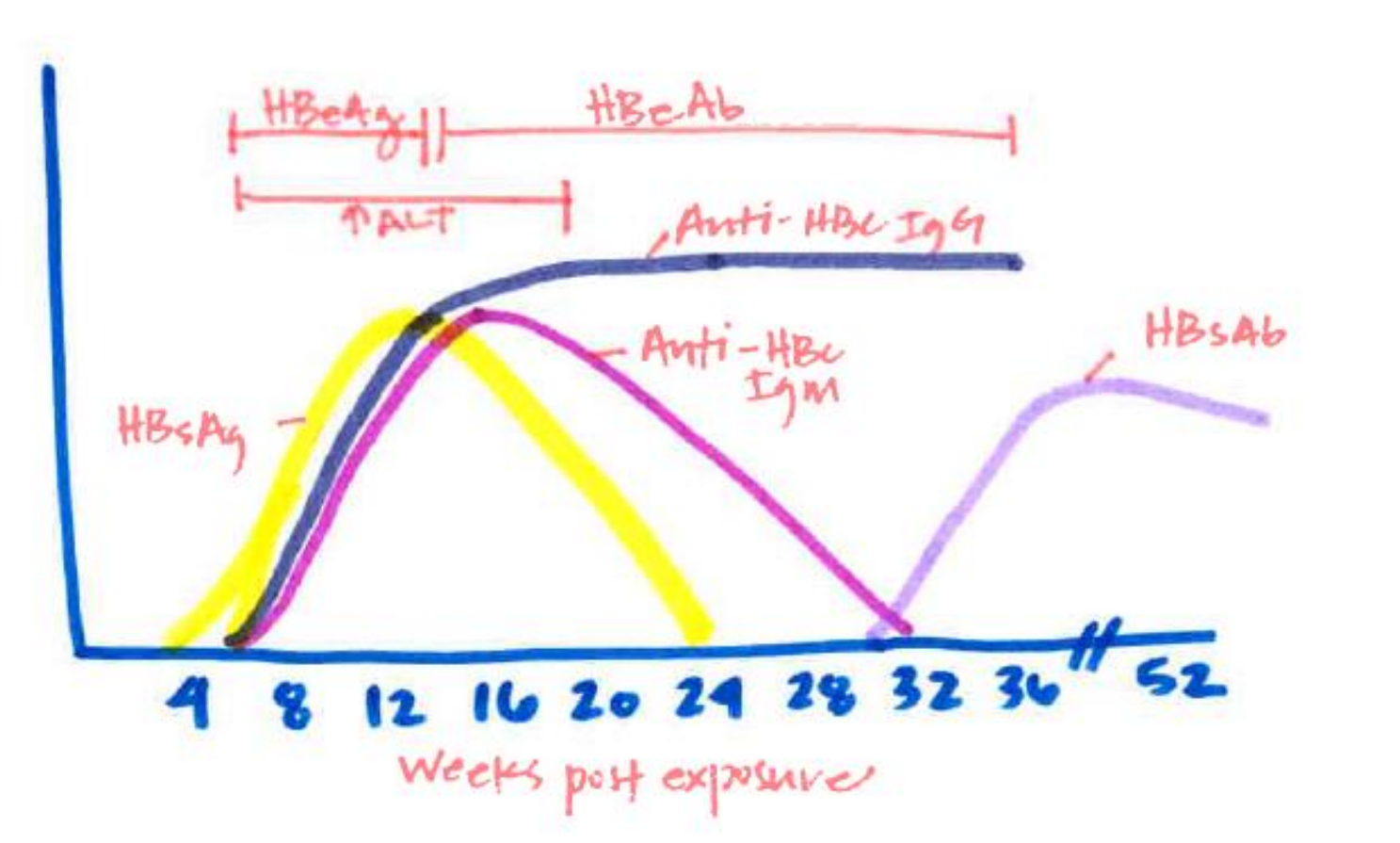


- Compact **DNA** structure
  - Part of Hepadnaviridae family
  - Ten different genotypes
- Virion can survive outside the body for > 7 days
- Highest incidence in Asia and Western Pacific
- Parenteral, sexual, perinatal transmission (most common!!)

Hepatitis B Serologies

- Anti-HBc or HBcAb – hepatitis B core antibody
- Anti-HCs or HBsAb – hepatitis B surface antibody
- HBsAg – hepatitis B surface antigen
- HBeAg – hepatitis B envelope antigen

Acute Hepatitis B Serology



Acute Hepatitis B Treatment

- Primarily supportive and self-limited
- Exception:
  - Patients with fulminant hepatitis
  - Prolonged, severe acute hepatitis B

  - 1st line: lamivudine or telbivudine

Hepatitis B Continuum

Acute self-limited infection

Fulminant hepatic failure

Chronic disease

Chronic Hepatitis B

- Definition: positive HBsAg test > 6 months
- 15-40% of patients develop cirrhosis and/or HCC

- Is there a cure???
- What is goal of treatment?
  - Suppress viral replication, halt progression of liver disease, prevent hepatocellular carcinoma

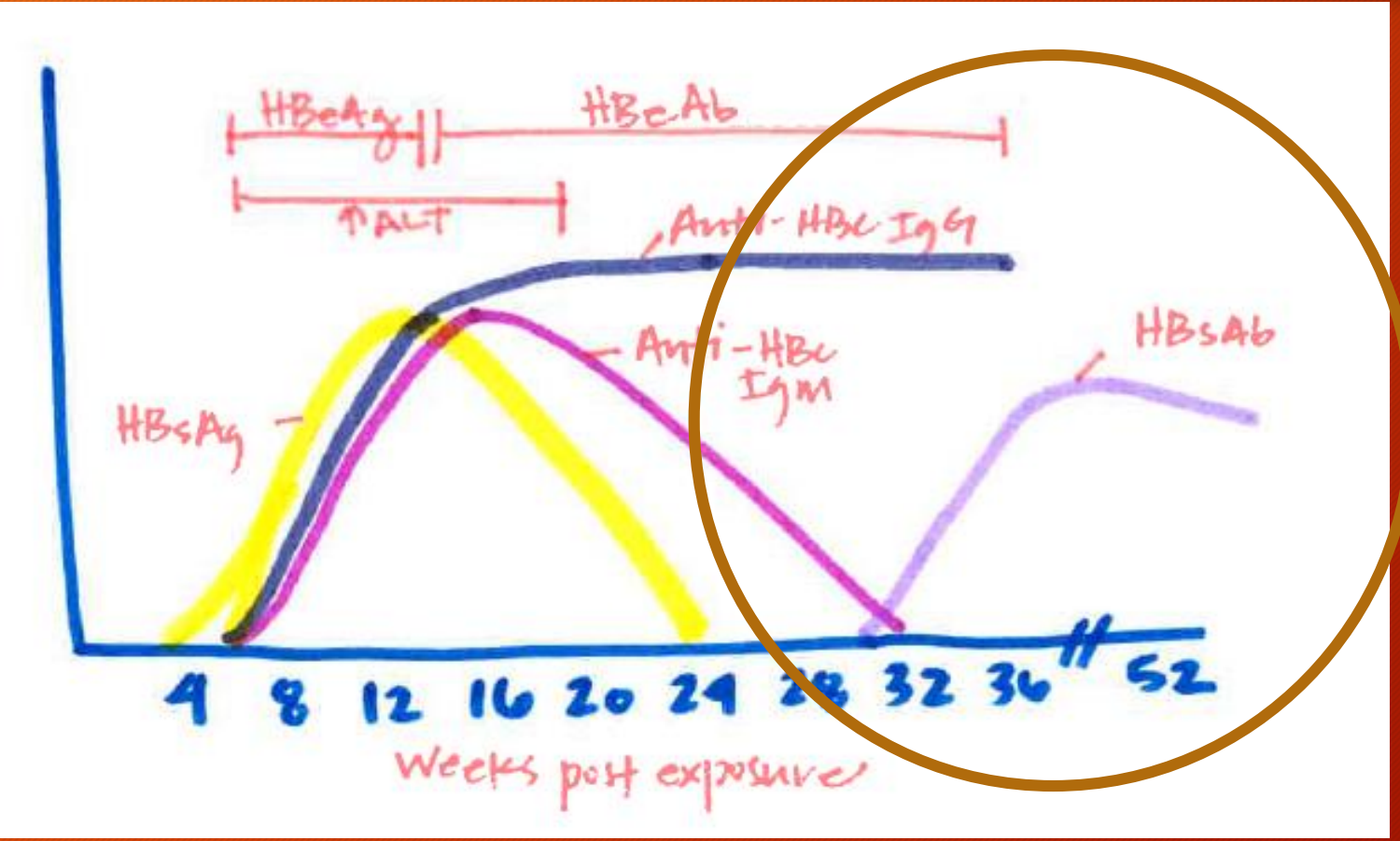
Chronic Hepatitis B

- Four phases:
  - Immune-tolerant phase –
    - Little hepatic inflammation with normal liver tests
    - Elevated HBV DNA and +HBV e antigen
  - Immune-active phase –
    - Hepatic inflammation with elevated liver tests
    - Decreased HBV DNA levels. (-) HBV e antigen and (+) HBV e antibody
  - **Inactive carrier phase** –
    - Normal liver tests, low HBV DNA levels (<2,000 units/mL), and (-) HBV e antigen
    - Hep B surface antibody – negative, Hep B core total antibody – positive
  - Reactivation phase –
    - Normal or high liver tests, high HBV DNA levels
    - Can be HBV e antigen negative or revert to HBV e antigen positive

Chronic Hepatitis B Work up

- Serologies:
  - HBsAg +
  - HBcAb IgG +
  - HBcAb IgM –
  - HBsAb –
  - HBeAg variable
- HBV DNA --- viral load
- AST and ALT
- Biopsy???

Chronic Hepatitis B Serology



Chronic Hepatitis B – Treatment

- Immune-tolerant phase – NO TREATMENT
- Immune-active phase – TREAT!
  - Peginterferon and entecavir and tenofovir
- Inactive carrier phase – NO TREATMENT
- Reactivation phase – TREAT!

*** If cirrhosis, give therapy!

Chronic Hepatitis B – Treatment Side Effects

Pegylated interferon	Entecavir**	Tenofovir
Flu-like symptoms	Headache	Depression
Mood changes/outbursts	Fatigue	Back pain
Insomnia	Dizziness	Lactic acidosis
Loss of appetite, N/V	Nausea	Insomnia
Severe fatigue		Rash, N/V

***must take on empty stomach

Hepatitis B Serologies

	Surface Antigen (HBsAg)	Core Antibody (Anti-HBc or HBcAb)	Surface Antibody (Anti-HBs or HBsAb)	Envelope Antigen (HBeAg)
Acute Infection	+	IgM+/IgG-	-	+
Recovered from past Infection/immune	-	IgM-/IgG+	+	-
Vaccine	-	-	+	-
Chronic Infection	+	IgM-/IgG+	-	+

Hepatitis B Screening

- U.S. Preventive Services Task Force recommends:
  - Persons born in countries and regions with a high prevalence of HBV infection (≥2%), such as Asia, Africa, the Pacific Islands, and parts of South America
  - US-born persons not vaccinated as infants whose parents were born in regions with a very high prevalence of HBV infection (≥8%)
  - HIV-positive persons
  - Persons with injection drug use
  - Men who have sex with men
  - Household contacts or sexual partners of persons with HBV infection

Hepatitis B Prevention

- Universal precautions needed
- Preventative HBV vaccine: → not an option if allergic to yeast
  - For most people, 3 doses recommended. Month 0,1, and 6.
  - Recommended for all children within 24 hours of birth, at 1-2 months, and 3rd at least at 24 weeks.
- Post exposure prophylaxis:
  - Hepatitis B immunoglobulin + HBV vaccine
    - Perinatal, post needle stick, and IV drug use
- Prevention of vertical transmission
  - consider antiviral therapy at 28-32 weeks gestation in pregnant women with hepatitis B surface antigen (HBsAg)-positive chronic hepatitis B and HBV DNA > 200,000 units/mL

Side Note on Hepatitis D

Hepatitis D

- Small, defective RNA virus
- MUST BE COINFECTED WITH HEPATITIS B
- Transmission through blood, sexual, percutaneously, and perinatally
- Incubation period of 30-180 days
- Symptoms:
- Diagnosis:
  - Anti-HDV IgM with initial infection
  - HDV RNA in serum

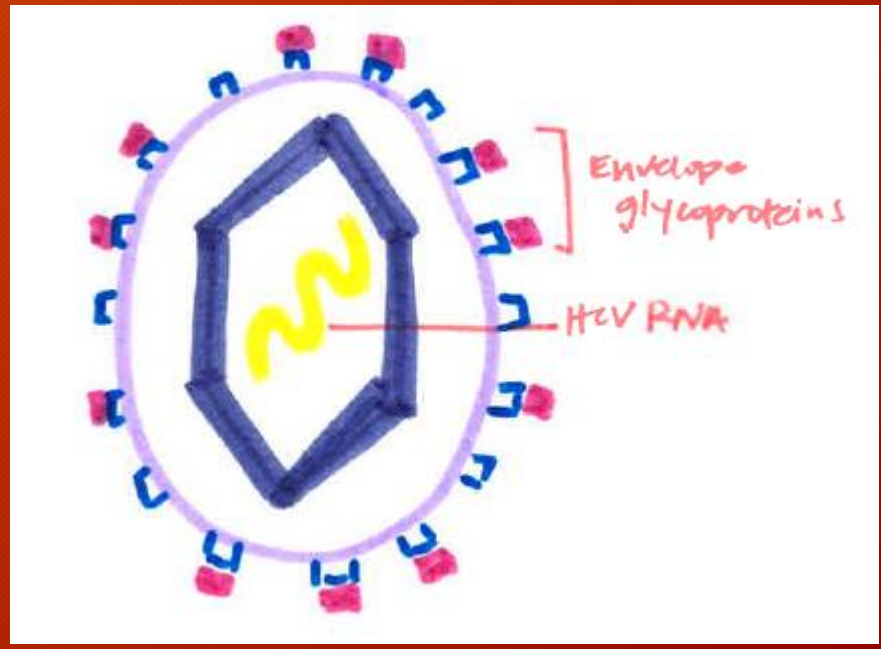
Hepatitis D

- Treatment:
  - WHO recommendation: PEGylated interferon alpha x 48 weeks
- Prophylaxis:
  - Hepatitis B vaccine administration

Hepatitis C

Hepatitis C

- Single-stranded **RNA** virus – Flaviviridae family
- 6 genotypes
  - Genotype Ia (46%), Ib (26%), Ic
  - Genotype 2 (10%)
  - Genotype 3 (9%)
  - Genotype 4 (6%)
  - Genotype 5
  - Genotype 6 (1%)
- Primarily transmitted parentally
- Incubation period of 14-180 days



Acute Hepatitis C – Incidence and Symptoms

- ??????
- Increased in American Indian and Alaska Natives

- Asymptomatic!

Acute Hepatitis C - Clinical Course

- Pre-ramp up phase (7-21 days)
  - Low or undetectable blood viral levels
- Ramp-up phase (8-10 days)
  - Significant increase in viral levels
- Plateau phase (40-60 days)
  - Stable HCV RNA levels
- Two possible outcomes:
  - Spontaneously clear virus, ending infection, associated with loss of detection of HCV RNA or
  - Progress to chronic infection, associated with stable long-term HCV RNA levels

Acute Hepatitis C - Diagnosis

- Two tests:
  - HCV RNA testing → viral load **GOLD STANDARD**
  - Anti-HCV testing → antibodies
  - Plus ALT & AST???
- How do I interpret them??
  - Acute infection
    - HCV RNA +
    - HCV antibody -
  - Biopsy or not????

Hepatitis C Serologies (48 hrs post exposure)

Anti-HCV	HCV RNA	Diagnosis	Follow Up
Negative	Negative	No hepatitis C	Repeat at six months
Positive	Negative	Prior infection, but resolved	Repeat at six months
Negative	Positive	Acute hepatitis C	Recheck within six months to see if virus cleared
Positive	Positive	Chronic hepatitis C	Treat!

Acute Hepatitis C - Treatment

- Mixed opinions
  - Wait to see if they convert versus start antiviral treatment

- 20% of patients will resolve infection
- 80% will develop into chronic (>6 months of elevated viral load)

- After six months, of HCV RNA is still elevated → chronic hep C
- After six months, if HCV RNA is negative → recheck in 12 weeks

Chronic Hepatitis C

- Criteria: elevated viral load > 6 months
- Over 20 years, 20-30% will develop cirrhosis

Acute versus Chronic Hepatitis C

	Acute Hepatitis C Infection	Chronic Hepatitis C Infection
Clinical presentation	Asymptomatic Vague symptoms of illness +/- jaundice or peak serum ALT levels > 200 units/L	Asymptomatic Long-term: chronic liver disease
Viremia concentration and stability	Low levels (<105 IU/mL) with significant fluctuations	Higher levels than acute; Stable with little fluctuation
ALT levels	>250 U/L may suggest acute infection Higher than chronic disease	Lower than acute disease Can be normal

Chronic Hepatitis C – Diagnosis

- Serology:
  - Anti-HCV – positive
  - HCV RNA – positive
- AST/ALT levels baseline
- Genotype testing MUST be done in this setting
- May need to check for resistance associated substitutions (RASs)
  - Specific recommendations exist for the genotype and antiviral combination you are considering
- Liver fibrosis evaluation

Fibrosis Assessment

If evidence of cirrhosis already, no need to do fibrosis assessment

- Elastography
  - US or MRI guided
  - Fibrotic changes to the liver increase its stiffness → increasing wave velocity
  - Limitations:
    - Ascites, acute hepatitis, CHF, severely obese
- Liver Biopsy
  - Primarily if biomarkers and elastography are discordant or if other etiologies of liver damage

Who and Why to Treat?

- Recommended for ALL patients with hepatitis C except:
  - Pregnant
  - Short life expectancy
  - Severe liver disease (maybe??)
- What about kids?

- Why?
  - Slow progression of liver fibrosis
  - Improved LFTs
  - Lower mortality

Treatment Goal

- Virologic cure as evidenced by sustained viral response (SVR) in order to reduce all-cause mortality and liver-related adverse health consequences, improve quality of life and remove stigma, and prevent HCV transmission

Labs Prior to Antivirals

- Stage hepatic fibrosis
- CBC, INR, AST/ALT, T. bili, albumin, alk phos
- HCV RNA
- HBsAg, anti-HBs, anti-HBc
- Need to know what genotype and direct treatment

Chronic Hepatitis C Treatment - Historically

- Interferon alfa weekly x 24 weeks + ribavirin
  - Side effects: flu-like symptoms, cognitive changes, depression/suicidal ideation
  - Poorly tolerated → poor compliance → poor response

Chronic Hepatitis C Treatment - Newer

NS5B RNA Polymerase Inhibitors "-buvirs"	NS3/4A Protease Inhibitors "-previrs"	NS5A Protein Inhibitors "-asvirs"
Dasabuvir Sofosbuvir	Grazoprevir Paritaprevir Simeprevir	Daclatasvir Elbasvir Ledipasvir Ombitasvir Velpatasvir

- Combinations for genotype 1a without cirrhosis:
  - Ledipasvir/sofosbuvir (Harvoni) for 8-12 weeks **
  - Elbasvir/grazoprevir (Viekira) for 8 weeks **
  - Sofosbuvir/velpatasvir for 12 weeks

Antiviral Side Effects & Warnings

- Ledipasvir/sofosbuvir (genotype 1, 4, 5, 6)
  - Amiodarone contraindicated → bradycardia
  - Rifampin, St. John's wort contraindicated
  - Watch: antacids, anticonvulsants, statins
  - Side effects: fatigue, weakness, headache
- Elbasvir/grazoprevir (genotype 1, 4)
  - Co-administration of moderate or strong inducers of CYP3A → decreased plasma concentrations → reduced therapeutic effect
  - Only in Child-Pugh Class A
  - Side effects: fatigue, headache, nausea

Antiviral Side Effects & Warnings

- Sofosbuvir/velpatasvir (ALL genotypes)
  - Amiodarone contraindicated → bradycardia
  - Rifampin, St. John's wort, PPI's, phenytoin, phenobarbital, and carbamazepine not recommended
  - Side effects: headache, fatigue

Hepatitis C Prophylaxis & Screening

- Prophylaxis:
  - Universal Precautions
  - Screen blood products well
  - Behavior modification
    - Condoms, regular screening, new needles
    - No sharing of razors, toothbrushes, nail clippers
  - No immunoglobulins or vaccines
- Screening
  - U.S. Preventive Services Task Force recommends screening all adults from ages 18-79 and those that have high risk behavior (IV drug use) more frequently and regardless of age.

Hepatitis Complications

- Cirrhosis – HBV and HCV
- Cryoglobulinemia and glomerulonephritis-HBV and HCV
- Polyarteritis nodosa- HBV
- Hepatocellular cancer- HBV, HCV
- Parkinson's disease- HBV, HCV
- Fulminant hepatitis- HBV

Fulminant Hepatitis

- Etiology: Hepatitis B/D, drugs (acetaminophen)
- Symptoms/Signs:
  - FAST deterioration!
  - Portosystemic encephalopathy
  - Coagulopathy
  - Hepatorenal syndrome
- Treatment:
  - Acute Hep B treatment (nucleoside/tide analog)
  - Liver transplant ultimately

Role of Liver Transplantation

- Three primarily causes:
  - Presence of hepatocellular cancer
  - Decompensated cirrhosis
  - Fulminant hepatitis
- Cirrhosis from hepatitis C is highest need for liver transplant
- Hepatitis B reinfection rates have decreased post liver transplantation due to antiviral medication
- Liver transplant on the rise
  - 40K in 2019 in US; 8, 372 were deceased donors

Hepatocellular Cancer

- Incidence 2-5% of HBV and HCV patients
  - Increased in those with cirrhosis
  - Increased in HCV>HBV
- Liver ultrasound every six months for Hep B carriers who are:
  - Asian males > 40 years old
  - Asian females > 50 years old
  - African/North American Black
  - with family history of hepatocellular carcinoma

Take Home Points

- Acute hepatitis B is primarily self limited, unlike hepatitis C where the majority will become chronically infected
- Chronic hepatitis C can be cured with antivirals, which are well tolerated and shorter treatment than historically
- Hepatitis B more frequently causes fulminant hepatitis when the host is coinfected with hepatitis D
- If infected with hepatitis C, vaccinate the patient for hepatitis A and B
- Treatment for chronic hepatitis C will commonly cause an activation of hepatitis B → check serologies before treatment!

References

- Ferrarese A, Zanetto A, Gambato M, et al. Liver transplantation for viral hepatitis in 2015. *World J Gastroenterol*. 2016;22(4):1570-1581. doi:10.3748/wjg.v22.i4.1570
- Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016 Sep 14;22(34):7824-40. doi: 10.3748/wjg.v22.i34.7824. PMID: 27678366; PMCID: PMC5016383.
- Recommendation: Screening for Hepatitis B Virus Infection in Adolescents and Adults | United States Preventive Services Taskforce (uspreventiveservicestaskforce.org) Accessed February 3, 2021
- http://www.hcvguidelines.org/full-report/initial-treatment-hcv-infection Accessed February 7, 2021

Questions?

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