Understanding Viral Hepatitis (Screening, Vaccinating and Treating)

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5 Types of Viral Hepatitis

	Нер А	Нер В	Нер С	Hep D	Hep E
Type of virus	RNA	DNA	RNA	RNA	RNA
Possible chronic infection	No	Yes	Yes	Yes	Yes
Transmission route	Fecal-oral	Blood and other body fluids	Blood and other body fluids	Blood and other body fluids	Fecal-oral
Incubation time	14-28 days	30-180 days	14-180 days	HDV requires HBV for replication	14-70 days
Treatment	No	Yes	Yes	Yes	No
Cure	Yes	No	Yes	No	Yes
Vaccine	Yes	Yes	No	No	Yes (China only)

Hepatitis B

Global Prevalence of HBV Infection (2017)



Hepatitis B. WHO (2017). http://www.who.int/mediacentre/factsheets/fs204/en/.

Modes of HBV Transmission



CDC. Morb Mortal Wkly Rep. 2008;57:1-20, CDC. Morb Mortal Wkly Rep. 2005;54:1-31.

Complications Associated With Chronic HBV Infection



Up to 40% of patients with CHB will develop cirrhosis, liver failure, or HCC

Hepatitis B Vaccines Available!

- Expanded CDC/ACIP vaccination recommendation just issued
- Recommendations
 - All children 18 years and younger
 - What's new: universal vaccination
 - All adults aged 19-59 years
 - Adults <u>>60</u> years with risk factors for hepatitis B or without identified risk factors but seeking protection

Hepatitis B Vaccines

- Single antigen vaccines
 - HEPLISAV-B (Dynavax) for adults and requires 2 doses
 - Energix-B (GSK) requires 3 doses
 - Recombivax-B (Merck) requires 3 doses
- Triple antigen vaccine (S, pre-S1, and pre-S2 surface antigens)
 - NEW: PreHevbrio (VBI Vaccines) for adults and requires 3 doses
- Combination vaccine
 - Twinrix (GSK) approved for adults and vaccinates against HAV and HBV

Interpreting Labs

Serologic Markers in HBV Infection



Interpreting HBV Screening Tests

Possible test results										
HBsAg	+	-	-	_						
Anti-HBs –		+/-	+	_						
Anti-HBc	+	+	-	_						
Interpretation	Acute or chronic infection*	Exposure to HBV At risk for reactivation	Immune due to vaccination	At risk for HBV infection						
Action	Evaluation and further testing	Follow up as appropriate	No further action required	Vaccinate						

*Patient is chronically infected if HBsAg+ for ≥6 months. Patients with acute infection will be positive for anti-HBc IgM.

Terrault NA et al. *Hepatology*. 2018; 67: 1560-1599; Abara WE et al. *Ann Intern Med*. 2017; 167: 794-804.

Four Phases of Chronic HBV Infection



Antiviral Therapy Delays Overall Disease Progression in Chronic Hepatitis B



"Proof of Principle"

HBV Treatment Landscape in 2022

First line agents



Hepatitis B Reactivation in the Setting of Immunosuppression

Screening Labs Prior to Immunosuppressive or Cytotoxic Therapy

- Labs needed to identify hep B status prior to starting immunosuppressive therapy are Hep B surface Antigen (HBsAg) and Hep B Core Ab Total (anti-HBc total) for previous positive exposure.
- Most commercial labs offer hepatitis panels but not all panels contain these tests.
- Be sure that the following tests are part of any panel* or order them separately
 - Hep B surface Antigen (HBsAg) and
 - Hep B core Antibody Total (anti-HBc total)

*LabCorp Test 144473 (Hepatitis B virus screening and diagnosis) is a panel that tests both.

Drug Classes and Risk of HBV reactivation

	B cell	Anthracyclin	Steroids >	4 weeks	TNF-α	Other cytokine or	Tyrosine kinase inhibitors	
	agents	e derivatives	Moderate or high dose	Low dose	inhibitors	integrin inhibitors		
HBsAg+/ anti-HBc+	High	High	High	Moderate	Moderate	Moderate	Moderate	
HBsAg-/ anti-HBc+	High	Moderate	Moderate	Low	Moderate	Moderate	Moderate	

High risk: > 10%; Moderate risk: 1-10%; Low risk: < 1%

Summary

- Good news: Vaccines available.
- Bad news: There is no cure; however, antiviral therapy can delay/reverse progression of HBV-related liver disease.
- HBV DNA and stage of liver disease (e.g., cirrhosis) are key factors in deciding whether to treat.
- Patients receiving immunosuppressant therapy should be screened for HBV (HBsAg and anti-HBc total).
 - All HBsAg positive and/or anti-HBc positive patients should be referred to a liver specialist prior to immunosuppressant therapy.
- HCC surveillance critical in this patient population.
 - Ultrasound +/- AFP every 6 months.
- Patients with HBV should be managed by a liver specialist.

Hepatitis D (Delta Hepatitis)

Delta Hepatitis

- First discovered in 1977
- Smallest human RNA virus
- Known as a "satellite virus" or an "incomplete virus"
 - Can only infect people who are also infected with the hepatitis B virus (HBV)
 - Uses HBsAg to form the HDV envelope
- Estimated that 12-60 million people infected worldwide
- Coinfection with HDV/HBV can lead to more rapidly progressing liver damage than HBV alone

Types of Delta Hepatitis Infections

Superinfection

When someone with chronic hepatitis B becomes infected with hepatitis D



- More common
- Likelihood of developing chronic hepatitis B and D is 70-90%
- Children and adults usually develop chronic, lifelong infections of both viruses

Coinfection

When somone becomes infected with hepatitis B and D at the same time



- Less common
- Likelihood of developing chronic hepatitis B and D is <5%
- Adults usually clear both viruses within 6 months

Screen for Delta Hepatitis in HBsAg Positive Individuals

Test Name	HDV Antibody, IgG			HDV Antibody, IgM			HDV RNA, Quantitative		HDV RNA, Qualitative			HDV Antigen	HDV Genotyping and NAT		
Test Code	4990	20799	20799	99202	20799	35664	30336	98507	37889	2013881	34469	3900	1844	2006450 -	CDC-10328
Reference Lab	Quest Diagnostics*	LABORATORIES		🔅 Viracor Eastins Clinical Diagnestics	BioAgilytix 🎆	Quest Diagnostics*	🔅 Viracor Cuestins Clinical Diagnostics	LABORATORIES	Quest Diagnostics*	LABORATORIES	Quest Diagnostics"	Viracor Eurofes Clinical Diagnostice	BioReference	LABORATORIES BioAgilytix	CDC
CPT Code	86692							87799		87798			87380	Not CLIA approved	

https://testdirectory.questdiagnostics.com/test/home accessed Feb 8, 2022; https://www.aruplab.com/testing accessed Feb 8, 2022; https://www.mayocliniclabs.com/testcatalog/search?q=hepatitis+delta accessed Feb 15, 2022; https://www.eurofins-viracor.com/clinical/test-menu/?search_field=HDV accessed Feb 15, 2022; https://www.bioagilytix.com/bioagilytix-diagnostics/ accessed Feb 15, 2022, https://www.bioreference.com/physicians/resources/test-directory/?type=by_test&test_id=1840 accessed Feb 15, 2022

Hepatitis C

Populations at Risk

Baby Boomers (born 1945-1965)



AASLD/IDSA HCV Guidance Document Recommendations for Screening

- One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years or older.
- One-time HCV testing should be performed for all persons less than 18 years old with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection.
- Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy.

AASLD/IDSA HCV Guidance Document Recommendations for Screening

- For patients with ongoing risk factors:
 - <u>Annual</u> HCV testing is recommended for
 - All persons who inject drugs
 - HIV-infected men who have unprotected sex with men and
 - Men who have sex with men taking pre-exposure prophylaxis (PrEP)
 - <u>Periodic</u> testing should be offered to other persons with ongoing risk factors for exposure to HCV

HCV Can Be Cured

- Unlike HIV and HBV infection, HCV infection is a curable disease
 - HCV does not archive its genome in the nucleus and does not integrate in the host DNA
- What does cure mean?
 - Undetectable HCV RNA 12 weeks after completion of antiviral therapy for chronic HCV infection
 - SVR12 is almost invariably durable

Recommended Testing Sequence for Identifying Current HCV Infection or Reinfection



AASLD-IDSA Hep C Guidance Panel, Hepatology, 71 (2), 2020

Does a Reactive HCV Antibody Test Mean My Patient Has Chronic HCV Infection?

- No! It's a SCREENING test
- Individuals who were successfully treated and cured will remain antibody positive but will be HCV RNA negative
- Approximately 15%-25% of individuals clear the virus without treatment and do not develop chronic infection
- HCV RNA (viral load) is required to confirm chronic infection

Hepatitis A and Hepatitis E

Hepatitis A Epidemiology

- Highly endemic in some areas, particularly Central and South America, Africa, the Middle East, Asia, and the Western Pacific
- Hepatitis A vaccine available and children routinely vaccinated.



Hepatitis A

- Transmission: fecal-oral route
 - Inadequate sanitation and hygiene
 - Food or waterborne outbreaks
 - Contaminated food or water
 - Raw or undercooked shellfish
 - Foods contaminated by infected food handlers
 - International travel
 - Sexual transmission
 - \uparrow men who have sex with men
 - Close contact
 - Households
 - Institutionalized settings
 - Military personnel
 - Daycare center

Hepatitis A Clinical Presentation

- Incubation period: mean 30 days (rage 15-49)
- Acute, self-limited illness
 - Fatigue, malaise, anorexia, N/V, fever, and RUQ pain
 - Jaundice with dark urine, acholic stools
 - May be subtle in children
- Extrahepatic manifestations
 - Leukocytoclastic vasculitis, cryoglobulinemia
 - Arthritis
 - Thrombocytopenia, aplastic anemia, red cell aplasia
 - Glomerulonephritis
 - Myocarditis
 - Optic neuritis
 - Transverse myelitis

Hepatitis A Clinical Presentation

- Acute liver failure rare
 - Increased risk if underlying liver disease \rightarrow vaccination recommendation
- Cholestatic hepatitis
 - Prolonged episode, bilirubin > 10 x 2-3 months
 - Alkaline phosphate Λ
- Relapsing hepatitis
 - Apparent clinical recovery followed by increase in LFTs and symptoms

Hepatitis A diagnosis

- Chemistries
 - AST and ALT usually >1000 IU/L
 - Bilirubin usually <10 mg/dL
 - Most infections are asymptomatic
- Serologies
 - Hepatitis A IgM
 - Diagnostic of acute infection in a symptomatic person
 - Usually persists for 4 to 6 months
 - Hepatitis A antibody total
 - Includes IgM and IgG
 - Remote infection if no active symptoms

Hepatitis A Treatment

- Supportive care
- Consider admission if unable to maintain PO intake, dehydration, acute kidney injury, bile-cast nephropathy
- Transfer to liver transplant center if signs of acute liver failure
 - Prolonged PT
 - Altered mental status

Hepatitis A Vaccination

- Advisory Committee on Immunization Practices (ACIP) recommendations
- Children: All at one year of age
- Adults:
 - Traveling to or working in countries with high or intermediate rates of hepatitis A
 - Chronic liver disease
 - Clotting factor disorders
 - Men who have sex with men
 - Illicit drug users (injection and noninjection)
 - Close personal contact with an international adoptee from a country of high or intermediate endemicity during the first 60 days following arrival

Hepatitis E Epidemiology

- HEV is a leading cause of icteric hepatitis and acute liver failure in the developing world.
- Worldwide, the estimated annual incidence of HEV infection is 20 million, resulting in 56,600 deaths.



Donnelly MC, et al., AP&T, Vol 46, Issue 2, 2017, pp. 126-141.

Chronic Hepatitis E

- Patients with detectable HEV RNA after 6 months
- Populations: HIV, immunocompromised patients (including liver disease, post transplant), pregnant women
- Treatment
 - Reduce immunosuppression in transplant patients
 - Ribavirin: 12-week course, Dose: 600-1000 mg

Summary

- HBV
 - No cure but medications to slow the progression of liver disease
 - CDC: Hepatitis B vaccination recommendation
 - Vaccinate all children and adults <59 yo and <a>>60 yo if risk factors
 - Be sure to order Hep B surface antigen (HBsAg) and Hep B core antibody total (anti-HBc total) prior to starting immunosuppressant therapy.
 - Coinfection of HBV/HDV has a worse prognosis for patients so test all HBsAg+ patients for HDV.
- HCV
 - No vaccine but curable disease
 - Cure rates >95% with 8-12 weeks of oral therapy for most
 - One time HCV testing is recommended for all <a>>
 18 years old, those <18 years old with high-risk behaviors and pregnant women with each pregnancy
- HAV and HEV
 - Fecal-oral transmission
 - In US, HAV vaccine available
 - HEV very rare in US