Hepatitis A, B and C: Current Recommendations for Screening and Management

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Disclosure Statement

I am on the Speakers Bureau for:
- Gilead
- Merck
- Abbvie

I am an Advisory Board Member for:
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What is Hepatitis?

The word "hepatitis" means inflammation of the liver. Chemical exposure, certain drugs, some diseases, heavy alcohol use, bacterial and viral infections can all cause hepatitis.
Hepatitis

- If left untreated or undetected, has the potential to cause irreversible liver damage

Viral Hepatitis

- Hep A (HAV)
- Hep B (HBV)
- Hep C (HCV)
- Hep D (HDV) only possible to have hepatitis D if you have hepatitis B. Rare in US
- Hep E (HEV) most common in parts of South Asia, Africa, and Central America. No chronic infection caused by hepatitis E.

Goal for Today?
You become the viral hepatitis expert in your practice!

Hep A: What is it?
HAV has a single molecule of RNA
Likely been around for centuries but isolated in 1973


Goals
• Be aware of the common clinical presentations of viral hepatitis A, B and C
• Know patient populations at risk
• Select the appropriate diagnostics
• Develop screening/management/treatment strategies for these individuals
Hepatitis A
- Found in stool and blood of infected person about 15 - 45 days before symptoms occur and during the first week of illness

Hep A Transmission
- Food or water that has been contaminated by fecal material containing the hep A virus (fruit, shellfish, ice, water, vegetables)
- Contact with stool of infected person (poor hygiene, handwashing)
- Sexual contact with infected person via oral/anal contact

Risk Factors: Hep A
- Incidence higher in certain foreign countries
- IV drug use
- Living in a nursing home or rehabilitation center
- Working in a health care, food, or sewage industry
Risk Factors Hep A

- a household member or close personal contact (e.g., grandparent or other extended family member, caregiver, or regular babysitter) of an international adoptee recently arriving from a country with high or intermediate prevalence of hepatitis A.**

Adapted from: "Do I Need Any Vaccinations Today?" Immunization Action Coalition
http://www.immunize.org

How common is Hepatitis A virus (HAV) infection in the United States?

- Hepatitis A rates in the United States have declined by 89% since hepatitis A vaccine first became available in 1995.
- In 2006, 3,579 acute symptomatic cases of hepatitis A were reported; the incidence was 1.2/100,000, the lowest rate ever recorded. After adjusting for asymptomatic infection and underreporting, the estimated number of new infections was 32,000. (CDC, 2009)

Hepatitis A clinical presentation

Hepatitis A is usually a mild illness characterized by sudden onset of fever, malaise, nausea, anorexia, and abdominal discomfort, followed in several days by jaundice.

The infectious dose is unknown but presumably is 10-100 virus particles.
Hep A

- Some individuals have had Hep A infection and are unaware; experienced a GI illness and are surprised to find months or years later that they are HAV antibody positive.
- However, there are acute presentations.

Who Can Get Hep A?

- Anyone who has not been previously exposed or been immunized can become infected and ill from the Hep A virus

How is the Hep A Virus Spread?

- Oral ingestion usually
- Passed in feces
- Virus may be transmitted on infected person’s hands and spread by direct contact, or
- Spread by consuming food or drink handled by an infected person
Transmission

- Uncooked HAV-contaminated foods have been recognized as a source. Cooked foods also can transmit HAV if temperature during food prep is inadequate to kill the virus, or food is contaminated after cooking, as occurs in outbreaks associated with infected food handlers.

Transmission

- In some cases, may be spread by sexual contact or by consuming water or food that has been contaminated by sewage.

Incubation Period

- Symptoms may appear within 2-6 weeks after initial exposure (usually within 4 weeks)
Hep A

- An individual is **contagious approx 2 weeks before symptoms appear**
- Close contacts of infected person may get vaccine or immune globulin to reduce chance of becoming ill.
- For persons aged >40 years, IG is preferred because of the absence of information regarding vaccine performance in this age group (CDC)

Post Exposure

- **Immune globulin or Hepatitis A vaccine.**
  - Vaccine or immune globulin must be given within the first 2 weeks after exposure to be effective.

Vaccination

Adults who:
- Travel to areas with increase rates of HAV
- Men who have sex with men
- Drug use
- Chronic liver disease
- Clotting disorder
- 2 doses 6 months apart
Why people with clotting disorder?

- Hepatitis A has been found in solvent detergent-treated clotting factor because hepatitis A can resist the viral-killing methods. Transmission of hepatitis A remains a risk for people with bleeding disorders who use plasma-derived products. If vaccinated, this is not a problem.

Pediatric

- Hepatitis A vaccination is recommended for all children at age 1 year
- Children who have not been vaccinated by age 2 can be vaccinated at subsequent visits.

http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#vaccine

Hep A: Case Study

Sarah

- 55 yr old female
- admitted for eval of RUQ
- Pain, scleral icterus, Abnormal LFT’s
Labs/Sarah

- Total bili  5.6
- Alk phos  301
- ALT  1995
- AST  4438

Hep A Prevention

- Hand washing
- Avoid raw shellfish from potentially contaminated waters
- Infected people should not handle foods during prep (stay home from work!)
- Vaccination!

Hep A Diagnostics: Understanding Serologies

IgM Antibody
(anti-HAV or HAV IgM ab)
- Positive result defines recent HAV infection
- May be negative in early infection
- Present for 3-6 months after acute symptoms
Serology HAV

Hep A Total Antibody
(Anti-HAV Ab or HAV Ab)
- Limited value in diagnosis of acute infection
- **Positive** result indicates *past* infection and immunity!

Hep A serologies

**Hep A IGG:**
usually positive when IGM is no longer detectable and HAV Total is positive.

Hepatitis B
- HBV is a double-stranded enveloped virus
- HBV replicates in the hepatocytes of humans and other higher primates
HBV

- Two billion worldwide have been infected with Hepatitis B
- 600,000 die annually secondary to Hep B
- HBV is more infectious than HIV
- Important occupational hazard
- It is preventable with vaccination!

WHO Fact Sheet July 2016

Hepatitis B: United States

- In 2010, an estimated 38,000 persons in the US were newly infected.
- Rates highest among males, age 25-44.
- Estimated 1.2 million in US have chronic HBV infection

www.cdc.gov/hepatitis/HBV 2013
Hep B

The rate of new HBV infections in the US has declined by approximately 80% since 1991. The decline has been greatest among children born since 1991, when routine vaccination of children was first recommended.

http://www.cdc.gov/hepatitis/hbv/statisticshbv.htm

Hep B

chronically infected may be unaware of infection

virus can go 20 to 30 years before they develop symptoms or feel sick.

even though a person has no symptoms and may appear healthy, the virus can still be detected in the blood and damage to the liver can still be occurring.
Hep B Transmission
- transmitted through puncture through the skin or mucosal contact with infectious blood or body fluids (semen, saliva)
- This is a strong virus! Can live on surfaces for up to a week.

Who Is at Risk?
- Babies born to infected mothers
- Sex partners of infected persons
- Persons with multiple sex partners
- Persons with STD’s
- Men who have sex with men
- Injections drug users
- Household contacts of infected

At Risk
- Healthcare and public safety workers exposed to blood/body fluids on the job
- Hemodialysis patients
- Residents/staff of facilities for developmentally disabled
- Traveling to a regions with rates of Hep B Surface Ag+ prevalence >2%
- Persons born in locations with high rates of HBV
IN THE UNITED STATES, 1 IN 12 ASIAN AMERICANS IS CHRONICALLY INFECTED WITH HEPATITIS B IN COMPARISON TO 1 IN 1000 NON-HISPANIC WHITES.

ASIAN AMERICANS CONSTITUTE ONLY 4% OF THE POPULATION IN THE UNITED STATES BUT THEY COMPRISE OVER HALF OF THE NATION'S 1.2-2 MILLION PEOPLE CHRONICALLY INFECTED WITH HEPATITIS B.

http://liver.stanford.edu/education/whatishepb.html

Who to Screen for Hep B?

- All pregnant females
- Persons born in regions where high rates of Hep B
- US born persons not vaccinated as infants who parents born in regions with high rates of Hep B
- Infants born to Hep B Surf Ag positive females
- Household, needle sharing or sex contacts of HBsAG positive persons
- Men who have sex with men.

Hep B: Signs and Symptoms

- May be absent
- Fever
- Fatigue
- Nausea/vomiting
- Anorexia
- RUQ pain
- Scleral icterus/jaundice
- Arthralgias
- Light stool (clay)
- Dark Urine
Hep B: Incubation

- Long! Symptoms may present 60-150 days after exposure.

Prevention After Exposure to Hepatitis B

The hepatitis B vaccine or a hepatitis B immune globulin (HBIG) shot may help prevent hepatitis B infection if given within 24 hours of exposure.

Hep B Vaccine

- There are several inactivated virus vaccines.
- A combination vaccine is also available which contains Hep B and a Hep A vaccine.
- The hepatitis B vaccine is usually given as a series of 3 - 4 shots over a 6-month period.
In the United States a comprehensive strategy to eliminate HBV has been developed and encompasses the following four components:

1. universal vaccination of infants at birth
2. prevention of perinatal HBV through routine screening of all pregnant women for HBV and the provision of immunoprophylaxis to infants born either to infected women or to women of unknown infection status
3. routine vaccination of previously unvaccinated children and adolescents
4. vaccination of adults at increased risk for infection, including health-care workers, dialysis patients, household contacts and sex partners of persons with chronic HBV infection, recipients of certain blood products, persons with a recent history of having multiple sex partners concurrently, those with a sexually transmitted disease, MSM, and IDUs.


Who to Vaccinate?

- Children and adolescents less than 18 yrs old and not previously vaccinated
- Partners/household contacts of infected
- IV drug users
- Pts who require frequent blood/blood products
- Solid organ recipients

Vaccinate

- Those with occupational risk of HBV, including health care workers
- Travelers to countries with high rates of HBV

World Health Organization Fact Sheet 2012
Hep B

- If symptoms occur, individual may be ill for several weeks.
- Acute infections range from totally asymptomatic to fulminant hepatitis.

Chronic Hep B

- Most Americans, if infected, will clear the virus and have long term immunity
- Infants and children at high risk for chronic disease
- According to CDC, 90% of infants and 25-50% of children aged 1-5 will remain chronic
- Many chronic HBV pts in US who were born to HBV infected mothers outside US

Case Studies

Josh: **Acute Hepatitis B**
- 36 year old male
- Never vaccinated for HBV
- No significant health issues until recent ED visit for Jaundice and ‘feeling like I have the flu’
Josh
- Transferred from community hospital
- Jaundice
- Fever
- RUQ pain
- Diffuse arthralgias
- Loss of appetite
- Low grade fever

Josh: Etiology
Sexually active with female who has had hepatitis since birth
She is *Hepatitis B surface antigen positive* and *Hepatitis B DNA positive*

Hep B: Diagnosis
- Serologic markers
- Difficult to understand, can be confusing
- Know your basics
Most Americans who contract Hep B will develop acute infection, clear the virus and develop long term immunity.

What does the blood test of someone look like who has had the disease?

What does the blood test look like for someone who was vaccinated?

**Hep B Surface Antigen**

*Hepatitis B surface antigen (HBsAg):* A protein on the surface of HBV; can be detected in serum during acute or chronic HBV infection. The presence of HBsAg indicates that the person is infectious.

**Hep B IGM**

*IgM antibody to hepatitis B core antigen (IgM anti-HBc):* If positive, indicates recent infection with HBV (≤6 months). Its presence indicates acute infection.

Josh had a positive Hep B IGM.
Hep B Surface Antibody

- **Hepatitis B surface antibody (anti-HBs):**
  - Presence of anti-HBs is generally interpreted as recovery and immunity from HBV.
  - Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.

Hep B Core Antibody

- **Total hepatitis B core antibody (anti-HBc):** The person had, or has, the actual disease.

Hep B DNA

- Will be positive in acute disease.
- Positive in most chronic disease.
- This is the 'viral load'.
Hep B

- Josh test results during acute phase of Hep B?
- Josh test results 6 months later if he developed immunity?

The development of chronic HBV infection is inversely related to the age of acquisition occurring in approximately 80–90% of people infected perinatally, about 30% of children infected before the age of 6 years, and in <5% of infections occurring in otherwise healthy adults.


Hep B

Treatment?
- Acute infection: supportive therapy
- Chronic infection: antiviral drugs available; viral suppression, not cure.
- People with chronic infection at risk for hepatocellular carcinoma, cirrhosis.
Case Study 2

- Esther
- 83 yr old female
- No known prior hx of liver disease or abnormal liver function tests
- Diabetic
- Living at home with rotating staff of HHA

Hepatitis B

People with chronic HBV infection have a 15–25% risk of dying prematurely from HBV-related cirrhosis and liver cancer


Treatment Chronic HBV

Medicines for treatment of chronic HBV may delay progression of cirrhosis, reduce the incidence of HCC and improve long-term survival.

Pharmacologic Treatment HBV
Entecavir
Lamivudine
Tenofovir
Telbivudine
Adefovir

HEP B
- Most Americans who contract Hep B will develop acute infection, clear the virus and develop long term immunity
- What does the blood test of someone look like who has had the disease?
- What does the blood test look like for someone who was vaccinated?

Understanding Hep B Serologic Markers
- Online training available
  - [www.cdc.gov/hepatitis/ResourceCntr/Professional/Training/Serology](http://www.cdc.gov/hepatitis/ResourceCntr/Professional/Training/Serology)
Hep B Prevention

- Vaccine(s) available
- Single antigen and combinations available

Prevention/Vaccine

- Contraindicated in those who have had allergic reaction to a prior dose of Hep B single or combo vaccine
- Those with hx serious allergic reaction to yeast

[cdc.gov.hepatitis/HBV]

Patients in your practice with chronic HBV will need lifelong follow up!
**Hepatitis C**

**Hep C**
- RNA virus
- Formerly known as ‘non A, non B’ or transfusion associated hepatitis
- Virus isolated and named in the late 1980’s
- Unlike Hep A and B, *there is no vaccine!!*

**Hep C: How Does One Acquire It?**
- **Blood to Blood** transmission only
- **Rare** sexual transmission
- Blood transfusion, needle sharing, tattoo, intranasal cocaine
**Hepatitis C Disease Burden: US**

- Hepatitis C is the most common chronic blood-borne viral infection in the US\(^1\)
  - ~ 1/2 of cirrhotic patients\(^2\)
  - ~ 1/3 of HCC patients\(^3\)
  - #1 reason for liver transplants\(^4\)
  - #1 cause of death in HIV patients\(^5, 6\)

It is estimated that 4 million Americans are infected with HCV\(^7\)

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**Prevalence of Hepatitis C**

- Hepatitis C is 4 times more prevalent than HIV\(^1, 2\)

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**Prevalence of Hepatitis C by Age and Sex**

Retrospective review of claims from 1997–1999 in US Health Plan with 3.0 million members

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Who Should Be Screened: HCV

The prevalence of anti-HCV among persons born during 1945–1965 is 3.25% (3), five times higher than among adults born in other years. The high prevalence of HCV among persons in this birth cohort reflects the substantial number of incident infections throughout the 1970s and 1980s and the persistence of HCV as a chronic infection. Males in this cohort had almost twice the prevalence as their female counterparts; HCV infection prevalence was highest among non-Hispanic black males (8.12%), followed by non-Hispanic white males (4.05%) and Mexican-American males (3.41%).

CDC Recommendations and Reports
August 17, 2012 / 61(RR04);1-18
Screening: HCV

CDC (2012) recommending that everyone born during 1945 through 1965, also known as baby boomers, get a blood test for Hepatitis C. This recommendation calls for one-time testing of baby boomers.

HCV: DIAGNOSTICS

- First line test is HCV Antibody
- If positive, order HCV PCR RNA and HCV Genotype

Why Important to Screen??
Hepatitis C Is Often Undiagnosed

- Despite its high prevalence, HCV often remains undiagnosed

<table>
<thead>
<tr>
<th>24%</th>
<th>Diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>76%</td>
<td>Undiagnosed</td>
</tr>
</tbody>
</table>

More than three-fourths of those with hepatitis C are undiagnosed.

The Majority of Patients Are Asymptomatic

- Symptoms of HCV include¹,²
  - Fatigue
  - Nausea
  - Poor appetite/weight loss
  - Muscle and joint pain/muscle weakness
  - Jaundice
  - Abdominal pain or swelling
  - Dark urine
  - Itching
  - Fluid retention

- However, symptoms differ from patient to patient and some patients may not have any symptoms for up to 20 years, yet their liver disease may be progressing¹

- 80% of patients with HCV have no signs or symptoms²

Normal ALT Does Not Mean “Healthy”

- Up to 40% of HCV patients may have persistently normal ALT¹
- ALT levels fluctuate in and out of the normal range over the course of HCV infection²

Typical ALT pattern in Chronic Hepatitis C Infection

1. CDC. 2016. Available at http://www.cdc.gov/hepatitis/HEP_FactSheets/ALTTest/fs.htm
2. CDC. 2016. Available at http://www.cdc.gov/hepatitis/HEP_FactSheets/ALTTest/fs.htm
HCV Disease Progression in Patients With Normal ALT

- Despite 'persistently normal' ALT levels, > 75% have some degree of liver damage on biopsy, with 32% having portal and bridging fibrosis.
- There are no known factors that predict which patient with persistently normal ALT will have disease progression.

HCV Genotypes in US

- Hepatitis C virus:
  - thick area – high mutation rates
  - divided different genotypes
- 6 known genotypes:
  - Genotype 1 (75%)
  - Genotype 2 (10%)
  - Genotype 3 (10%)
  - Genotype 4-6 (5%)
- Genotypes 1-3 are the most common in the United States.
- Little difference in mode of transmission or natural history of infection among different genotypes.
- Predicts treatment response and may help to determine treatment duration.

HCV: Disease Progression

- Time: 20-30 years
- HCV infection
- Chronic HCV
- Cirrhosis
- Hepatic Failure
- Liver Cancer
- Liver Transplant Candidates

Liver Cancer Has the Fastest Growing Death Rate in the US

Trends in US Cancer Mortality Rates

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annual Percent Change (1996-2005)*</th>
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</thead>
<tbody>
<tr>
<td>All Cancers (Average)</td>
<td>0.9</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.1</td>
</tr>
<tr>
<td>Lung and Bronchus (Females)</td>
<td>0.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.2</td>
</tr>
<tr>
<td>Esophagus</td>
<td>0.3</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.5</td>
</tr>
<tr>
<td>Liver</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Represents the annual percent change over the time interval.


Projected Prevalence of Chronic HCV, Cirrhosis, and Complications Over 4 Decades

<table>
<thead>
<tr>
<th>Year</th>
<th>HCV Infection</th>
<th>Cirrhosis</th>
<th>Decompensated Cirrhosis</th>
<th>Hepatocellular Carcinoma</th>
<th>Liver-related Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>2,940.8</td>
<td>47.1</td>
<td>6.5</td>
<td>7.271</td>
<td>13,000</td>
</tr>
<tr>
<td>2010</td>
<td>2,670.3</td>
<td>72.0</td>
<td>9.7</td>
<td>11,185</td>
<td>27,732</td>
</tr>
<tr>
<td>2020</td>
<td>2,685.5</td>
<td>85.8</td>
<td>9.9</td>
<td>13,183</td>
<td>36,483</td>
</tr>
<tr>
<td>2030</td>
<td>2,433.7</td>
<td>87.0</td>
<td>9.4</td>
<td>13,183</td>
<td>39,875</td>
</tr>
<tr>
<td>2040</td>
<td>2,177.0</td>
<td>82.0</td>
<td>9.5</td>
<td>13,183</td>
<td>39,064</td>
</tr>
</tbody>
</table>


HCV Screening Algorithm

- EIA for anti-HCV
  - Negative: Stop testing
  - Positive: RT-PCR for HCV RNA
    - Negative: Stop testing; diagnosis of prior HCV infection likely
    - Positive: Repeat RT-PCR for HCV RNA in 2-6 months

- Diagnosis of chronic HCV
  - Perform work-up for disease staging and possible treatment

- Refer to specialist

*For negative result in immunocompromised patients: HCV Ab, HCV RNA, and HCV envelope antigen test. Positive HCV RNA or envelope antigen test in a positive test for anti-HCV.
The Good News
HEPATITIS C CAN BE CURED!

Andy: Case Study
- 48 years old. Tried to donate blood and was denied. Told he had Hep C and should see his family doctor.
- Nick is in your office. He has a \textbf{+Hep C antibody}. Very anxious

Andy
- Has been abstinent from drugs and alcohol for 15 years.
- Married, father of two teenage daughters.
- General health is good
- Denies any symptoms of liver disease
- Works full time for software company
ANDY

- Does a positive Hep C antibody indicate active disease?
- How does one contract Hep C?
- Is it easily communicable to others?
- What would your best next step be?

Andy

- To determine active infection, you would order a Hepatitis C PCR RNA
- To determine ‘strain’ of Hep C, order HCV Genotype
- The result of PCR RNA will give you a viral load
- If positive, pt has the disease

Andy/Hep C

- Diagnosis of Hep C is usually made as an ‘incidental finding’; attempt to donate blood, get health or life insurance, or new healthcare provider runs blood test based on pt history.
Diagnostics/Andy
- Probable source of infection was remote IVDA
- What other diseases should he be tested for?
- Additional diagnostics?
- Should family be tested?
- Is there treatment for Hep C?

Hepatitis C
- Refer to specialist for. Even with no symptoms, Andy could still have significant liver disease.
- Treatments are oral.
- Duration from 8-24 weeks.
- Goal is cure

Chance of clearing the virus with treatment depends on genotype, stage of disease and compliance with treatment regimen.