Hepatitis B and C: New Medications, New Hope and New Opportunities for Primary Care

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I have no disclosures

Hepatitis B and C

- Transmission
  - Contaminated blood
  - Sexual (greatest for HBV)

- Chronic infection causes most morbidity and mortality
  - 20-25% lifetime risk of cirrhosis and HCC
  - Extrahepatic disease risks

- Prevention
  - Hepatitis B Vaccination
  - Reduce viral exposures – universal precaution, safer sex, safe needles
  - HBV and HCV testing, care and treatment –
    - Curative for HCV

Hepatitis B Virus (HBV) Epidemiology

- 850,000 – 2.2 million people in the US have chronic HBV
- Globally 240 million - most common bloodborne infection
- Since 2013, number of new cases per year is rising, linked to the opioid epidemic
- Highest rates of chronic infection are people born outside US
- Highest rates of acute infection are age 30-49 and PWID
- 10% of HIV infected persons are coinfected with HBV
- 50% of HBV infected persons are unaware of their infection


Groups Who Should be HBV Screened

- Born in areas of high prevalence or intermediate prevalence including immigrants and adopted children
- Household and sexual contacts of HBsAg+ persons
- US born persons whose parents were born in regions of high HBV endemicity
- Ever injected drugs
- Men who have sex with men
- Persons needing immunosuppressive therapy including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatological or gastroenterologic disorders.
- Chronically elevated ALT or AST
- ESRD, including dialysis
- HIV or HBV infected
- All pregnant women
- Multiple sexual partners
- History of STDs or seeking STD evaluation
- Persons who are not in a long-term mutually monogamous relationship (e.g., >1 sex partner during the previous 6 months)
- Persons seeking evaluation or treatment for a sexually transmitted disease
- Inmates of correctional facilities

Serologic Markers in HBV Infection

- HBsAg
  - Marker of chronic hepatitis B when found in serum > 6 mos
- Anti-HBs, HBsAb
  - Marker of immunity
- HBeAg
  - An index of active viral replication and high infectivity
- Anti-HBe, HBeAb
  - Appears in recovery phase or reactivation phase
- Anti-HBc, HBcAb Total
  - Marker of past and possibly current infection
- Anti-HBcIgM, HBcAb IgM
  - marker of acute infection

Phases of Chronic Hepatitis B Virus Infection

<table>
<thead>
<tr>
<th>Phase</th>
<th>HBV DNA</th>
<th>eAg</th>
<th>ALT</th>
<th>Liver Disease</th>
<th>Age Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune tolerant</td>
<td>&lt;2 × 10^5 IU/mL</td>
<td>Normal</td>
<td>Non/min</td>
<td>&lt;20</td>
<td>Favorable</td>
</tr>
<tr>
<td>Immune clearance</td>
<td>2 × 10^5 – 10^6 IU/mL</td>
<td>Elevated</td>
<td>Persistently or intermittently elevated</td>
<td>ALT &gt; 5x ULN</td>
<td>May develop advanced liver disease if HBeAg-positive phase prolonged for 20-40 yrs.</td>
</tr>
<tr>
<td>Reactive carrier</td>
<td>&gt;2 × 10^6 IU/mL</td>
<td>Normal</td>
<td>Fluctuating</td>
<td>Half of any liver disease progression</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Reactivation</td>
<td>Fluctuating, &gt;2 × 10^5 IU/mL</td>
<td>Elevated</td>
<td>Persistently or intermittently elevated</td>
<td>Advanced</td>
<td>&gt;35</td>
</tr>
</tbody>
</table>

Terrault, AASLD Guidelines, Hepatology, 2018
Phases of Chronic HBV Infection

- Immune tolerant
- Immune clearance
- Inactive carrier state
- Reactivation

Dynamic Nature of Carrier State

After spontaneous HBeAg seroconversion, 67% to 80% of carriers remain in inactive carrier phase.

Factors Associated with Progression of HBV-related Liver Disease

- Older age (longer duration infection)
- HBV genotype C
- High levels HBV DNA
- Alcohol
- Coinfection with HCV, HDV or HIV
- Carcinogens (aflatoxin)
- Smoking

Cumulative Incidence of Liver Cirrhosis for Five HBV DNA Categories (n=3,774)

Chen CJ, JAMA. 2006;295:65-73
Staging and Assessment of Hepatic Fibrosis (HBV and HCV)

**Why test for fibrosis?**
- Determine treatment urgency
- Assess need for additional care
- Cirrhosis requires additional management

**How to test for fibrosis?**
- Gold standard: liver biopsy
- Serum markers—FibroSURE, APRI, Fib-4
- Elastography (fibroScan®, MRE)
- Imaging may detect cirrhotic features

Calculators for Hepatic Fibrosis (HBV and HCV)

**APRI**
\[
\text{APRI} = \frac{\text{AST (Upper Limit of Normal)}}{\text{ALT (Upper Limit of Normal)}} 	imes 100
\]

**FIB-4**
\[
\text{FIB-4} = \left( \text{Age} + \text{ALT} - \text{AST} \times 0.5 \right) \times 100
\]

http://www.hepatitis.uw.edu/page/clinical-calculators/fib4

Treatments for Hepatitis B

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Non-Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN alpha-2a</td>
<td>Lamivudine (LVD)</td>
</tr>
<tr>
<td>Entecavir (ETV)</td>
<td>Adefovir (ADV)</td>
</tr>
<tr>
<td>Tenofovir dipivoxil fumarate (TDF)</td>
<td>Telbivudine (LdT)</td>
</tr>
<tr>
<td>Tenofovir alafenamide (TAF)</td>
<td></td>
</tr>
</tbody>
</table>

Terrault, et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2016 Hepatitis B: Guidelines HEPATOLOGY, VOL. 67, NO. 4, 2018

First Line Oral Therapies for HBV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Approval in HIV</th>
<th>Approval in HBV</th>
<th>Dose</th>
<th>Lowest CrCl without dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entecavir</td>
<td>NA</td>
<td>2005</td>
<td>0.5mg</td>
<td>60 mL/min</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>2001</td>
<td>2008</td>
<td>300 mg</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>Tenofovir alafenamide</td>
<td>2015</td>
<td>2016</td>
<td>25 mg</td>
<td>15 mL/min (not recommended at &lt;15 mL/min)</td>
</tr>
</tbody>
</table>

HBV Therapy Reduces Risk of Disease Progression

Prospective cohort study in pts with HBV and first-onset complications of decompensated cirrhosis (N = 707) treated predominantly with lamivudine (n = 203) or entecavir (n = 198)


Treated, responder (n = 245)
Treated, nonresponder* (n = 178)
Untreated (n = 284)

Bonferroni-adjusted P < .0003

LT-Free Survival (%)

HBsAg-Positive: Recommended Monitoring Strategy

HBV DNA <20,000 IU/mL
Monitor HBV DNA, ALT
HBsAg q3-6 mos
ALT < 2x upper limit normal
Consider assess fibrosis if >40 yo
Treat if mod-severe inflammation

HBV DNA > 20,000 IU/mL
ALT > 2x upper limit normal
Treat

HBsAg-Negative: Recommended Monitoring Strategy

HBV DNA <2,000 IU/mL
Monitor HBV DNA, ALT q3-6 mos
ALT < 2x upper limit normal
Consider assessment of fibrosis if >40 yo or persistent elevated ALT
Treat if mod-severe inflammation

HBV DNA > 2,000 IU/mL
ALT > 2x upper limit normal
Treat

Reasons for Isolated HBcAb +

1. May be a marker of immunity after recovery from prior infection
2. May be an indicator of chronic HBV infection where sAg has decreased to undetectable levels but DNA is detectable.
   • Seen in high prevalence regions and HIV +, HCV +
3. May be a false positive test result
4. May be the only marker of infection during the window phase of acute hepatitis B; these persons should test positive for anti-HBc IgM.
HBV Screening in the Setting of Immunosuppressant or Cytotoxic Drugs

- Use both HBsAg and HBcAb (total, IgG) needed for screening
- HBV reactivation from anticancer therapies
  - Occurred in 41%-63% of HBsAg +, HBcAb + patients
  - Occurred in 8%-18% of HBsAg -, HBcAb + patients
- HBV reactivation from antirheumatic therapies
  - Occurred in 12.3% of HBsAg +, HBcAb + patients
  - Occurred in 1.7% of HBsAg -, HBcAb + patients


HBV Antiviral Prophylaxis Versus On-Demand Therapy

- HBsAg (+) patients should be put on antivirals prophylactically, 7 days before initiation of immunosuppressive or cytotoxic therapy
  - 3 RCTs
- HBsAg (-) patients can either be put on prophylaxis or can be monitored for on-demand therapy if needed
- Recommended to use entecavir or tenofovir
- Duration of prophylactic antiviral therapy – until 6-12 months after discontinuation of anticancer therapy or immunosuppression

Take Home Points on HBV Therapy for Primary Care

- Close monitoring of patients not on treatment
  - Treat based on HBV DNA, ALT, eAntigen, degree of Fibrosis
- Highly effective therapies, not curative, long-term therapy
- ETV, TAF or TDF similar for most patients
  - TAF improved renal safety compared to TDF
  - ETV can be dose reduced for CrCl <10 mL/min
- Screen if initiating immunosuppressive therapy - HBsAg, HBcAb
  - HBsAg (+) patients need prophylaxis
  - HBsAg (-) HBcAb (+) patients can be monitored or on prophylaxis

Hepatitis C
Hepatitis C Virus (HCV) Epidemiology

- 3.5 million people in the US have chronic HCV
- May be up to 5 million
- Globally, an estimated 71 million people have chronic hepatitis C infection
- 75% of people with HCV are baby boomers, born 1945-1965
- Between 2010 and 2014, 250% increase in acute HCV infections after years of relatively stable rates. Rise is linked to opioid epidemic
- 20% of HIV infected persons are coinfected with HCV


Decompensated Cirrhosis and HCC
Projected Prevalence Rises Through 2020

- Although the overall prevalence of HCV infection is decreasing, the prevalence of cirrhosis is increasing
- Decompensated cirrhosis more common after 1995
- HCC rise steeply after 1990, predicted to peak in 2019 at 14,000/year


Deaths from liver cancer have increased at the highest rate of all cancers

- HCC has second highest rise in incidence
- second only to thyroid cancer
- Death rates from HCC highest of all cancer sites
- During same time, death rates decline from all cancers combined
- HCV associated liver cancer death rates highest among persons born 1945-65

Ryerson AB et al. Cancer 2016 May 1;122(9):1312-17

HCV Screening Recommendations

- Persons born from 1945 through 1965
- Injection-drug use (current or ever, including those who injected only once)
- Intranasal illicit drug use
- Long-term hemodialysis (ever)
- Percutaneous/parenteral exposures in an unregulated setting
- Healthcare, emergency medical, and public safety workers after needle-stick, sharps, or mucosal exposures to HCV-infected blood
- Children born to HCV-infected women
- Prior recipients of transfusions or organ transplants before July 1992
- Received clotting factor concentrates produced before 1987
- Ever incarcerated
- HIV infection
- Sexually-active persons about to start pre-exposure prophylaxis (PrEP) for HIV
- Unexplained chronic liver disease and/or chronic hepatitis, including elevated alanine aminotransferase (ALT) levels

Algorithm for HCV Screening and Diagnosis

- HCV Antibody
- HCV RNA level

DX = Chronic HCV infection: If > 6 mos since suspected Infx, HCV Genotype

Spontaneous clearance of HCV Likely
Consider repeat RNA to confirm

Dr. false positive HCV Ab
Autoimmune disease (+) RNA: Less likely

US HCV Treatment During Interferon-Ribavirin Era

40 % 30 % 20 % 10 % 5 % 0 %
Diagnosed Referred for care Treated Successfully treated


Direct Acting Antivirals (DAAs)
Against specific HCV targets

Sites:
- NS3
- NS4a
- NS5A
- NS5B

The Essentials on DAA Therapies
- Short course of 8-12 weeks, all oral therapy, few side effects, few drug interactions, no longer using ribavirin
- >95% treated are cured
  - Cure = Sustained Virological Response (SVR) defined as undetectable HCV 12 weeks after end of treatment
  - 50%-74% reduction in all cause mortality
- SVR associated with
  - 75% reduction in liver cancer, 93% reduction in liver failure, 93% reduction in liver-related mortality
  - In 2016, HCV mortality declined 7%
The newest regimen in HCV treatment

- Glecaprevir/pibrentasvir (GLE/PIB)
  - Recently approved as oral regimen – 3 tablets daily with food
  - Pangenotypic – patients with any genotype
    - No cirrhosis: 8 wks
    - Cirrhosis: 12 wks
    - Contraindicated in decompensated cirrhosis (ascites, varices, etc)
- Also indicated for many patients who were previously treated and failed – activity against NS5A resistant strain
- Lower cost than other regimens has made this more widely available

Current Hepatitis C Treatment Regimens

Only 4 regimens are now recommended for first line treatment
- Glecaprevir/Pibrentasvir (Mavyret®)
- Grazoprevir/Elbasvir (Zepatier®)
- Sofosbuvir/Ledipasvir (Harvoni®)
- Sofosbuvir/Velpatasvir (Epclusa®)

For retreatment of the small number of DAA-relapses, 2 regimens
- Glecaprevir/Pibrentasvir (Mavyret®)
- Sofosbuvir/Velpatasvir/Voxpataprevir (Vosevi®)

Hepatitis C Treatment in Active IDU

- Recent or active IDU should not be seen as an absolute contraindication to HCV therapy
- Treating PWID necessary to reduce transmissions and new infections
- Important for the impact on the HCV epidemic
- Increase in new HCV infections in the US primarily among young white adults with injection drug use
Hepatitis C Treatment in Patients Without Cirrhosis

- Noncirrhotic pts were commonly denied access to HCV treatment due to restrictive reimbursement policies
- Many patients with mild-moderate fibrosis may be able to receive treatment now even if previously denied, as restrictions lessen
- Medi-cal HCV Policy liberalized in 2015
- Benefits of SVR are not limited to patients with cirrhosis

SVR is associated with an 79% reduction in HCC risk

What about HCV Reinfection?

- Among patients with ongoing high risk behaviors (PWID, high risk MSM) 10 cases of reinfection over 2 year follow up of >200 patients. Rate of 2.3 reinfections/100 person-years
- High rate of spontaneous viral clearance in reinfections (30%)
- Reinfections happen --- but not reason to withhold

Whole Sale Costs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir x 8 wks-12 wks</td>
<td>$63,000 - $94,500</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir x 12 wks</td>
<td>$54,600</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir x 12 wks</td>
<td>$147,000</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatavir x 12 wks</td>
<td>$74,760</td>
</tr>
<tr>
<td>Sof/Vel/Vox x 12 weeks</td>
<td>$74,760</td>
</tr>
<tr>
<td>Olexaprevir/Flibrentavir x 8wks-12 wks</td>
<td>$26,400 - $39,600</td>
</tr>
</tbody>
</table>

http://hepatitisc.uw.edu/page/treatment/drugs

Dore, Sylvestre, ChiBian 2017 AASLD
Treatment is Cost-Effective

1. “Real world” SVR rates comparable to clinical trials
2. HCV treatment for genotype 1 patients at all fibrosis stages, Ledipasvir/Sofosbuvir was cost effective.
3. Cost-effective yes, but affordable no.
4. Advanced fibrosis no longer always required by payors

Take Home Points on HCV Treatment
Opportunities for Primary Care -

- HCV treatment is not hard –
  - Well tolerated
  - Highly effective
  - Short courses
  - Rewarding for physicians and for patients and families
  - Treatment can be done in primary care, community settings and specialty clinics, many resources to assist

California Medi-Cal HCV Policy
Any of the following identify candidates for treatment

1. Fibrosis stage F2 or greater by biopsy OR FibroScan™ 7.5 kPa; OR FibroSure® score of <0.48; OR A2B5 score greater than 1.7; OR FIB-4 greater than 3.25
2. Men who have sex with men with high-risk sexual practices
3. Active injection drug users
4. Persons on long-term hemodialysis
5. Women of childbearing age who wish to get pregnant
6. HCV-infected health care workers who perform exposure-prone procedures
7. Extra-hepatic manifestation of hepatitis C virus, eg, cryoglobulinemia, porphyria cutanea tarda
8. Fatigue impacting quality of life (eg, secondary to extra-hepatic manifestations and/or liver disease)
9. HCC with a life expectancy of >12 months
10. Pw and past liver transplant
11. HIV co-infection
12. Hepatitis B co-infection
13. Other consistent liver disease (eg, nonalcoholic steatohepatitis)
14. Type 2 diabetes mellitus (insulin resistant)

HCC Screening
Ultrasound every 6 months
- With or without AFP

In regions where ultrasound is not readily available, then screen with AFP every 6 months
Recommended Groups for HCC Surveillance

- Asian or Black males 40 years of age or older
- Asian females 50 years of age or older
- All cirrhotic patients with HBsAg
- Family history of HCC

Hepatitis C
- All cirrhotic hepatitis C patients including patients who have achieved SVR

Opportunities for Primary Care in Care of HBV and HCV

- HCV elimination is a goal for SF and other cities in the US
- HCV screening and counseling, reduce transmission
- HCV uncomplicated cases – primary care can treat or can refer
- HBV identification and monitoring
- HBV screen before immunosuppression
- HBV initiate treatment or refer when possible
- HCC risk reduction and screening