New Developments in Viral Hepatitis

Primary Care Update: 2013

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I have nothing to disclose

Hepatitis C Update

What is the disease burden of HCV in the US?

Who should be screened for HCV, which tests to order and how to interpret those test results?

Which patients are most likely to develop cirrhosis or HCC?

Where are we with options for HCV treatment?

Which patients should we be treating now?

Prevalence of HCV in the US

- 1.6-1.8% of general population (2.7-3.9 million)
  - Does not include incarcerated or homeless.
- Incarcerated: 30-40% HCV positive
- Adjusted estimated 5% of the US population
- 45%–85% are unaware of their infection status

Prevalence of HCV by Age and Race in US, 1988-94

- Black
- Mexican-American
- White

Hepatitis C Infection
1 in 33 Baby Boomers


HCV related deaths
- 73.4% occurred among persons aged 45–64 yrs
- median age of death of 57 yrs
  - approximately 20 yrs less than the average lifespan of U.S. persons
- Modeled that within 40-50 yrs:
  - 1.76 million persons with untreated HCV infection will develop cirrhosis
  - The peak prevalence estimated at 1 million cases of cirrhosis from mid-2020s through the mid-2030s
  - 1 million will die from HCV-related complications


Hepatocellular Carcinoma
- HCV current leading cause of HCC in US
  - Infection with HCV accounts for approximately 50% of incident HCC
- HCC is fastest growing cause of cancer related mortality currently
- Models project that during the next 40–50 years, approximately 400,000 will develop HCC

Deaths Due to Hepatitis C Now Exceed Deaths Due to HIV in the U.S.


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Groups Recommended for HCV Screening
- Injection drug use – ever, even if only used once
- HIV-infected individuals
- Hemophiliacs with clotting factors before 1987
- Hemodialysis recipients
- Unexplained aminotransferase abnormalities
- Transfusion or transplantation before July 1992
- Children born to women infected with HCV
- Healthcare, public safety, emergency medical personnel following needle injury or mucosal exposure
- Sexual partners with HCV-infected person


CDC New Screening Recommendation

Birth Cohort Screening
All persons born between 1945-1965
One time HCV Ab testing

Algorithm for HCV Diagnostic Testing
Ab for screening, but not for diagnosis!

HCV Antibody

(+)
- HCV RNA level
- Chronic HCV Infection
- HCV Genotype
- Spontaneous clearance of HCV
- Likely
- HCV RNA qualitative to confirm
- Or, false positive HCV Ab
- Less likely
- Autoimmune disease
- HCV RIBA to confirm Ab

(-)
- HCV RNA level
- Only if:
- Chronic HCV Infection
- HIV, ESRD, immunocompromised

If suspect acute infection
If suspect false negative HCV Ab

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Natural History and
potential clinical outcomes in HCV

Do affect disease
progression
- Alcohol
- HIV or HBV co-infected
- Obese, NAFLD
- Male sex
- Long duration of infection which occurred in adulthood

Do not affect disease
progression
- HCV RNA “viral load”
- HCV genotype
- Mode of infection
- ALT elevation
- Female sex
- Infection during childhood
**HCV RNA Testing**
- HCV RNA mandatory to make Chronic HCV diagnosis
- But, Quantitative RNA (Viral Load)
  - Does not correlate with degree of fibrosis
  - Does not predict progression of disease
  - Does not change significantly over time
- But if not on HCV treatment, no role for repeated viral load testing
  - Will not change management
  - Confuses patients about state of their HCV disease

**Hepatitis C Update**

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**Outcomes of HCV Treatment**

**Aim = Sustained Virological Response (SVR)**
- HCV RNA undetectable at 6 months after treatment has ended
- A surrogate marker
- Defined as “cure”

**Clinical outcomes**
- 99-100% remain undetectable 5-10 yrs follow up
- SVR reduces complications of HCV cirrhosis
- Less liver failure, longer survival
- Lower rate of HCC, cirrhosis, decompensation

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**Current Treatment of HCV**

**Pegylated interferon + ribavirin**
- From 2001-2011, the only regimen available
- Genotype 1: SVR in 42-46% patients
- Genotype 2,3: SVR in 76-82% patients

**Boceprevir and Telaprevir - 2011**
- DAAs (Direct Acting Antivirals)
- These 2 are both Protease Inhibitors
- Used only for Genotype 1 patients
- Genotype 1: SVR in 61-69% first time patients
- Triple therapy with peg interferon and ribavirin
Addition of TVR or BOC to Peg / Riba Improves SVR in Genotype 1 Patients


<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Naive</td>
<td>36-44</td>
</tr>
<tr>
<td>Relapse</td>
<td>63-75</td>
</tr>
<tr>
<td>Partial Responders</td>
<td>24-29</td>
</tr>
<tr>
<td>Null Responders</td>
<td>65-83</td>
</tr>
<tr>
<td>PegIFN + RBV</td>
<td>49-89</td>
</tr>
<tr>
<td>BOC/TVR + pegIFN + RBV</td>
<td>29-38</td>
</tr>
</tbody>
</table>

Contraindications to HCV Treatment

- Major uncontrolled depressive illness
- Pregnancy or unwilling to comply with contraception
- Autoimmune condition which may be exacerbated by interferon
- Solid organ transplant
- Severe concurrent medical condition such as uncontrolled HTN, CHF, CAD, COPD, DM
- Severe untreated thyroid disease

Ghany MG et al, Hepatology 2009;49:1335

New (and Near) Future Treatment of HCV

- DAA (Direct Acting Antivirals)
- Numerous ongoing trials with different compounds
- Increasing SVR rates with oral regimens
- Shortened treatment duration
- Good safety profile
- Future – finite duration of combination therapy without interferon
- ? Eradication of HCV worldwide

Characteristics of HCV DAA Classes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protease Inhibitors</th>
<th>Nucleos(t)ide Polymerase Inhibitors</th>
<th>Nonnucleoside Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Barrier to resistance</td>
<td>Low 1a &lt; 1b</td>
<td>High 1a = 1b</td>
<td>Very low 1a &lt; 1b</td>
<td>Low 1a &lt; 1b</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Rash; anemia; blisters</td>
<td>Mitochondrial; nuc interactions (ART)</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd-generation PI, better barrier; pan-genotypic</td>
<td>Single target; good tolerability in agalectinoprophylaxis (PR)</td>
<td>Many targets</td>
<td>Multiple antiviral MOA</td>
</tr>
</tbody>
</table>
Ongoing Clinical Trials of Interferon-Free Regimens

<table>
<thead>
<tr>
<th>Study Name</th>
<th>DIT</th>
<th>Protease Inhibitor</th>
<th>Polymerase Inhibitor</th>
<th>Other Drug</th>
<th>Weeks</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVIATOR (Kowdley)</td>
<td>1</td>
<td>ABT-450</td>
<td>ABT-333</td>
<td>Ribavirin</td>
<td>12</td>
<td>87-97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Sulkowski)</td>
<td>1, 2/3</td>
<td>Sofosbuvir</td>
<td>Daclatasvir</td>
<td>Ribavirin</td>
<td>80-100%</td>
<td></td>
</tr>
<tr>
<td>ZEPHYR (Jacobson)</td>
<td>1</td>
<td>Telaprevir</td>
<td>VX-222</td>
<td>Ribavirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOUND-2 (Zeuzem)</td>
<td>1</td>
<td>Faldaprevir</td>
<td>B1207127</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELECTRON (Gane)</td>
<td>1, 2/3</td>
<td>Sofosbuvir</td>
<td>GS-5885</td>
<td>Ribavirin</td>
<td>12</td>
<td>100%</td>
</tr>
<tr>
<td>MATTHERHORN (Feld)</td>
<td>1b</td>
<td>Danoprevir</td>
<td>Merbamidine</td>
<td>Ribavirin</td>
<td>24</td>
<td>38-55%</td>
</tr>
</tbody>
</table>

Daclatasvir Plus Sofosbuvir in GT1 Treatment-Naive Patients

- PIs with poor prognostic indicators: GT1a (73%), male (52%), black (20%), IL28B CT/TT (64%); advanced liver disease: 14%
- Mean HCV RNA: 6.6 logs
- No impact of RBV on viral response
- SVR24, %
  - GT1
    - Sofosbuvir
    - Daclatasvir + Sofosbuvir
    - Daclatasvir + Sofosbuvir + RBV
    - Daclatasvir + Sofosbuvir + RBV
    - Daclatasvir + Sofosbuvir + RBV

Treat Now vs Wait: Many Issues to Consider

**Treat now**
- Triple therapy increases SVR
- Earlier treatment has higher success rates
- Successful treatment may arrest progression of liver disease
- Uncertainty about timelines for approval and reimbursement

**Defer**
- First-generation PIs complex, associated with adverse events
- Does current treatment failure affect future treatment?
- Potential for higher SVR, including in challenging populations
- Potential for simpler regimens, QD or BID, fewer adverse effects, especially IFN-free
- Activity in non-genotype 1

Hepatitis B Update

What do we now know about HBV natural history that we didn’t know before?

Who should be screened for HBV, which tests to order and how to interpret those test results?

Which patients are most likely to develop HBV related cirrhosis or HCC?

What is the role of primary care in managing patients with chronic HBV?

What options exist for HBV treatment and which patients should be considered?
~ 2 million people have chronic hepatitis B

400,000-600,000 diagnosed

200,000-300,000 entered into care

< 50,000 are receiving antiviral treatment


Phases of Chronic HBV Infection

HBeAg

HBV DNA

ALT

Immunotolerant

Immune clearance

HBeAg-positive chronic hepatitis

Inactive carrier state

Reactivation

HBeAg-negative chronic hepatitis


Dynamic Nature of Carrier State

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

Immunotolerant \rightarrow Inactive carrier \rightarrow HBeAg-negative CHB

4% to 20% of inactive carriers have reversion back to HBeAg positive

10% to 20% have reactivation after yrs of quiescence disease

Serial testing is necessary during the "inactive carrier state"

Natural History Depends on Transmission

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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
- Multiple sexual partners or history of STDs
- Men who have sex with men
- Inmates of correctional facilities
- Persons needing immunosuppressive therapy
- Chronically elevated ALT or AST
- HCV or HIV infected
- Renal dialysis
- All pregnant women

Lok, AASLD Guidelines, Hepatology, 2009

Serologic Markers in HBV Infection
- HBsAg
  - Marker of chronic hepatitis B when found in serum > 6 mos
- Anti-HBs
  - Marker of immunity
- HBeAg
  - An index of active viral replication and high infectivity
- Anti-HBe
  - Appears in recovery phase or reactivation phase
- Anti-HBc
  - Marker of past and possibly current infection
- Anti-HBcIgM – marker of acute infection
Hepatitis B Serologic Markers

<table>
<thead>
<tr>
<th></th>
<th>Acute Hepatitis B</th>
<th>Recovery from Hepatitis B</th>
<th>Chronic HBV (sAg +/−)</th>
<th>Reactive Hepatitis B</th>
<th>Successful Vaccination</th>
<th>Isolated HBcAb +</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x or −</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x or −</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBc IgM</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x or −</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x or −</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x or −</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td>x</td>
<td></td>
<td>x (usually &gt;2000 IU/mL)</td>
<td>x (usually &lt;2000 IU/mL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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Annual Rates of Disease Progression in Hepatitis B Infection

- HBeAg (+) chronic hep B: 5% Cirrhosis → 1-2% All HbsAg (+)
- HBeAg (-) chronic hep B: 3% Decompensation → 2% HCC → 0.4% Decompensation
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)

P-value for log-rank test, <0.001.

Chen CJ. JAMA. 2006;295:65-73

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Initial Evaluation of HBsAg+ Patient (1)

- Clinical evaluation
- Lab tests
  - HBeAg, anti-Hbe, HBV DNA
  - HCV, HDV, HIV or other causes of liver disease if indicated such as lipids, A1c
  - Tests of liver disease severity – liver chemistry, CBC/platelet, INR
- +/- Abdominal ultrasound – assess changes in liver, spleen or focal mass
- +/- Liver biopsy
Initial Evaluation of HBsAg+ Patient (2)

- Vaccination against hepatitis A
- Counseling
  - Transmission
  - Alcohol, BMI, lifestyle
  - Natural history, disease progression
- Reducing transmission
  - Testing household and close contacts
  - Vaccination of sexual partners, close contacts if negative for HBsAg and negative for HBsAb
- Importance of long term follow up and testing

Frequent Recommended Monitoring
for patients not on treatment (by AASLD)

**Inactive carriers**
- ALT every 6-12 months
- If ALT increases, then serial HBV DNA
- If HBV DNA >2000 serially, refer to consider liver biopsy

**Chronic HBV with normal ALT**
- ALT q 3-6 mo + HBV DNA and HBeAg q 6-12 mo
- If HBV > 20,000 and elevated ALT, refer for biopsy and/or treatment

Why Monitor So Often if Not on Treatment?

- Dynamic disease with changing states
- HBV DNA is the determining factor for treatment
- Frequent monitoring in order to capture right time for treatment
- Patients may have inactive disease for years and then reactivation is time for treatment

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Who Should Be Treated?

- Not a question of who to treat, but when: treat now or monitor and treat later when indicated.
- All HBV carriers are potential treatment candidates.
- A patient who is not a treatment candidate now can be a treatment candidate in the future.
  - Changes in HBV replication status and/or activity/stage of liver disease.
  - Availability of new or improved treatments.

Determining Treatment Candidacy for HBV

- Determining treatment candidacy at its most basic is a simple 2-step process of measuring.
  - HBV DNA
  - ALT
- Also consider other parameters:
  - Family history of HCC
  - eAntigen status
  - Liver biopsy – fibrosis stage
  - Coinfection with HIV or HCV

Primary Factors to Consider in HBV Therapy

- Profile of drug resistance
- Presence of cirrhosis
- HIV coinfection
- Age of patient
- Prior treatment experience

First line recommendations:
Tenofovir, Entecavir, Peg Interferon
Undetectable* HBV DNA After 1 Yr of Treatment

5-Yr Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients

How to Use Entecavir or Tenofovir

### Dosage and administration

- **Entecavir:** oral administration
  - Patients naive to lamivudine therapy: 0.5 mg QD
  - Patients who are refractory/resistant to lamivudine: 1.0 mg QD
  - Dose adjustment needed if eGFR < 50 mL/min

- **Tenofovir:** oral administration
  - 300 mg QD
  - Dose adjustment needed if eGFR < 50 mL/min

HCC Surveillance Is Recommended for:

#### Hepatitis B
- Asian males 40 years of age or older
- Asian females 50 years of age or older
- All cirrhotic hepatitis B patients
- Family history of HCC
- Africans older than 20 years of age

#### Hepatitis C
- All cirrhotic hepatitis C patients
Screen with Ultrasound
AFP not necessary

- In Hep C, based on observational data and expert opinion, but no prospective trials
- In Hep B, based on one prospective controlled trial, and observational data.
- Recommended: Ultrasound q 6-12 months
- AFP is no longer recommended for screening
  - Elevated AFP seen in chronic liver disease without HCC
  - 23% of HCV patients have elevated AFP
  - Specificity 41-65%, Sensitivity 80-94%

Comparison of Hepatitis B and C
Similar Tests, Different Meaning

<table>
<thead>
<tr>
<th></th>
<th>Hep B</th>
<th>Hep C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody</td>
<td>Vaccinated (sAb)</td>
<td>Exposed (HCV Ab)</td>
</tr>
<tr>
<td>ALT</td>
<td>Indicates active disease, strong predictor of treatment response</td>
<td>Does not determine active disease, not predictor of treatment response</td>
</tr>
<tr>
<td>Viral load</td>
<td>Predictor of cirrhosis and HCC</td>
<td>No correlation w/ cirrhosis or HCC</td>
</tr>
<tr>
<td>Genotype</td>
<td>Weak predictor of treatment response</td>
<td>Strong predictor of treatment response</td>
</tr>
<tr>
<td>Chronic</td>
<td>HBsAg positive</td>
<td>HCV RNA positive</td>
</tr>
<tr>
<td>Resolved</td>
<td>sAg (-) sAb (+) cAb (+) Ab (+) qualitative RNA (-)</td>
<td></td>
</tr>
</tbody>
</table>

References

- AASLD Practice Guidelines - www.aasld.org
  - Hep B, Hep C, HCC, Liver Biopsy
- NIH Consensus Statements - consensus.nih.gov
  - Hep B, Hep C
- CDC Recommendations - www.cdc.gov
  - Hep B screening, Hep C screening
- National VA Hepatitis Website - www.hepatitis.va.gov