Updates on Hepatitis B and Hepatitis C

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University of California San Francisco

Disclosures
Grants/Research Support: Conatus, Genfit, Intercept, Gilead
Consultant: Gilead

Chronic Hepatitis B

- Epidemiology and natural history
- Recommendation for screening
- Initial evaluation and identifying candidates for therapy
- Therapeutic options

Prevalence of Chronic Hepatitis B

Estimated 248 million HBsAg positive globally (2010)

- ~2 million Asians
- ~400,000 South Americans
- ~350,000 Africans
- 3.4% of FB in U.S. have chronic hepatitis
Total with CHB may be as high as 2.2 million

Estimating HBV Disease Burden in Foreign-born Americans

Country-specific pooled CHB prevalence rates multiplied by # of FB living in U.S. in 2009 by country of birth to yield total # of FB with CHB in U.S.

- 2010 Census: % Asian
  - Bay Area: 23%
  - SF: 33%

3.4% of FB in U.S. have chronic hepatitis
Who should be screened for HBV?
- Individuals born in high (8%) or intermediate (2-7%) prevalence areas
  - Asia, Africa, Middle East (except Israel), Spain, Eastern Europe, Central/South America
- Pregnant women
- Infants of HBsAg+ mothers, household contacts
- Behavioral contacts: HIV+, MSM, IVDU, inmates
- Renal dialysis patients
- Patients receiving immunosuppressive therapy
- Abnormal ALT of unknown cause

Routes of Transmission Vary Depending on Prevalence of Infection in the Population

Risk of Chronic HBV After Acute HBV Varies with Age of Exposure

Annual Age-Adjusted Death Rate Due to Chronic HBV
**HBV: Epidemiology**
- Estimated 2.2 million with chronic HBV infection
- Chronic infections largely among foreign-born (FB)
  - Most are Asians and Africans who are typically infected as infants and children
  - American-born infections typically acquired as adolescents and adults
- Deaths due to HBV are declining, likely reflecting benefits of antiviral therapy

**Summary**
- Dynamic disease
  - Life-long monitoring
  - Treatment is selective
- Not curable
  - HBV can be suppressed but not eliminated
  - Barriers to cure:
    - Integration into host DNA
    - cccDNA reservoir (not affected by nucleoside analogues)

**Natural History of Chronic HBV Infection**
- Dynamic disease
- Life-long monitoring
- Treatment is selective
- Not curable
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  - Barriers to cure:
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    - cccDNA reservoir (not affected by nucleoside analogues)

**Interpretation of tests → Next steps**

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<thead>
<tr>
<th>HbsAb</th>
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<th>Next Step</th>
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<tbody>
<tr>
<td>−</td>
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<td>−</td>
<td>Not immune</td>
<td>Vaccinate</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Immune</td>
<td>Nothing</td>
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<tr>
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<td>+</td>
<td>Chronic infection</td>
<td>Determine state of infection</td>
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**Initial tests to determine HBV status**
- HBV surface antigen (sAg)
- HBV surface antibody (sAb)
- HBV core antibody (cAb)
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### Initial approach to the HBsAg+ patient

1. **STEP 1**: Platelet count
2. **STEP 2**: INR/Albumin
3. **STEP 3**: Abd U/S: liver contour, spleen size, portal vein
   - Fibroscan

### Chronic

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Initial approach to the HBsAg+ patient

**STEP 1**
- Platelet count
- INR/Albumin
- Abd U/S: liver contour, spleen size, portal vein
- Fibroscan

**Initial approach to the HBsAg+ patient**

**STEP 2**
- Risk Factors for Accelerated Disease
  - HIV/HCV/HDV coinfection
  - Heavy alcohol consumption
  - Hepatitis A immunity → vaccinate if not immune

**STEP 3**
- Fibrosis Stage
  - HBeAg
  - Anti-HBe
  - HBV DNA
  - ALT

**Phases of Chronic HBV**

<table>
<thead>
<tr>
<th>Phase</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td>HBeAg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
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- Immune tolerant
- Immune clearance
- HBsAg vve CHB (Carrier not used)
- Inactive CHB
- Reactivation HBsAg vve CHB
- HBsAg cleared

Highlights need for regular monitoring and reassessment of phase – need to intervention

**Phases of Chronic HBV**

**Active Disease Warrants Treatment**

**Step 1**
- State of Infection
  - ALT
  - HBV DNA
  - HBV e antigen / antibody

**Step 2**
- Risk Factors for Accelerated Disease
  - HIV/HCV/HDV coinfection
  - Heavy alcohol consumption
  - Hepatitis A immunity → vaccinate if not immune

**Step 3**
- Fibrosis Stage
  - HBsAg cleared
  - HBsAg positive
  - HBsAg negative (precore/BCP mutation)

**Phase**

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Phases 1 2 3 4 5

**Active Disease Warrants Treatment**
Chronic HBV: Life-Long Management

- Balancing benefit and risk in the absence of curative therapy

TREAT NOW
Significant or severe liver disease

TREAT NOW OR MONITOR?
Predicting future risk

MONITOR
Defer Treatment Until Clear Indication

Risk of Cirrhosis, Liver Failure and Liver Cancer

HBV: The importance of monitoring

60%
40%

Require monitoring...
- Inactive disease may not remain inactive
- Liver damage may occur if HBV reactivates

TREAT NOW OR MONITOR?

Predicting future risk

Risk of Cirrhosis, Liver Failure and Liver Cancer

Treatment of Immune Active CHB: Who and With What?

| Criteria for Antiviral Therapy | Insufficient data to support or refute treatment with ALT > ULN
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>1) ALT &gt; 2 X ULN</td>
<td>&gt;20,000 IU/mL if HBeAg+</td>
</tr>
<tr>
<td>2) Sufficient HBV DNA</td>
<td>&gt;2000 IU/mL if HBeAg neg</td>
</tr>
<tr>
<td>HBV DNA compatible with IA</td>
<td>Family history of HCC</td>
</tr>
<tr>
<td>disease</td>
<td>Older age (&gt;40)</td>
</tr>
<tr>
<td>3) Other factors to consider</td>
<td>Presence of cirrhosis</td>
</tr>
</tbody>
</table>

Preferred Treatments

- Peginterferon alfa-2a
- Entecavir (ETV)
- Tenofovir dipivoxil fumarate (TDF)
- Tenofovir Alafenamide (TAF)

1st-line HBV Treatment Options

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<td>0.5 mg per day</td>
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<td>Pregnancy Category</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault N. Hepatology 2016;63;261-83

Pregnancy Category

- B
**Tenofovir Alafenamide (TAF)**
Next Generation Prodrug of Tenofovir

- TFV
- TDF
- TAF

**Gut**
- TFV
- TDF
- TAF

**Plasma**
- TFV
- TDF
- TAF

**Lymphoid Cells**
- TAF
- TFV-MP
- TFV-DP

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**Risk of HCC Among Patients with Chronic HBV**

- REVEAL: long-term follow-up (mean, 11.4 yrs) of untreated HBsAg positive individuals in Taiwan (N = 3653)
- HBV DNA (copies/mL)
  - < 300
  - 300-9999
  - 10,000-99,999
  - 100,000-999,999
  - ≥ 1 million

<table>
<thead>
<tr>
<th>HBV DNA (copies/mL)</th>
<th>HCC (%) per Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 300</td>
<td>0.4-0.6%</td>
</tr>
<tr>
<td>300-9999</td>
<td>1.2</td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>1.0</td>
</tr>
<tr>
<td>100,000-999,999</td>
<td>0.8</td>
</tr>
<tr>
<td>≥ 1 million</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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**HCC screening criteria**

- HCC screening (abdominal U/S + AFP every 6 months) for:

<table>
<thead>
<tr>
<th>Population group</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male &gt; 40 years</td>
<td>0.4-0.6% per year</td>
</tr>
<tr>
<td>Female &gt; 50 years</td>
<td>0.3-0.6% per year</td>
</tr>
<tr>
<td>Family history of HCC at any age</td>
<td>Higher than without a family history</td>
</tr>
<tr>
<td>African</td>
<td>HCC risk is high at any age</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>3-8% per year</td>
</tr>
</tbody>
</table>

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**Chronic Hepatitis B Final Points**

- Chronic HBV is common among foreign-born; screening to identify patients is critical
- Chronic HBV is dynamic disease, requiring life-long monitoring
- HBV is controlled not cured – long term treatment plan needed
- Tenofovir (TDF/TAF), entecavir and peg-IFN are preferred drugs
- HCC screening with abdominal ultrasound +/- AFP in:
  - Males > 40 years, females > 50 years, all Africans, HCC fhx, cirrhosis
Chronic Hepatitis C

- Epidemiology of HCV
- Therapeutic options in 2017
- Cost of Treatment

Prevalence in Asian Americans

- HCV in Asia, 94 million
- HCV prevalence in the general US population is 1.6%
- HCV prevalence in Asian Americans is 5.5%
- Highest HCV prevalence
  - Vietnamese 8%
  - Chinese 6.0%


Epidemic of HCV-Associated Morbidity and Mortality in the U.S.

- 3.5 M persons living with HCV
- 81% are persons born 1945-1965
- 70% of Baby Boomers have Moderate to Severe Liver Disease
- CDC and USPSTF recommendations (2013):
  - All individuals born between 1945-1965 (50-70 yo) should be screened
  - 45% are expected to have cirrhosis by 2020!

Reported Number of Acute Hepatitis C Cases in United States, 2000–2015

- New HCV infections on the rise
- 2.5-fold increase since 2010
- 30,340 new cases in 2015

Source: National Notifiable Disease Surveillance System (NNDSS)
2015 Age Distribution of Incident HCV

N=30,000 new infections per year

70% of new infections occur in 20-40 year olds
More likely to be White and non-Urban

HCV Can Now Be Cured in Most Patients

- Unlike HIV and HBV infection, HCV infection is a curable disease
- HCV does not archive its genome

What does cure mean?
- Undetectable HCV RNA 12 weeks after completion of antiviral therapy for chronic HCV infection
- SVR12 is almost invariably durable

What is Gained by Achievement of Cure?

ERCHIVES cohort (Veterans)
Follow-up to 18 months

- DAA-induced SVR is associated with a 57% reduction in mortality

HCV: The Cure is Here!!!!

- DAA-induced SVR is associated with a 71% reduction in HCC risk

Ionnou GN, J Hepatol 2017, Sept 5
Essentials to make treatment decision:
- Stage of disease
- HCV genotype and viral load
- Tests of liver and renal function
- Patient level of engagement/adherence

Treatment options: Direct Acting Antiviral Agents

HCV Therapies in 2017
Many Tools in the Toolbox

SVR rate ~95%

Choosing Among DAA Regimens
- Provider/patient preferences:
  - Short duration: 8 vs 12; 12 vs 16 wks
  - Simple
  - Few side effects
  - Highest efficacy ≥95%

- External factors:
  - Approved drugs and their “label”
  - Access and ease of getting DAA approved
U.S. Veterans Real World Cohort
SVR Rates by Treatment Regimen

- VA National Health System: 167 medical centers and 875 ambulatory care clinics
- 24,089 treatments initiated; 17,487 with currently recommended regimens

Cost To Cure*  

<table>
<thead>
<tr>
<th>Drug</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
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<tbody>
<tr>
<td>Sofosbuvir + Simeprevir</td>
<td>$180,432</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir + Daclatasvir</td>
<td>$176,400</td>
<td></td>
</tr>
<tr>
<td>Ombitasvir-paritaprevir + dasabuvir</td>
<td>$99,982</td>
<td></td>
</tr>
<tr>
<td>Ledipsavir-sofosbuvir</td>
<td>$75,600</td>
<td>$113,400</td>
</tr>
<tr>
<td>Elbasvir-grazoprevir</td>
<td>$65,520</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir-velpatasvir</td>
<td>$89,712</td>
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<td>Sofosbuvir-velpatasvir-voxilaprevir</td>
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<tr>
<td>Glecaprevir-pibrentasvir</td>
<td>$31,680</td>
<td>$47,520</td>
</tr>
<tr>
<td>Ribavirin‡</td>
<td></td>
<td>$5007</td>
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*Average Wholesale Price (AWP) on 8/29/17

Conceptual Framework for Treatment Success vs. Failure

Failure to Achieve SVR

Multiplicity of negative factors increases risk of treatment failure

HBV Reactivation in the Setting of DAA Therapy

- FDA report
  - FDA Adverse Event Reporting System (FAERS)
  - HBV reactivation with DAA therapy
    - 29 cases, 5 within the US
    - Temporally related to DAA initiation
    - Occurred within 4-8 weeks (mean time: 53 days)
    - Hepatitis B surface antigen versus Hep B core Antibody+ ?

Summary of HCV Treatment

- HCV is curable!
- Multiple all-oral DAA regimens are available:
  - Success rates of treatment (> 95%)
  - Treatment duration of 8-12 wks
- Challenges:
  - Screening
  - Increase in new cases of acute HCV
  - Access/linkage to care

THANK YOU

bilal.hameed@ucsf.edu

“Is life worth living? It all depends on the liver.”
William James, American philosopher (1842)
HBV risk of reactivation

- For HBsAg+ patients who are not already on HBV suppressive therapy, monitoring of HBV DNA levels during and immediately after DAA therapy for HCV is recommended and antiviral treatment for HBV should be given if treatment criteria for HBV are met.

Rating: Class IIa, Level B

HBV Cure: How is it Defined?

- True Cure of infection
  - True cure = all traces of HBV gone from the liver (ie. like HCV)
  - This is VERY difficult (if not impossible) → cccDNA

- Functional cure
  - HBsAg loss (ideally with anti-HBs)
  - Infrequently achieved

- More frequently achieved and associated with low risk of future complications: Sustained off treatment inactive disease
  = HBeAg–ve, HBV DNA undetectable, normal ALT but HBsAg positive

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Advantages of Latest DAA Combinations

- 3 pangenotypic regimens available
  - BUT, genotype still needed as determines treatment duration for most regimens
- Several excellent ribavirin-free combos
- Shortening of treatment regimens
  - GLE/PIB for non-cirrhotics = 8 weeks
  - SOF/VEL/VOX for DAA experienced = 12 weeks

Chronic HBV Cases in U.S.

- Majority among Foreign Born
  - Reflected in CDC Guidelines for HBV Screening
    - Persons born in countries with ≥ 2% HBsAg prevalence
    - US-born persons not vaccinated as infants whose parents were born in regions with ≥ 8% HBsAg prevalence

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<td>Gen—Lactic acidosis</td>
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<td>Toler—Generally</td>
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AASLD 2015 guidelines “suggests no preference b/n entecavir and tenofivir regarding potential long-term risks of renal complications.”

Algorithm Used to Determine Need for Treatment

- HBeAg Positive
  - HBV DNA >20,000 IU/mL
  - ALT Evaluation
    - Elevated ALT (≥2 ULN)
    - Normal ALT

- HBeAg Negative
  - HBV DNA >2,000 IU/mL
  - Monitor ALT
  - Consider Liver Biopsy if >40yrs
  - Significant fibrosis or inflammation

Treat