Hepatitis A to E

AASLD Transplant Hepatology Board Review Course 2020

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Outline

- Hepatitis A and Hepatitis E
- Hepatitis C
- Hepatitis B and Hepatitis D
Hepatitis A

- Acute infection, fecal oral transmission
- Previously declining incidence by 95% between 1995-2011
- However, now increasing in 2016-2018 by 294%
  - ~15,000 cases reported
  - Primary risks: persons who report drug use or homelessness
  - MSM
  - Contaminated food

Hepatitis A

- Typical Presentation: jaundice, malaise, hepatomegaly, hepatitis with AST/ALT >1000
  - Symptoms typically resolve within 2 months
  - Jaundice peaks within the first few weeks
- Fulminant Hepatitis A
  - Rare cause of acute liver failure (ALF), <1% of reported cases
  - If ALF occurs, prognosis is poor
  - US ALF Study group (n=29)
    - 55% spontaneously recovered
    - 31% liver transplant, 14% died
Hepatitis A

- Other clinical presentations
  - Cholestatic
    - Itching, ↑↑↑ Bilirubin, prolonged course
    - Supportive care
  - Prolonged
  - Relapsing
    - IgM still detectable when liver tests increase after initial downtrend

Hepatitis E

- Seen most commonly in developing countries but not exclusively
- 4 genotypes
  - Genotypes 1 and 2 Fecal oral
  - Genotypes 3 and 4 Zoonotic transmission from animal reservoirs
- Commonly causes acute hepatitis with very high AST/ALT
- Can present with neurologic symptoms: Guillain-Barre, Bell’s palsy, acute meningoencephalitis
Hepatitis E

- HEV reported to be misdiagnosed as DILI
- High mortality rates for patients with chronic liver disease/cirrhosis
  - Pork consumption
  - Acute liver failure
- Pregnant women
  - Genotypes 1 and 2
  - Mortality 20-25% in third trimester

Davern TJ et al. Gastroenterology, 141:1665-1672

- Difficult to diagnose
- Accuracy of antibody and RNA tests variable
- Symptoms typically present 4 weeks after post infection
- HEV RNA undetectable about 3 weeks after symptom onset
- Virus shed in stool for 5 weeks after symptom onset

Kamar N et al. Lancet 2012
Patients with detectable HEV RNA after 6 months
- Occurs predominantly with genotype 3 (zoonotic transmission)
- Populations: HIV, immunocompromised patients (including liver disease, post transplant)

Treatment:
- Reduce immunosuppression in transplant patients
- Ribavirin: 12 week course, Dose 600-1000
  - Leads to viral clearance in a few weeks
Outline

- Hepatitis A and Hepatitis E
- Hepatitis C
- Hepatitis B and Hepatitis D

Hepatitis C

- March 2020: USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years Grade B
- Acute HCV- treatment recommended once viremia identified
- Recommend reviewing www.hcvguidelines.org
  - Last update 2019
**Simplified HCV Treatment Algorithm for Treatment-Naive Adults Without Cirrhosis**

**WHO IS ELIGIBLE FOR SIMPLIFIED TREATMENT**
- Adults with chronic hepatitis C (any genotype) who do not have cirrhosis and have not previously received hepatitis C treatment

**WHO IS NOT ELIGIBLE FOR SIMPLIFIED TREATMENT**
- Patients who have any of the following characteristics:
  - Prior hepatitis C treatment
  - Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis)
  - End-stage renal disease (i.e., eGFR <30 mL/min/m²) (see Patients with Renal Impairment section)
  - HIV or HBsAg positive
  - Current pregnancy
  - Known or suspected hepatocellular carcinoma
  - Prior liver transplantation

**RECOMMENDED REGIMENS**
- **Glecaprevir (300 mg)/pibrentasvir (120 mg)** taken with food for a duration of 8 weeks
- **Sofosbuvir (400 mg)/velpatasvir (100 mg)** for a duration of 12 weeks

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**Simplified HCV Treatment Algorithm for Treatment-Naive Adults With Compensated Cirrhosis**

**WHO IS NOT ELIGIBLE FOR SIMPLIFIED TREATMENT**
- Current or prior episode of decompensated cirrhosis, defined as Child-Turcotte-Pugh (CTP) score ≥7 (ascites, hepatic encephalopathy, total bilirubin ≥2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7)
- Prior hepatitis C treatment
- End-stage renal disease (i.e., eGFR <30 mL/min/m²) (see Patients with Renal Impairment section)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

**WHO IS ELIGIBLE FOR SIMPLIFIED TREATMENT**
- **Adults with chronic hepatitis C (any genotype) who have compensated cirrhosis (Child-Pugh A) and have not previously received hepatitis C treatment**
- Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or any of the following findings from a previously performed test:
  - Transient elastography indicating cirrhosis (e.g., FibroScan stiffness >12.5 kPa)
  - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (e.g., FibroSure, Enhanced Liver Fibrosis Test, etc.)
  - Clinical evidence of cirrhosis (e.g., liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm³, etc.)
- Prior liver biopsy showing cirrhosis

**RECOMMENDED REGIMENS**
- **Genotype 1-6:** **Glecaprevir (300 mg)/pibrentasvir (120 mg)** taken with food for a duration of 8 weeks
- **Genotype 1, 2, 4, 5, or 6:** **Sofosbuvir (400 mg)/velpatasvir (100 mg)** for a duration of 12 weeks

*NOTE: Patients with genotype 3 require baseline NS5A resistance-associated substitution (RAS) testing. Those without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, see HCV guidance for treatment recommendations.*
HCV Treatment Experienced


Decompensated cirrhosis
- MELD>20 may not benefit from treatment and may benefit more from LT
- Concern for further decompensation with use of protease inhibitor containing regimens- do not use

HCC/HCV
- SVR 91% cirrhosis without HCC vs. 74% cirrhosis with HCC
- Treat HCC first, then treat HCV

Renal impairment/Renal Transplant
- No specific dose adjustments
- Sofosbuvir: renal clearance

www.hcvguidelines.org
HCV pos and HCV neg recipient outcomes equivalent in DAA Era

Adjusted P values

<table>
<thead>
<tr>
<th></th>
<th>D-1yr, Post-DAA Era</th>
<th>D-1yr, Pre-DAA Era</th>
<th>D-2yr, Post-DAA Era</th>
<th>D-2yr, Pre-DAA Era</th>
<th>D-3yr, Post-DAA Era</th>
<th>D-3yr, Pre-DAA Era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted P</td>
<td>0.002</td>
<td>0.003</td>
<td>&lt;0.001</td>
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</table>

Number at risk (number censored):

<table>
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<tr>
<th></th>
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<th>D-1yr, Pre-DAA Era</th>
<th>D-2yr, Post-DAA Era</th>
<th>D-2yr, Pre-DAA Era</th>
<th>D-3yr, Post-DAA Era</th>
<th>D-3yr, Pre-DAA Era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (years)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>827 (793)</td>
<td>14.30 (0.05)</td>
<td>1.30 (0.05)</td>
<td>12.05 (0.05)</td>
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</table>

Recommendations When Considering Use of HCV-Viremic Donor Organs in HCV-Uninfected Recipients

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
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</thead>
<tbody>
<tr>
<td>Informed consent should include the following elements:</td>
</tr>
<tr>
<td>• Risk of transmission from an HCV-viremic donor (and with a PHS-defined</td>
</tr>
<tr>
<td>increased risk donor, the potential risks for other viral infections)</td>
</tr>
<tr>
<td>• Risk of liver disease if HCV treatment is not available or treatment is</td>
</tr>
<tr>
<td>unsuccessful</td>
</tr>
<tr>
<td>• Benefits, specifically reduced waiting time and possibly lower waiting</td>
</tr>
<tr>
<td>list mortality</td>
</tr>
<tr>
<td>• Unknown long-term consequences (hepatic and extrahepatic) of HCV exposure</td>
</tr>
<tr>
<td>(even if cure is attained)</td>
</tr>
<tr>
<td>• Risk of graft failure</td>
</tr>
<tr>
<td>• Risk of HCV transmission to partner</td>
</tr>
<tr>
<td>Transplant programs should have a programmatic strategy to:</td>
</tr>
<tr>
<td>• Document informed consent</td>
</tr>
<tr>
<td>• Ensure access to HCV treatment and retreatment(s), as necessary</td>
</tr>
<tr>
<td>• Ensure long-term follow-up of recipients (beyond SVR12)</td>
</tr>
</tbody>
</table>

RATING: I, C
Organ Transplantation From HCV Viremic Donors to HCV Negative Recipients

Recommendations Regarding Timing of DAA Therapy

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic/preemptive treatment(^*) with a pangenotypic DAA regimen is recommended.</td>
<td>II, B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALTERNATIVE</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with a pangenotypic DAA regimen within the first week after transplantation, is a reasonable alternative. A genotype-specific regimen may be used if genotype information from the donor or recipient is available to guide therapy.</td>
<td>II, B</td>
</tr>
</tbody>
</table>

* Prior to HCV RNA results, typically day 0 to 1 post-transplant

- Shortened courses of HCV treatment should not be considered in liver transplant of HCV+ donor to HCV- recipient

Table. DAA Interactions With Calcineurin Inhibitors

<table>
<thead>
<tr>
<th>DAA</th>
<th>Cyclosporine (CSA)</th>
<th>Tacrolimus (TAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir (SOF)</td>
<td>4.5-fold ↑ in SOF AUC, but GS-57107 metabolite unchanged, no a priori dose adjustment</td>
<td>No interaction observed, no a priori dose adjustment</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>No data; no a priori dose adjustment</td>
<td>No data; no a priori dose adjustment</td>
</tr>
<tr>
<td>Elbasvir / grazoprevir (EVR/GZR)</td>
<td>15-fold ↑ in GZR AUC and 2-fold ↑ in EVR AUC, combination is not recommended</td>
<td>43% ↑ in TAC, no a priori dose adjustment</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>No interaction observed, no a priori dose adjustment</td>
<td>No data; no a priori dose adjustment</td>
</tr>
<tr>
<td>Glecaprevir / pibrentasvir (GLE/PNB)</td>
<td>5-fold ↑ in GLE AUC with higher dose; 400 mg dose of CSA, not recommended in patients requiring stable CSA doses &gt;100 mg/day</td>
<td>1.45-fold ↑ in TAC AUC, no a priori dose adjustment, monitor TAC levels and titrate TAC dose as needed</td>
</tr>
<tr>
<td>Sofosbuvir / velpatasvir / voxilaprevir (SOF/VEL/VOX)</td>
<td>9.4-fold ↑ in VOX AUC, combination is not recommended</td>
<td>No data; no a priori dose adjustment</td>
</tr>
</tbody>
</table>

*Many prefer SOF/VEL due to favorable drug-drug interaction profile

www.hcvguidelines.org
Fibrosing Cholestatic Hepatitis

- Rare, first described in HBV
- Mainly seen in HCV post solid organ transplant
- Histology: ductular proliferation (A), canalicular cholestasis (C), hepatocyte swelling (D), and sinusoidal/pericellular fibrosis (C)
- Elevated Alk Phos, TBili
- Rapidly progressive, associated with graft failure and death
- DAA therapy has been reported to reverse process in some cases

Outline

- Hepatitis A and Hepatitis E
- Hepatitis C
- Hepatitis B and Hepatitis D
HBV: Who to treat, HBeAg pos

**HBeAg positive**

- **ALT ≤ULN**
  - HBV DNA >20,000 IU/mL
  - HBV DNA >20,000 IU/mL
  
  *Note: HBV DNA 2000-20,000 IU/mL may represent seroconversion, so monitor every 1-3 months and if persists for >6 months, treat.*

- **ALT >ULN but <2XULN**
  - HBV DNA >20,000 IU/mL

- **ALT ≥2XULN**
  - HBV DNA >20,000 IU/mL
  
  *HBV DNA 2000-20,000 IU/mL may represent seroconversion, so monitor every 1-3 months and if persists for >6 months, treat.*

**Recommendations:**

- **Treat**
  - Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBeAg every 6-12 months.
  - Exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If other causes of ALT >ULN excluded and elevation persists, treat, especially if age >40.

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HBV: Who to treat, HBeAg neg

**HBeAg-negative**

- **ALT ≤ULN**
  - HBV DNA >2000 IU/mL
  - HBV DNA <2000 IU/mL

- **ALT >ULN but <2XULN**
  - HBV DNA >2000 IU/mL

- **ALT ≥2XULN**
  - HBV DNA >2000 IU/mL
  - HBV DNA <2000 IU/mL

**Recommendations:**

- **Treat**
  - Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBeAg annually.
  
  *If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months. If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT >ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.*
Treatment of HBV

- Preferred regimens in HBV
  - Entecavir, TDF, and TAF

- Treatment of HBV in cirrhosis
  - Treatment of HBV indicated in all patients with cirrhosis regardless of ALT or HBV DNA
  - Lactic acidosis rare but serious side effect of NA/s
    - Need to closely monitor patients with decompensated cirrhosis

Acute HBV

- Benefit of treating acute HBV with NA's unclear
- Risks of treatment are low, thus antiviral treatment recommended in severe acute HBV (bilirubin >3 mg/dL or direct bilirubin >1.5 mg/dL, INR>1.5, encephalopathy, or ascites

- Entecavir, TDF, or TAF preferred
  - Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation
  - Peg-IFN is contraindicated
HBV/HIV Co-Infection

- All patients with HBV/HIV coinfection should initiate ARVT, regardless of CD4 count.
  - Regimen should be TDF or TAF plus lamivudine or emtricitabine.
- Patients who are already receiving effective ARVT that does not include a drug with antiviral activity against HBV should have treatment changed to include TDF or TAF with emtricitabine or lamivudine. Alternatively, entecavir is reasonable if patients are receiving a fully suppressive ARVT.
- If ARVT regimens are changed, care should be taken to ensure that a drug active against HBV is part of the regimen.

**Risk of HBV Reactivation**

<table>
<thead>
<tr>
<th>RISK OF HBV REACTIVATION</th>
<th>HBsAg +, HBcAb +</th>
<th>HBsAg neg, HBcAb +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD 20 (rituximab, ofatumumab, Obinutuzumab)</td>
<td>VERY HIGH (&gt;20% risk)</td>
<td>MODERATE (1-10%)</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplantation</td>
<td>VERY HIGH</td>
<td>MODERATE</td>
</tr>
<tr>
<td>High dose corticosteroids (&gt;20mg for 4 weeks)</td>
<td>HIGH (11-20% risk)</td>
<td>Low</td>
</tr>
<tr>
<td>Other Cytokine Inhibitors (e.g. anti-CD52)</td>
<td>HIGH</td>
<td>Low</td>
</tr>
<tr>
<td>Combination Cytotoxic Chemo without corticosteroids (cyclophosphamide, adriamycin, vincristine)</td>
<td>MODERATE (1-10% risk)</td>
<td>Very low risk</td>
</tr>
<tr>
<td>Anti-TNF inhibitors</td>
<td>MODERATE</td>
<td>Very low risk</td>
</tr>
<tr>
<td>Anti-rejection therapy for solid organ transplant</td>
<td>MODERATE</td>
<td>Very low risk</td>
</tr>
<tr>
<td>Methotrexate, Azathioprine, 6-MP</td>
<td>Low (&lt;1% risk)</td>
<td>Very low risk</td>
</tr>
</tbody>
</table>

Modified from Di Bisceglie AM et al. Hepatology 2014
HBV reactivation

- **Very high risk, high risk, and moderate risk** of HBV reactivation should start prophylaxis
  - Entecavir, TDF, or TAF preferred
  - Start as soon as possible before or at the latest simultaneously with immunosuppressive therapy.
  - Continue prophylaxis during immunosuppressive therapy and at least 6 months after
    - Monitor at least 12 months after for patients receiving anti-CD20 therapies

- **Low/Very low risk** of HBV reactivation can be monitored
  - Check HBV-DNA levels q1-3 months while on treatment
  - Monitor for up to 12 months after cessation of immunosuppressive therapy

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**HBV Reactivation with HCV DAA Treatment**

- Test HBV Markers in All DAA Candidates:
  - 1) HBsAg, 2) Anti-HBc, 3) Anti-HBs

- **HBsAg POSITIVE**
  - HBV DNA Detectable
    - Meets AASLD criteria for initiation of HBV therapy
    - Treat with HBV drug
  - HBV DNA Low or U/D
    - Monitor for HBV:
      - Check HBV DNA q4-8 weeks on treatment and 3 months post treatment if otherwise does not meet AASLD criteria for treatment

- **HBsAg NEGATIVE**
  - anti-HBc POSITIVE (± anti-HBs)
    - Monitor ALT at baseline, end of treatment, and at follow up

**HBV Standard Definition:**
- Marked increase in HBV DNA (≥2 log increase from baseline levels) OR
- New appearance of HBV DNA to a level of >100 IU/mL in a person with previously undetectable levels.

Modified from Lieber SR and Fried MW. Clin Liv Dis 2017
Terrault N et al. AASLD Guidance for HBV, 2018
HBV in Liver Transplant Recipients

- HBsAg pos recipients
  - Reinfection rates now <10% with NA’s
  - HBsAg-positive receiving LT should receive NA’s lifelong
    - Effectively prevents recurrent HBV disease
    - NA’s should be used with or without HBIG
    - Entecavir, TDF, and TAF preferred
    - HBIG monotherapy should not be used
    - Combination antiviral therapy and HBIG reserved for groups at highest risk of progression: HDV or HIV coinfected patients

- Anti-HBc–positive donor graft
  - Long term NA recommended for prevention of viral reactivation
  - Entecavir, TDF, and TAF preferred

Hepatitis D

- In Western countries, under recognized
  - Risk factors for HDV → screen for HDV
  - <5% of chronic HBV
- HDV can replicate independently but uses HBV envelope protein to infect cells (assembly, secretion)
- HDV IgM/IgG, HDV RNA
- Co-infection biphasic rise in liver tests (initial rise followed by another rise several weeks later)
- Superinfection- acute hepatitis that can progress to liver failure

<table>
<thead>
<tr>
<th>TABLE 7. HBsAg Positive Persons at High Risk of HDV Infection Who Should Be Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons born in regions with reported high HDV endemicity*</td>
</tr>
<tr>
<td>Africa (West Africa, horn of Africa)</td>
</tr>
<tr>
<td>Asia (Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Taiwan)</td>
</tr>
<tr>
<td>Pacific Islands (Kiribati, Nauru)</td>
</tr>
<tr>
<td>Middle East (all countries)</td>
</tr>
<tr>
<td>Eastern Europe (Eastern Mediterranean regions, Turkey)</td>
</tr>
<tr>
<td>South America (Amazonian basin)</td>
</tr>
<tr>
<td>Other (Greenland)</td>
</tr>
<tr>
<td>Persons who have ever injected drugs</td>
</tr>
<tr>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>Individuals infected with HCV or HIV</td>
</tr>
<tr>
<td>Persons with multiple sexual partners or any history of sexually transmitted disease</td>
</tr>
<tr>
<td>Individuals with elevated ALT or AST with low or undetectable HBV DNA</td>
</tr>
</tbody>
</table>

Terrault N et al. AASLD Guidance for HBV, 2018
Chronic HDV

- HBV viral loads low/suppressed in patients with HDV
- Treatment:
  - First, treat HBV
  - Peg-IFN-α for 12 months recommended in AASLD guidelines, but not particularly well tolerated or effective
- HDV Post LT
  - Goal is to prevent HBV from recurring
  - HDV can recur by itself without HBV post LT, not particularly harmful to graft

Terrault N et al. AASLD Guidance for HBV, 2018
Roche B et al. Sem Liver Dis 2012

- Thank you and good luck!