Hepatitis C: Clinical Update

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Disclosures

I have no disclosures
Learning objectives

1. Describe the epidemiology of HCV infection in the United States
2. Outline strategies for diagnosis, evaluation and treatment of persons with chronic HCV infection
3. Discuss outcomes of HCV treatment and implications of access
HCV infects human hepatocytes

- Discovered in 1989 as the cause of non-A, non-B hepatitis
- Based on genetic differences, HCV classified into 6 genotypes
- 1990- HCV antibody testing of blood and plasma donors
- 1992- 2nd generation HCV antibody tests eliminated transfusion associated HCV infections
- Primarily parenteral transmission
- Sexually transmission risk among men who have sex with men esp. with HIV infection
  - Lower risk of heterosexual or vertical transmission
Natural History of HCV Infection

- Exposure (Acute Phase)
  - Resolved ~15%
  - Stable ~80%
  - Chronic ~85%

- Chronic
  - Stable ~80%
  - Cirrhosis ~20%
  - Slowly Progressive ~75%

- Cirrhosis
  - ESLD ~6%/yr
  - HCC ~3%-4%/yr
  - Transplant/Death ~4%/yr

5-year survival in patients with HCC is <5%*

Chronic HCV infection can lead to cirrhosis, end-stage liver disease, and hepatocellular cancer

Fibrosis

Chronic HCV infection can lead to the development of fibrous scar tissue within the liver.

Cirrhosis

Over time, fibrosis can progress, causing severe scarring of the liver, restricted blood flow, impaired liver function, and eventually liver failure.

Hepatocellular Carcinoma (with cirrhosis)

Cancer of the liver can develop after years of chronic HCV infection.

Accelerators of liver disease progression
- Alcohol
- HIV infection
- Obesity/fatty liver
- Aging

Decompensated cirrhosis:
- Ascites
- Bleeding gastroesophageal varices
- Hepatic encephalopathy
- Jaundice

HCV infection causes more deaths in the United States than 60 other reportable infectious diseases combined

Hepatitis C cure aka Sustained virologic response (SVR) prevents death

Bryony Simmons et al. CID 2015
The US HCV Care Cascade

How do we fix this?

- Identification
- Linkage to care
- HCV treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic HCV-Infected*</td>
<td>100%</td>
</tr>
<tr>
<td>Diagnosed and Aware†</td>
<td>50%</td>
</tr>
<tr>
<td>Access to Outpatient Care†</td>
<td>43%</td>
</tr>
<tr>
<td>HCV RNA Confirmed§</td>
<td>27%</td>
</tr>
<tr>
<td>Underwent Liver Biopsy†</td>
<td>17%</td>
</tr>
<tr>
<td>Prescribed HCV Treatment§</td>
<td>16%</td>
</tr>
<tr>
<td>Achieved SVR**</td>
<td>9%</td>
</tr>
</tbody>
</table>

Yehia et al PLOS one 2014
Epidemiology of HCV in the US: It’s changing

- Overall, ~ 3.5 million Americans with chronic HCV infection
- Majority of infections in baby boomers: born 1945-1965
- Rising incidence of HCV in young injectors
- In 2016, CDC estimates ~ 41,200 (95% CI, 32,600–140,600) new HCV infections

HCV Screening

HCV testing is recommended at least once for persons born between 1945 and 1965.

1. Risk behaviors
   - Injection-drug use (current or ever, including those who injected once)
   - Intranasal illicit drug use

2. Risk exposures
   - Long-term hemodialysis (ever)
   - Getting a tattoo in an unregulated setting
   - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood
   - Children born to HCV-infected women
   - Prior recipients of transfusions or organ transplants, including persons who:
     - were notified that they received blood from a donor who later tested positive for HCV infection
     - received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
     - received clotting factor concentrates produced before 1987
   - Persons who were ever incarcerated

3. Other medical conditions
   - 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 levels
   - Solid organ donors (deceased and living)

Screen with hepatitis C antibody test

All pregnant women

hcvguidelines.org accessed 6/1/2018
Recommended testing sequence for identifying current HCV infection

Consider simultaneous anti-HCV and HCV RNA
A. Immunocompromised patients
   • Patients on hemodialysis
   • Transplant recipients
   • Advanced HIV
B. Acute HCV / Recent exposure

Follow up of initial HCV testing

- If HCV antibody positive and HCV RNA negative by PCR, patient counseled that they do not have current (active) infection
  - However at risk for reinfection
- If ongoing risk factors for reinfection:
  - Screen for reinfection with HCV RNA
Frequency of Hepatitis C Screening

• Birth cohort
• Risk factors without ongoing exposures
  - Individuals who inject drugs
  - HIV-positive men who have unprotected sex with men

Once

• Ongoing HCV risk exposures
  - At least Annual

hcvguidelines.org
Newly diagnosed patients with HCV: Transmission and harm reduction

- Educate regarding HCV transmission
  - Sex: Screen sexual partners, but CDC does not recommend barrier methods for monogamous heterosexual partners
    - Higher risk of sexual transmission among MSM, particularly those with HIV infection
    - Mother to child: Children born to HCV-positive mothers should be screened (~ 3% risk)
    - Injection drug use: Needle/syringe exchange, medication assisted therapy
  - Screen for immunity to hepatitis A (HAV antibody total) and hepatitis B (anti-HBs)
    - Vaccinate if non-immune
Newly diagnosed patients with HCV: Alcohol

- Alcohol use screen, brief intervention and referral for treatment (SBIRT)
  - There is no “safe” amount of alcohol consumption for patients with HCV

- Defining hazardous alcohol use
  - Men: >2 drinks/day (>14/week) or more than 4 in one day
  - Women: >1 drink/day (>7/week) or more than 3 in one day

What is a standard drink?

12 fl oz of regular beer = 8–9 fl oz of malt liquor (shown in a 12 oz glass) = 5 fl oz of table wine = 1.5 fl oz shot of 80-proof spirits (“hard liquor”—whiskey, gin, rum, vodka, tequila, etc.)

The percent of “pure” alcohol, expressed here as alcohol by volume (alc/vol), varies by beverage.

Newly diagnosed patients with HCV: Link to HCV treatment

All persons with current active HCV infection should be linked to a practitioner who is prepared to provide comprehensive management.

Most people can achieve HCV cure following oral antiviral treatment.

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR).

AASLD/IDSA. HCV Guidelines. www.hcvguidelines.org
When and in whom to initiate HCV therapy

Treatment is recommended for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy.

AASLD/IDSA. HCV Guidelines. www.hcvguidelines.org
## Recommended laboratory testing

<table>
<thead>
<tr>
<th>Within 12 weeks prior to starting antiviral therapy</th>
<th>At any time prior to starting antiviral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ CBC</td>
<td>✓ HCV genotype and subtype</td>
</tr>
<tr>
<td>✓ INR</td>
<td>✓ Quantitative HCV RNA (HCV viral load)</td>
</tr>
<tr>
<td>✓ Comprehensive metabolic panel includes, albumin, total and direct bilirubin, ALT, AST, and calculated GFR</td>
<td>✓ HIV serology</td>
</tr>
<tr>
<td></td>
<td>✓ HAV antibody (total)</td>
</tr>
<tr>
<td></td>
<td>✓ HBV serology</td>
</tr>
</tbody>
</table>

All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg testing, and for evidence of prior infection with anti-HBs and anti-HBc testing.

AASLD/IDSA. HCV Guidelines. www.hcvguidelines.org
Non-invasive methods to determine cirrhosis status: Liver biopsy not required

Blood tests

- FIB-4, APRI, or FibroSURE™
- Liver elastography to measure liver stiffness
  - FibroScan®

**Fibrosis-4 (FIB-4) Calculator**

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

\[
FIB-4 = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10^9/L)} \times \sqrt{\text{ALT (U/L)}}}
\]

**Interpretation:**

Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis ( Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

APRI: AST to platelet ratio index; FIB-4: fibrosis-4.
HCV Life Cycle and DAA Targets

Many DAAs are no longer recommended and no novel DAAs are expected to be approved in the future.
Choosing an HCV regimen: Based on virus and patient characteristics

- HCV RNA level (< or > 6 million IU/mL)
- HCV genotype; if genotype 1, subtype 1a or 1b
- eGFR (CMP)
- Cirrhosis: Yes or No
- If cirrhosis, CTP score (albumin, bilirubin, INR) and liver imaging
- Concurrent medications
  - PPIs, anti-seizure medications, amiodarone, ART
- Prior HCV treatment: Yes or No
Online tools for HCV treatment support

AASLD/IDSA. HCV Guidelines. www.hcvguidelines.org
High HCV Cure rates for genotype 1 infection

- Sofosbuvir
- Ledipasvir
- Grazoprevir
- Elbasvir
- Daclatasvir
- Glecaprevir
- Pibrentasvir

TN G1
TN G1 No Cirrhosis
TN G1 Cirrhosis
Sofosbuvir/velpatasvir highly effective in patients with HCV genotype 1, 2, 3, 4, 5 and 6

Total GT1 GT2 GT3 GT4 GT5 GT6
323 328 23 7 23 8 26 4 27 7 11 6 11 6 34 35 41 41

1 death
2 relapse
2 LTFU
1 WC
11 relapse
2 others
1 LTFU

Jacobson IM. HEPDART 2015
Similar adverse event profile with velpatasvir/sofosbuvir vs placebo

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo (N = 116)</th>
<th>SOF/VEL (N = 624)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to AEs</td>
<td>2 (2)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>0</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Any AE</td>
<td>89 (77)</td>
<td>485 (78)</td>
</tr>
</tbody>
</table>

**Common AEs (≥ 5%)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 116)</th>
<th>SOF/VEL (N = 624)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>33 (28)</td>
<td>182 (29)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (20)</td>
<td>126 (20)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12 (10)</td>
<td>79 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (11)</td>
<td>75 (12)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (9)</td>
<td>50 (8)</td>
</tr>
</tbody>
</table>

Efficacy of GZR + EBR in people who inject drugs (PWID)

- Phase 3, double-blind RCT in pts on opioid agonist therapy for >3 months
  - 20% with cirrhosis
  - 7% HIV coinfected
  - 79% had positive drug toxicology during follow up

Dore G, et al. AASLD 2015, San Francisco. #40
HCV treatment regimens for HIV/HCV infected patient identical to those recommended for HCV monoinfected patients
Drug Interactions with oral DAA

- Other major classes
  - Anti-seizure medications
  - Statins
  - Antacids
  - Amiodarone
  - Antipsychotics

- Help with assessing for drug interactions

http://www.hep-druginteractions.org/
Real-world SVR rates are similar to those observed in clinical trials

SVR by HCV provider type

- ASCEND trial: Open label phase 4 trial of HCV infected patients in 2 DC community centers
- Providers received 3 hour training on AASLD/IDSA guidelines
- Received LDV/SOF

Kattakhuzy SM et al. EASL 2016

SVR/ Cure rates by provider type
Enhancing hepatitis C testing and LTC at BCHD

- Hepatitis C testing and linkage to care program at public STD clinics in Baltimore, Maryland
- Collaborator
  - Johns Hopkins Viral Hepatitis Division
- Funding
  - CDC Foundation/Viral Hepatitis Action Coalition
Methods: HCV Testing

- **HCV Antibody Screening**
  - **If positive**
  - **HCV RNA Testing**

Rapid HCV Antibody Test:
- Orasure Oraquick HCV Test
- Results in 20 minutes
- Clinical sensitivity and specificity ~ 100%

HCV RNA
- Performed at a commercial laboratory
- Results available in 1 week
- Linkage to Care
  - Counseling
  - Peer support for linkage

Linkage to Care

- **STD Clinic Services**
  - Post test counseling
  - Medical education & risk reduction counseling
  - Alcohol use screening (AUDIT), brief intervention and referral
  - Hepatitis B immunization
  - HCV treatment discussion
  - Referral to HCV specialist for treatment

- **Patient navigation services**
  - Insurance evaluation
  - Assistance with insurance application for uninsured
  - Appointment scheduling with HCV treatment specialist
  - Reminder calls for appointments
  - Community outreach
STD Clinic Care Cascade

25% of patients who had not attended specialist appointments had been seen in the STD clinics 3 or more times since HCV diagnosis.

*Linkage to care through 08/15/2014
BCHD Response

- **Incorporate** HCV services into existing STD clinic infrastructure
- **Link** patients to care as early as possible
- **Train** non-specialist clinicians to provide on-site HCV treatment
- **Build** relationships with social service agencies to provide HCV services for new, harder-to-reach patients
- **Provide** extensive navigation support for patients before and during treatment
BCHD HCV Care Cascade vs. National Cascade

Telemedicine to cure HCV in rural Western MD

- Experienced on-site nurse at the Allegany County Health Department
- Expert HCV provider at JHH
- Strong relationship with Hopkins pharmacy for drug prior authorization, patient education and adherence support
- Hardware and software
- Aligned goals
# HCV Elimination by 2030? WHO targets

<table>
<thead>
<tr>
<th>Target Areas</th>
<th>2020 Target</th>
<th>2030 Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Service Coverage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention</td>
<td>Harm reduction (sterile syringe needle set distributed /year /PWID)</td>
<td>200</td>
</tr>
<tr>
<td>Treatment</td>
<td>HCV diagnosis (%)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Treatment (%)</td>
<td>3 million</td>
</tr>
<tr>
<td>Impact leading to elimination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of chronic HCV</td>
<td>30% reduction</td>
<td>90% reduction</td>
</tr>
<tr>
<td>Mortality from HCV</td>
<td>10% reduction</td>
<td>65% reduction</td>
</tr>
</tbody>
</table>
HCV treatment restrictions

2017 NVHR Update: Reduced Treatment Access in Many Settings for Pts With Mild Liver Disease

2017 Medicaid FFS Liver Damage Restrictions for HCV Treatment

HCV treatment restrictions

2017 NVHR Update: Drug/Alcohol Use Leads to Reduced Treatment Access in Some Settings

2017 Medicaid FFS Sobriety Restrictions for HCV Treatment

Barriers to HCV elimination

- Inadequate HCV testing and linkage to care
- Drug costs and access restrictions
  - Innovative models to address
- Prior authorization requirements
- Lack of engagement of people who inject drugs
HCV treatment uptake among older person with advanced liver disease has led to decreased listing for liver transplantation.

Number of Medicare prescriptions for HCV treatment

Number of new liver transplant wait-listing by disease

Goldberg D et al. Gastroenterology 2017
## Sharing the cure: expansion of HCV treatment delivery and training of clinicians

**CDC-funded program: Outcomes of HCV Training Programs at 3 Sites, Oct 2014-Dec 2016**

<table>
<thead>
<tr>
<th>Site</th>
<th># of Providers Trained</th>
<th># of clinics with trained providers contributing data on HCV treatment*</th>
<th># patients treated at clinics with trained providers contributing data on HCV treatment*</th>
<th>Methods used for training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baltimore Maryland</td>
<td>25</td>
<td>6</td>
<td>300</td>
<td>Didactics, in person mentorship</td>
</tr>
<tr>
<td>Chicago</td>
<td>165</td>
<td>8</td>
<td>190</td>
<td>Project ECHO</td>
</tr>
<tr>
<td>Seattle-King County</td>
<td>252</td>
<td>6</td>
<td>207</td>
<td>Project ECHO, large group didactics, in-clinic mentorships</td>
</tr>
</tbody>
</table>
Conclusions

• Hepatitis C is a major cause of morbidity and mortality in the United States
• We have the tools to eliminate hepatitis C
  • There are multiple effective, safe options for HCV treatment and cure
  • Harm reduction including syringe exchange and medication assisted treatment
• Major challenges to HCV cure are now
  • HCV testing and linkage to care
  • HCV drug costs/access
• Health departments can and should play a role in population level HCV control
Thank You!

Acknowledgements: Mark Sulkowski MD
Questions?

KEEP CALM AND LOVE YOUR LIVER