Hepatitis C Virus Infection

Brian L. Pearlman MD FACP
Medical Director, Center for Hepatitis C
Atlanta Medical Center, Atlanta, Georgia
Adjunct Professor of Medicine, Medical College of Georgia
Adjunct Professor of Medicine, Emory School of Medicine

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Hepatitis C Lecture Outline

- Prevalence
- Natural history/epidemiology
- Screening
- Therapy
- Prevention
Global Health Epidemic: 170 Million Persons With HCV Infection Worldwide

- Americas: 13.1 million (1.7%)
- Europe: 8.9 million (1.03%)
- Africa: 31.9 million (5.3%)
- Eastern Mediterranean: 21.3 million (4.6%)
- Western Pacific: 62.2 million (3.9%)
- Southeast Asia: 32.3 million (2.15%)

HCV is nearly 4 times as prevalent as HIV and HBV.
Increased Mortality

- Chronic HCV is associated with a 8- to 12-year reduction in overall life expectancy and reduced quality of life\(^1\)
- Chronic HCV patients have significantly higher mortality rate
  - HR 1.53; (95% CI, 1.13-2.07)\(^2\)
  - HR 1.37; (95% CI, 1.31-1.47)\(^3\)
  - Death rate 12-fold higher than general population\(^4\)

Age-adjusted HCV Mortality Surpasses that of HIV in the US, 1999-2007

Complications Due to HCV-Related Cirrhosis Expected to Rise Over the Next 10 Years

Projected Number of Cases of Hepatocellular Carcinoma and Decompensated Cirrhosis Due to HCV

- Hepatocellular cancer
- Decompensated cirrhosis

Year


Number of cases

0 20,000 40,000 60,000 80,000 100,000 120,000 140,000 160,000

HCV RISK FACTORS

Previously Acquired (prior to 1990’s) and Newly Acquired (1995-Now)

- **IV Drug Use**: 68% (60%)
- **Sexual**: 15% (18%)
- **Occupational**: 4%
- **Other**: 1%
- **Unknown**: 10% (9%)
- **Transfusion**: 10%

*Alter, NIH Consensus Conference, 2002*
Groups Recommended for HCV Testing by AASLD and USPHS

- Recent/past injection drug users—even if only used once
- Groups with high HCV prevalence
  - HIV-infected individuals
  - Hemophiliacs treated with clotting factor concentrates before 1987
  - Hemodialysis recipients
  - Patients with unexplained aminotransferase abnormalities

Groups Recommended for HCV Testing by AASLD and USPHS

- Recipients of transfusion or transplantation before July 1992
- Children born to women infected with HCV
- Healthcare, public safety, and emergency medical personnel following needle injury or mucosal exposure to HCV-infected blood
- Current sexual partners of individuals infected with HCV
- Persons who have used illicit drugs by noninjection routes
Two-Thirds of Those With Chronic HCV in the U.S. Were Born Between 1945 and 1965

Estimated Prevalence by Age Group

Hepatitis C Screening Approved for Baby Boomers

- In its National Coverage Determination the Center for Medicare & Medicaid Services (CMS) has approved HCV screening for:
  - “High risk” adults (eg. illicit injection drug use)
  - Adults who are not high risk but were born from 1945 through 1965
- Applies to Medicare Part A or B

www.modernhealthcare.com/article/20140602/NEWS/306029940
DO NOT SCREEN BASED ON ELEVATED LIVER TESTS ALONE!

- One-third of all patients infected with hepatitis C have persistently normal ALT.
- Patients may have intermittently normal ALT.
- Take-home point: Test for hepatitis C based on risk factors, *not* based on aminotransferase elevation.
Anti-HCV Antibody Testing for HCV

ELISA screening tests

- Detect circulating HCV antibodies
- Sensitivity: 97% to 100%
- Positive predictive value
  - 95% with risk factors and elevated ALT
  - 50% without risk factors and normal ALT

<table>
<thead>
<tr>
<th>False Positives More Likely in:</th>
<th>False Negatives More Likely in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with low risk of HCV infection</td>
<td>Severely immunosuppressed patients</td>
</tr>
<tr>
<td></td>
<td>Transplantation recipients</td>
</tr>
<tr>
<td></td>
<td>Patients with chronic renal failure on dialysis</td>
</tr>
<tr>
<td></td>
<td>HIV-positive patients</td>
</tr>
</tbody>
</table>

Question 1.

A 48 year old man with chronic HCV has been in a monogamous relationship with his girlfriend for 6 years. He wants your advice on avoiding sexual transmission.
Q1. You advise him to:

1. Practice safe sex 39%
2. Advise his girlfriend to seek immediate testing and treatment for HCV 52%
3. Avoid getting her pregnant under any circumstances because of fetal safety 0%
4. Not worry about safe sex because the risk of sexual transmission is very low 6%
5. Consult with a local infectious disease colleague 3%
Low Risk of HCV Transmission Between Monogamous Sexual Partners

- The HCV Partners Study
- 500 serodiscordant heterosexual monogamous couples
  - No condom use, no anal sex
  - Viral isolates in three couples (0.6%) were highly related, consistent with transmission
  - 8,377 person-years of follow-up, the maximum incidence of transmission was 0.07% per year (95% CI: 0.01-0.13)

Reports of Worldwide Epidemic of Sexually Transmitted HCV among HIV Positive MSM

• **Amsterdam**: Coinfection prevalence increased from 15 to 21% from 2000 to 2007 (1)

• **USA**: 6-fold higher incidence rate HCV in HIV+ versus HIV- MSM (2)

• **Swiss** HIV Cohort: HCV incidence increased 18-fold between 1998 to 2011 (3)

• **Australia**: 9% of HIV+ MSM coinfected relative to 2% HIV- MSM (4)

HCV Genotypes in US


<table>
<thead>
<tr>
<th>Genotype</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>All Others</td>
<td>2</td>
</tr>
</tbody>
</table>
Chronic HCV: Risk Factors for Progression

- Older age at infection acquisition
- Duration of infection
- Gender
- Coinfection
- Alcohol
- Obesity/NAFLD
- Insulin Resistance
- Genotype 3
- Cannabis

Harrison S, Clin Gastro and Hep, 2008
Leandro et al., *AASLD 2005; Hezode et al., Hepatol, 2005*
Progression to Cirrhosis
Becomes Nonlinear with Age
HCV/HIV Coinfection

- HIV coinfection promotes accelerated hepatic fibrosis progression
- In those who have progressed to cirrhosis, higher rates of liver failure and death are observed, relative to monoinfected HCV patients

Sherman KE, Hepatology 2014
Macias J et al. Hepatology, 2009
DISEASE PROGRESSION IN HEPATITIS C INFECTION

NEW INFECTION

Infection Clears Spontaneously

Chronic Hepatitis

15-40%

20-25%
15-20 yrs

Cirrhosis

15%
5-10 yrs

Hepatocellular Carcinoma

Stable or Slow Progression

Death

* 2% per year
Therapy
Q2. With successful therapy, Chronic Hepatitis C infection is?

1. Nearly always permanently eradicated or cured
2. Suppressible while on therapy but never curable
3. Not suppressible or curable, but controllable
4. Eliminated in the serum, but never eliminated intracellularly

81% 13% 0% 6%
HCV is Curable - HIV & HBV Are Not

HCV Sustained Virologic Response = Cure = Aviremia 12 weeks post-therapy
Sustained Virologic Response (SVR): Has the Patient Been “Cured”? 

- **187** patients with SVR followed up to 14 years (mean 29 months)\(^1\)
  - 85 patients IFN or IFN/ribavirin
  - 102 patients Peg-IFN/ribavirin
  - No Relapse

- **1546** patients with SVR followed up for five years\(^2\)
  - IFN or Peg-IFN +/- ribavirin
  - 19 patients (19/1546)= 1% Relapse

- **344** patients with SVR followed up to 18 years (mean 3.27 years)\(^3\)
  - 214 treated Peg/ribavirin
  - No Relapse
  - Residual liver RNA 1.7%

- **103** patients with SVR, followed up for up to 22 years\(^4\)
  - IFN or Peg +/- ribavirin
  - 3 patients = 1% Relapse

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\(^3\)Maylin, et al. Gastroenterology, 2008; \(^4\)Koh, et al. AASLD, 2010
SVR Improves Outcomes in Patients with HCV-associated Cirrhosis

AHR death/liver transplantation (HR = 0.17, 95% confidence interval [CI] = 0.06-0.46);
Development of liver-related morbidity/mortality (HR = 0.15, 95% CI = 0.06-0.38);
HCC (HR = 0.19, 95% CI = 0.04-0.80) for SVR compared to NR.

SVR and Reduced Risk of All-Cause Mortality
US VA Study: Treatment with Pegylated Interferon/Ribavirin

HCV Genotype 1

Cumulative Mortality

Years

0.00 0.05 0.10 0.15 0.20 0.25 0.30
0 1 2 3 4 5 6

P (log-rank) < 0.0001

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>SVR</th>
<th>Hazard Ratio for Death with SVR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12,166</td>
<td>35%</td>
<td>0.70</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2</td>
<td>2904</td>
<td>72%</td>
<td>0.64</td>
<td>0.006</td>
</tr>
<tr>
<td>3</td>
<td>1794</td>
<td>62%</td>
<td>0.51</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

The Importance of Sustained Virological Response

- Tantamount to cure
- Associated with improvement in liver histology (inflammation, fibrosis)
- Less frequent liver-related complications
- Reduced risk of decompensation
- Reduced risk of hepatocellular carcinoma
- Reduced liver-related mortality
- Reduced all-cause mortality

HCV-Infected Persons in the US: Estimated Rates of Detection, Referral to Care and Cure

- Infected: 3.2 M
- Diagnosed: 50%
- Referred to care: 32-38%
- HCV RNA test: 20-23%
- Treated: 7-11%
- ‘Cure’: 5-6%

Multiple Classes of Direct-Acting Antiviral Agents

5'UTR: Core E1 E2 p7 NS2 NS3 NS4B NS5A NS5B 3'UTR

Protease

Ribavirin

NS3 Protease Inhibitors
(Telaprevir) (Boceprevir) Simeprevir* Paritaprevir* Grazaprevir Asunaprevir Sovaprevir ACH-2684 GS-9857

NS5A Inhibitors
Ledipasvir* Ombitasvir* Daclatasvir* Elbasvir Velpatasvir ACH-3102 (Odalasvir) Samatasvir

Nucleoside/nucleotide Polymerase Inhibitors
Sofosbuvir* MK-3682 ACH-3422 AL-335

Non-Nucleoside Polymerase Inhibitors
Dasabuvir* Beclabuvir GS-9669 TMC647055

*In routine use in U.S.; ( ) Obsolete in the U.S.
SVR for Genotype 1-infected Treatment Naïve (non-cirrhotic) Patients

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Sustained Virologic Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN</td>
<td>10%</td>
</tr>
<tr>
<td>IFN/RBV</td>
<td>30%</td>
</tr>
<tr>
<td>PEG/RBV</td>
<td>45%</td>
</tr>
<tr>
<td>PEG/RBV/PI</td>
<td>70%</td>
</tr>
<tr>
<td>Poly/NS5a</td>
<td>99%</td>
</tr>
</tbody>
</table>

IFN=standard interferon; RBV=ribavirin; PEG=peginterferon; PI=protease inhibitor; Poly=polymerase inhibitor; NS5a=NS5a inhibitor
Phase III Studies of Sofosbuvir + Ledipasvir (NS5a inhibitor) FDC

ION-1[1,2]
Treatment-naive HCV GT1; cirrhosis in 15% to 17% per arm (N = 865)

ION-2[3]
Treatment-experienced HCV GT1; 20% cirrhotics (N = 440)

- ION-1,2: No difference in outcomes according to cirrhosis status, type of treatment failure

Phase III Study of SOF/LDV (Ledipasavir) ± RBV for 8-12 Wks in Treatment-Naive Noncirrhotic Genotype 1 Patients

SOF/LDV (n = 216)

SOF/LDV (n = 215)

SOF/LDV + RBV (n = 216)

SVR12, %

Wk 8

Wk 12

94
93
95

Treatment-naive, noncirrhotic pts with HCV GT1 (N = 647)

Progressive Improvement in SVR: Whites vs African Americans

IFN=interferon; RBV=ribavirin; PEG=peginterferon
PI=protease inhibitor; Poly=polymerase inhibitor; NS5a=NS5a inhibitor

Sustained Virologic response (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>IFN/RBV</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>PEG/RBV</td>
<td>52</td>
<td>19</td>
</tr>
<tr>
<td>PEG/RBV/PI</td>
<td>75</td>
<td>62</td>
</tr>
<tr>
<td>Poly/NS5a</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>

HCV-HIV Coinfection SVR: Genotype 1; 12 weeks Therapy

Sustained Virologic Response (percentage)

- SOF/LDV: 96% (n=327)
- PRT/OMB/DAS/r+RBV: 94% (n=31)
- SOF/DCV: 97% (n=168)

Genotype ONE Therapy 2015: Duration 8-24 weeks

- **HARVONI**
  
  sofosbuvir/ledipasvir = nucleotide polymerase inhibitor/NS5a inhibitor

- **VIEKIRA PAK** (often combined with Ribavirin)
  
  paritaprevir/ombitasvir/dasabuvir/(ritonavir)= protease inhibitor/NS5a inhibitor/non-nucleotide polymerase inhibitor/(booster)

- **OLYSIO/SOVALDI** (aka “Sim-Sof”)
  
  simeprevir/sofosbuvir = protease inhibitor/ nucleotide polymerase inhibitor
Adverse Effects of Current Therapies

- Headache
- Nausea
- Fatigue
- Insomnia
- Diarrhea

- Ribavirin-containing regimens only
- Pruritus
- Rash
- Hemolytic Anemia
- Leukopenia
AASLD/IDSA treatment recommendations 2015: [www.hcvguidelines.org](http://www.hcvguidelines.org); RBV=ribavirin.
Cost-Effectiveness of Current HCV Therapies

- $24,921 and $25,405 per QALY gained for Viekira Pak and Harvoni, respectively (1)
- Less than $50,000 per QALY gained for Harvoni (2)
- Harvoni cost-effective if less than $780/day; currently $1100/day AWP (3)
- Treatment of patients with moderate fibrosis (Stage 2 of 4) $37,300 per QALY gained (4)

Prevention
Question 3.

A 62 year old, HCV-infected, Vietnamese man has compensated cirrhosis but presently declines therapy. He is willing to do anything else you recommend for his health betterment.
Q3. As his primary care provider, all of the following testing and interventions should be ordered EXCEPT?

1. Abdominal ultrasound for hepatocellular carcinoma screening
2. Pneumonia and flu vaccinations
3. Hepatitis A and B vaccinations if already not immune
4. Sodium restricted diet
5. Upper endoscopy (EGD) for varices screening
The Importance of Vaccination

- All patients should be vaccinated against HAV and HBV if not already immune
- Coinfection with HBV speeds up the progression of HCV
- HAV fulminant liver failure rate:
  - 0.00003% of cases monoinfection HAV
  - 41% of cases coinfected HAV and HCV

Patients with HCV who drink more than 30 grams per day have a three times higher rate of cirrhosis compared to control patients.

- Alcohol enhances HCV replication.
- Alcohol lessens the effects of interferon; no data available on effect on DAA’s.
- History of alcoholism is not an absolute contraindication to treatment.

Screening for Hepatocellular Carcinoma

- Despite little evidence for improving survival, standard of care in the community is to screen all patients with cirrhosis for liver cancer
  - Alpha-feto protein no longer recommended
  - Ultrasound or other imaging every 6 months
- Do not screen patients without cirrhosis

AASLD Guidelines on HCC, 2010
Conclusions

- HCV is common and the majority of infected patients are undiagnosed
  - More aggressive screening strategies like birth cohort screening are recommended
- HCV progresses to cirrhosis over 20 years in about 20-30% of patients, but this rate can be accelerated by cofactors
- HCV infection is curable, and therapy has evolved rapidly; cure rates exceed 90% in most cases and is cost-effective
- Alcohol cessation, appropriate vaccination and hepatocellular carcinoma screening are all essential
Evaluation

- Please take < 90 seconds to evaluate this session.
- Time permitting, speaker will take questions following evaluation.
- Responses are not displayed and are important in maintaining high quality education.
The overall performance of the speaker:

1. Poor
2. Fair
3. Average
4. Good
5. Excellent

0% 3% 3% 11% 83%
How well were the learning objectives met?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent

[Bar chart showing: Poor 0%, Fair 0%, Average 3%, Good 11%, Excellent 86%]
Did speaker present a balanced view of therapeutic options?

1. Yes
2. No
3. N/A

91% Yes
6% No
3% N/A
How useful will this session be in your practice?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent
As a result of this program, do you intend to change your patient care?

1. Yes
2. No
Thank you!