HEPATITIS C IN 2017

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Disclosures

• **Lisa M. Chirch, MD, FIDSA** has disclosed that she has served on advisory boards for Gilead Sciences and Melinta Therapeutics.
Learning Objectives

- Review the most recent epidemiology of chronic hepatitis C infection.
- Describe the initial assessment of patients with chronic hepatitis C.
- Review recent guideline recommendations for the treatment of chronic hepatitis C virus (HCV) infection.
- Evaluate new and emerging treatments for hepatitis C.
- Recognize adverse effects and important drug-drug interactions with available therapies for hepatitis C.
China, Pakistan, Nigeria, Egypt and India account for an estimated half of the up to 180 million hepatitis C infections worldwide; 3-4 million new infections annually.

- Dr. Imad Waked, National Liver Institute, Cairo
In the United States, the number of people with chronic Hepatitis C infections is estimated at 5.2 million—slightly less than the combined populations of Connecticut, Rhode Island and Vermont.

Source: U.S. Census Bureau, Liver International
Magnitude of the U.S. Problem

- Nearly 4 million persons in United States infected
- Approximately 35,000 new cases yearly
  - >15,000 deaths annually
- Acute infections on the rise since 2010
  - Young MSM, rural vs urban (MMWR 2015)
- <10% chronically infected patients are treated
- Leading cause of
  - Chronic liver disease
  - Cirrhosis
  - Liver cancer
  - Liver transplantation

http://www.cdc.gov; Sulkowski M.ID Week 2015
Lack of Awareness – “Silent Epidemic”

<table>
<thead>
<tr>
<th>Virus</th>
<th>Prevalence</th>
<th>% Unaware of Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>800,000 – 1.4 million</td>
<td>About 65%</td>
</tr>
<tr>
<td>HCV</td>
<td>2.7 – 3.9 million</td>
<td>About 75%</td>
</tr>
<tr>
<td>HIV</td>
<td>1.1 million</td>
<td>About 21%</td>
</tr>
</tbody>
</table>
Hepatitis C Virus (HCV) in the US: Gaps in Current Practice

Increases in Hepatitis C Virus Infection Related to Injection Drug Use Among Persons Aged ≤30 Years — Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012

Hepatitis C virus (HCV) is a blood-borne infection in the United States affecting three million persons living with the infection (1). Percutaneous exposure to contaminated needles is the most efficient mode of transmission, and injection drug use (IDU) is the primary risk factor for infection in this country. State surveillance reports from the United States have demonstrated a nationwide increase in reported HCV infection, with the largest increases occurring in the Ohio River Valley, particularly among states in the Southern United States.
Southeast Indiana had previously recorded only about five cases of HIV infection annually, yet by June 10, 2015, a total of 169 people had been newly diagnosed with HIV in about half a year. More than 80% of them were coinfectected with hepatitis C virus (HCV). Needle exchange programs are illegal in Indiana.
Indications for HCV screening?

- HIV
- IDU
- History of chronic HD, transfusion, blood product or organ transplant prior to 1992
- Unexplained persistent elevation in ALT (?RNA)
- One-time testing without prior ascertainment of HCV risk for **persons born during 1945 - 1965**, a population with a disproportionately high prevalence of HCV infection and related disease.

– CDC 2012
Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965
Testing sequence

MMWR 2013

* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed.

†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Adapted from Centers for Disease Control and Prevention (CDC), 2013. (Centers for Disease Control and Prevention [CDC]. 2013 [1])
If 10 people are exposed to the hepatitis C virus, approximately how many will develop chronic infection?

1. 10
2. 8
3. 5
4. 2
5. 0
Hepatitis C Virus Infection
Natural History

Acute HCV
- Resolved: 15% (15%)
- Chronic HCV: 85% (85%)

Chronic HCV
- Stable: 80% (68%)
- Cirrhosis: 20% (17%)
- Slowly progressive: 75% (13%)
- *HCC: 25% (4% annually)

*Cirrhosis can lead to decompensation, transplant, or death (11%)

*HCC, hepatocellular carcinoma
*Nancy Reau. ID Week 2015
Hepatitis C Virus

Genotypes in the USA

Type 1: 72%
Type 2: 17%
Type 3: 10%
All others: 1%

Management of Chronic HCV

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Response to Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT</td>
<td>ALT</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>HCV RNA</td>
</tr>
<tr>
<td>Albumin</td>
<td>HCV genotype</td>
</tr>
<tr>
<td>Pro-time (INR)</td>
<td>Liver histology</td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
</tr>
<tr>
<td>Liver histology</td>
<td></td>
</tr>
<tr>
<td>Transient Elastography</td>
<td></td>
</tr>
</tbody>
</table>
Fibrosis Staging in Hepatitis: What You Need to Know

- Assess whether pt has advanced disease

<table>
<thead>
<tr>
<th>Metavir Stage 0-2</th>
<th>Metavir Stage 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fibrosis or portal fibrosis</td>
<td>Advanced fibrosis or cirrhosis</td>
</tr>
</tbody>
</table>

- Monitor for progressive fibrosis
  - Noninvasive strategies or biopsy
    - APRI (AST platelet ratio index), FIB-4, FibroSure, Fibroscan

Determines:
- Treatment duration
- Use of ribavirin
- Follow-up after cure

www.hepatitisc.uw.edu/page/clinical-calculators/APRI
Sampling error??

Fibrosis area: 65%
Fibroscan

Castera Transient Elastography Breakpoints

- 2.5 kPa: Absent or mild fibrosis (Metavir F0-F1)
- 7.0 kPa: Significant fibrosis (Metavir F2)
- 9.5 kPa: Severe fibrosis (Metavir F3)
- 12.5 kPa: Cirrhosis (Metavir F4)

75 kPa
HCV Treatment Goals

- Goals of treatment for chronic HCV
  - Viral eradication (undetectable viral load)
  - Delay progression of fibrosis
  - Prevent decompensation, HCC, transplant, and death (+ quality of life??)

- Best indicator of successful treatment is sustained virologic response (SVR)

Sustained virologic response

- **SVR**: serum HCV RNA is undetectable based on a quantitative HCV RNA assay with lower limit of detection of 50 IU/mL or less at **12 weeks after treatment ends**
Hepatitis C Virologic Cure Associated With Improved Outcomes

- Virologic cure does not protect against reinfection

Treatment of Chronic HCV

**Peginterferon and Ribavirin**

Time Course of Treatment-Associated Psychiatric Adverse Effects

Ribavirin

- Nucleoside analog
  - Inhibits inosine monophosphate dehydrogenase
  - Potentiates purine analogs, ie didanosine
  - Immune modulator, shift from Th2 to Th1 response

- Teratogenic
  - both men and women must use contraception during and for 6 months after treatment

- Dose-dependent hemolytic anemia
- Increased risk for lactic acidosis
FLAVIVIRUS

Yellow Fever

Dengue

West Nile

ZIKA
### Summary of Approved Direct-Acting Antivirals

[www.hcvguidelines.org](http://www.hcvguidelines.org)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Approved Genotypes</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEPATIER = EBR/GZR = PI + NS5A</td>
<td>4</td>
<td>Protease inhibitor</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/rit</td>
<td>4</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>Dasabuvir + dasabuvir</td>
<td></td>
<td>NS5B nonnucleoside polymerase inhibitor</td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir</td>
<td>1, 3</td>
<td>NS5B nucleotide polymerase</td>
</tr>
<tr>
<td>HARVONI = LDV/SOF = NS5A + NS5B</td>
<td>5, 6</td>
<td>NS5B nucleotide polymerase</td>
</tr>
<tr>
<td>Simeprevir + sofosbuvir</td>
<td>1, 4</td>
<td>NS5B nucleotide polymerase</td>
</tr>
<tr>
<td>EPCLUSA = VEL/SOF = NS5A + NS5B</td>
<td>4, 5, 6</td>
<td>NS5B nucleotide polymerase</td>
</tr>
</tbody>
</table>

Highly effective options for *every* genotype

Single-pill formulations or 2-pill combinations
Ledipasvir/Sofosbuvir
FDA Approved, October 2014

- One tablet daily for HCV GT1, 4, 5, 6 and HIV coinfection
- EXTREMELY well tolerated
  - adverse events rare
  - Fatigue and headache most common

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve, with or without cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment experiences without cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment experienced with cirrhosis</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Treatment naïve, without cirrhosis, baseline viral load &lt; 6 million IU/ml</td>
<td>Consider* 8 weeks</td>
</tr>
<tr>
<td>Treatment naïve AND experienced with DECOMPENSATED cirrhosis (CP B or C)</td>
<td>12 weeks + RIBAVIRIN</td>
</tr>
<tr>
<td>Transplant recipients</td>
<td>12 weeks + RIBAVIRIN</td>
</tr>
</tbody>
</table>
SVR12 by Treatment Regimen and Duration in Pts Without Cirrhosis

- Pooled data from multiple trials, HCV RNA < 6 M IU/mL in 8-wk arm

<table>
<thead>
<tr>
<th>Duration</th>
<th>With RAVs</th>
<th>No RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Wks</td>
<td>98/30/32</td>
<td>99/107/108</td>
</tr>
<tr>
<td>12 Wks</td>
<td>99/187/189</td>
<td>99/504/509</td>
</tr>
</tbody>
</table>

Zeuzem S, et al. AASLD 2015. Abstract 91
Drug Interaction Charts

Step 1: Choose one or more HEP drugs
Step 2: Choose one or more combination classes
Step 3: Choose one or more combination drugs
Step 4: View results
# Ledipasvir/Sofosbuvir - Medications to Avoid

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrythmics, Anticonvulsants/Antimycobacterials</td>
<td>Amiodarone, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampin, rifabutin</td>
<td>Coadministration not recommended.</td>
</tr>
<tr>
<td>HCV Products</td>
<td>Simeprevir</td>
<td>Coadministration not recommended.</td>
</tr>
<tr>
<td>Herbal Supplements:</td>
<td>St. John’s wort (<em>Hypericum perforatum</em>)</td>
<td>Coadministration not recommended.</td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitors:</td>
<td>Rosuvastatin</td>
<td>Coadministration not recommended.</td>
</tr>
</tbody>
</table>

Elbasvir/Grazoprevir

- NS5A inhibitor plus NS3/4A protease inhibitor
- Approved January 2016 for GT 1 and 4

FDA approves Zepatier for HCV genotypes 1, 4

January 29, 2016

Merck announced the FDA has approved Zepatier for the treatment of adult patients with chronic hepatitis C virus genotype 1 and 4 infection, with or without ribavirin.
C-SURFER: Grazoprevir/Elbasvir in Pts With GT1 HCV and Stage 4/5 CKD

Grazoprevir/elbasvir dosed orally 100 mg/50 mg once daily. This study also included a pharmacokinetic analysis (n = 11) in which pts were treated as in the randomized grazoprevir/elbasvir study group.

- 76% on dialysis
- 34% with diabetes
- 52% GT1a, 48% GT1b
- 6% cirrhosis

*Modified full analysis set population.

Adjust EBR/GZR Duration Based on Baseline NS5A RASs in GT1a

C-EDGE Treatment Naive: 12 Wks of Elbasvir/Grazoprevir

- All: 92%
- No BL NS5A RASs: 99%
- BL NS5A RASs: 58%
- GT1b: 99%

If NS5A RASs in GT1a, treat with EBR/GZR + RBV for 16 wks (alternative)

No baseline RAS testing needed in GT1b pts


Slide credit: clinicaloptions.com
Sofosbuvir/ Velpatasvir
NB5B plus NS5A

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection

**ASTRAL-1: SOF/VEL for 12 Wks in GT1, 2, 4, 5, 6 Pts With and Without Cirrhosis**

- 19% cirrhosis, 32% treatment experienced[^1]
- GT3 pts evaluated in separate study (ASTRAL-3)[^2]
- GT2 pts also studied with SOF/VEL vs SOF + RBV in ASTRAL-2 with similar results[^2]

### SVR12 (%)[^1]

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1a</th>
<th>GT1b</th>
<th>GT2</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>618/634</td>
<td>206/210</td>
<td>117/118</td>
<td>104/104</td>
<td>116/116</td>
<td>34/35</td>
<td>41/41</td>
</tr>
<tr>
<td>SVR12</td>
<td>99</td>
<td>98</td>
<td>99</td>
<td>100</td>
<td>100</td>
<td>97</td>
<td>100</td>
</tr>
</tbody>
</table>


Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
Genotype 3 Is Important

- Second most common genotype globally[^1]
  - 10% to 15% of HCV cases in the US
- Associated with more rapid progression of fibrosis and higher risk of HCC[^2]
- Suboptimal responses to first-generation DAAs

Avoiding Future Failure . . .

- ASTRAL 3: SVR12 rate with SOF/VEL relative to presence/absence of NS5A RAVs:

SO….for genotype 3, add **RIBAVIRIN IF**:
1) Y93H RAV present OR
2) RX-experienced and cirrhotic

*www.hcvguidelines.org*
SURVEYOR 2, Part 4: 8 Wks GLE/PIB For Pts With GT 2, 4, 5, 6 HCV Without Cirrhosis

- 99% SVR12 rate with 8-wk regimen in DAA-naive pts with GT2 HCV – noninferior to 95% historical control (SOF + RBV for 12 wks)

Slide credit: clinicaloptions.com

### ENDURANCE-3: Glecaprevir/Pibrentasvir in GT3 HCV Without Cirrhosis

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Cirrhosis</td>
</tr>
<tr>
<td>1, 2, 3, 4, 5, or 6</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

### Table 2. Recommended Duration for Treatment-Experienced Patients

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Patients Previously Treated With a Regimen Containing:</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>An NS5A inhibitor(^1) without prior treatment with an NS3/4A protease inhibitor</td>
<td>16 weeks</td>
</tr>
<tr>
<td></td>
<td>An NS3/4A PI(^2) without prior treatment with an NS5A inhibitor</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1, 2, 4, 5, or 6</td>
<td>PRS(^3)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>3</td>
<td>PRS(^3)</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

\(^1\) NS5A inhibitor: 
\(^2\) NS3/4A PI: 
\(^3\) PRS: 

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NS5B Polymerase Nucleotide Inhibitor (. . . buvir)</th>
<th>NS3/4A Protease Inhibitor (. . . previr)</th>
<th>NS5A Inhibitor (. . . asvir)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/velpatasvir/voxilaprevir</td>
<td>SOF</td>
<td>VOX</td>
<td>VEL</td>
</tr>
<tr>
<td>Glecaprevir/pibrentasvir</td>
<td>--</td>
<td>GLE</td>
<td>PIB</td>
</tr>
<tr>
<td>Grazoprevir/ruzasvir/uprifosbuvir</td>
<td>UPR</td>
<td>GZR</td>
<td>RZR</td>
</tr>
<tr>
<td>AL-335 + odalasvir + simeprevir</td>
<td>AL-335</td>
<td>SMV</td>
<td>ODV</td>
</tr>
</tbody>
</table>

www.filmratings.com  www.mpaa.org
To summarize…

• Several highly effective regimens approved for GT1
• Need for extended therapy and/or RBV in cirrhotics depending on regimen, GT1 subtype, and prior treatment status
• Data support 8 wks of LDV/SOF in GT1 treatment-naive noncirrhotics with HCV RNA < 6 M IU/mL
• High-dose PPIs should be avoided with LDV and with VEL
• 8 week course of G/P comparable efficacy
• Genotype 3 remains problematic, but not for long??
Key Points

- All pts born 1945-1965 should be screened for hepatitis C infection
  - Know risk-based screening recommendations
- Virtually all pts with hepatitis C infection should be treated, regardless of genotype and fibrosis
  - Prevents morbidity, progression of fibrosis, hepatocellular carcinoma
- Many pts can be treated in primary care setting
  - Must refer pts with decompensation
  - Current treatments include pangenotypic and ribavirin-free options
    - > 95% rate of cure for most genotypes
    - 8 to 12 wks, ribavirin free, all oral, once daily
Just a few more things…

• Hepatitis B reactivation
• HCC screening
HBV Reactivation Risk in HBV/HCV Coinfected Pts Receiving HCV DAAs

- Case reports of HBV reactivation in pts treated with several different DAA regimens

Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus
A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System

- Reactivation of HBV usually occurred 4 to 8 weeks after initiation
- Decompensated liver failure developed in 3 patients, 2 died and 1 required liver transplantation
- FDA – Black box warning
HBV Testing and Monitoring During HCV DAA Therapy: AASLD/IDSA Guidance

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - No HBV markers: VACCINATE (this is not new!)
  - HBV markers present:
    - HBsAg positive
      - HBV DNA detectable
        - HBV DNA meets criteria for treatment in AASLD HBV guidelines
        - Treat with HBV drug
      - HBV DNA low or undetectable
        - Monitor for reactivation; treat if HBV DNA level meets AASLD HBV guideline treatment criteria
    - HBsAg negative; Anti-HBc positive (± anti-HBs)
      - “Insufficient data to provide recommendations”
HCC Risk Persists After DAA Therapy in Pts With HCV-Related Cirrhosis

- Retrospective analysis of 344 HCV-infected pts with CP A or B cirrhosis treated with DAAs (SVR: 89%)
  - Pts followed for 12-24 wks after treatment completion
  - No HCC at baseline, but previous HCC permitted

- Overall HCC incidence after DAA therapy: 7.6%
  - In pts without previous HCC: 3.2%
  - In pts with previous HCC: 29.0%

- More advanced liver disease and previous HCC significant risk factors for HCC after DAAs

<table>
<thead>
<tr>
<th>Factor</th>
<th>No HCC (n = 318)</th>
<th>HCC (n = 26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP class B, %</td>
<td>10.1</td>
<td>26.9</td>
<td>.02</td>
</tr>
<tr>
<td>Mean liver stiffness, kPa</td>
<td>23.2</td>
<td>28.1</td>
<td>.01</td>
</tr>
<tr>
<td>Liver stiffness, n kPa</td>
<td></td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>- kPa &lt; 21.3</td>
<td>134</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>- kPa &gt; 21.3</td>
<td>101</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Mean platelets, x 1000/mm³</td>
<td>124.4</td>
<td>102.3</td>
<td>.02</td>
</tr>
<tr>
<td>Previous HCC, n</td>
<td></td>
<td></td>
<td>.0001</td>
</tr>
<tr>
<td>- Yes</td>
<td>42</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>276</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
HCC Screening Guidelines

- **EASL-EORTC Guidelines 2012**[1]: “Pts at high risk for developing HCC should be entered into surveillance programs. Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 mos”

- **AASLD/IDSA HCV Guidance 2016**[2]: “Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for pts with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve an SVR”

• **Enter the Nonspecialist:**
  – Will Evolving Hepatitis C Therapies Reduce the Need for Specialized Care?
  • Graham R. Foster, FRCP, PhD - 10/8/2013

• **Enter the ID Pharmacist:**
  – Multidisciplinary approach to HCV care
  – Improved adherence and SVR when pharmacists involved (Chastain C, CID 2015)
  • Education/counseling; attention to DDIs and toxicities, cost evaluation

“A rapid expansion of patients and providers will mirror improving efficacies and gentler adverse event profiles...the introduction of a single-tablet regimen for HCV therapy—a development that will propel hepatitis C care to its future in nonspecialist providers offices. Information will be the key to overcoming preconceptions about adverse events and regimen complexities, finally allowing nonspecialists to take a central role in caring for HCV-infected patients”.
AbbVie Wages HCV Drug-Price War on Gilead

By Max Nisen

Max Nisen is a Bloomberg Gadfly columnist covering biotech, pharma and health care. He previously wrote about management and corporate strategy for Quartz and Business Insider.

Aug 7, 2017 8:00 AM EDT (Corrected Aug 7, 2017 2:26 PM EDT)

GILEAD SCIENCES INC  +1.81  ABBVIE INC  +0.61
AS OF 1:00 PM EDT

Pharma already leads the business world in unpredictability, with billions in sales potentially riding on a few points of statistical significance in a clinical trial.

Summary

• HCV epidemiology and treatment landscape are rapidly evolving.
• Interferon free regimens are here for majority of patients, ribavirin may not be needed for most.
• Cost remains an issue…
• Generalists and pharmacists will play an increasingly important role in HCV management going forward.
• Remember to screen for hepatitis B, and for HCC even when cure achieved.
Thank you