Activity Overview

This activity provides an overview of the assessments needed before initiating direct-acting antiviral therapy, as well as an in-depth look at available methods for evaluating liver health in patients with HCV.

Target Audience

This activity is intended for primary care clinicians.
Accreditation / Designation Statements

In support of improving patient care, Indiana University School of Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Indiana University School of Medicine designates this enduring material for a maximum of 0.5 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure Policy

In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educational programs sponsored by Indiana University School of Medicine (IUSM) must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, and planning committee members participating in an IUSM-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity.

Indiana University School of Medicine and Med-IQ require any person in a position to control the content of an educational activity to disclose all relevant financial relationships with any commercial interest. The ACCME defines “relevant financial relationships” as those in any amount occurring within the past 12 months, including those of a spouse/life partner, that could create a conflict of interest (COI). Individuals who refuse to disclose will not be permitted to contribute to this CME activity in any way. Med-IQ has policies in place that will identify and resolve COIs prior to this educational activity. Med-IQ also requires faculty to disclose discussions of investigational products or unlabeled/unapproved uses of drugs or devices regulated by the US Food and Drug Administration.

Note: While it offers CME credits, this activity is not intended to provide extensive training or certification in the field.
Disclosure Statements

The content of this activity has been peer reviewed and has been approved for compliance. The faculty and contributors have indicated the following financial relationships, which have been resolved through an established COI resolution process, and have stated that these reported relationships will not have any impact on their ability to give an unbiased presentation.

Paul Y. Kwo, MD

The peer reviewers and activity planners have no financial relationships to disclose.

Acknowledgment of Commercial Support

This activity is supported by educational grants from AbbVie Inc. and Gilead Sciences, Inc.

Copyright
© 2018 The Indiana University School of Medicine
Instructions to Receive Credit

To receive credit, read the introductory CME material, listen to the audiocast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.

Contact Information

Call (toll-free) 866 858 7434
Email info@med-iq.com

Please visit us online at www.Med-IQ.com for additional activities provided by Med-IQ®.
Learning Objectives

Upon completion, participants should be able to:

• Describe treatment potential for patients with HCV and advanced liver disease

Faculty

Paul Y. Kwo, MD
Professor of Medicine
Chief of Hepatology
Stanford University
Stanford, CA
Activity Planners

Sara C. Miller, MS
Director, QI Institute, CE Strategy and Content
Med-IQ
Baltimore, MD

Jill Phillips
Compliance and Meeting Planning Specialist
Indiana University School of Medicine
Indianapolis, IN

Samantha Gordon
CME Specialist
Med-IQ
Baltimore, MD

Global Distribution and Prevalence of HCV Genotypes

Historically, the Majority of Persons Chronically Infected With HCV Were Baby Boomers (Those Born Between 1945 and 1965)

In New York, HCV Is No Longer a Disease of Baby Boomers—Rates Are Higher in Those Aged 20 to 39 Years
Acute HCV Infections vs Deaths From Heroin Overdose

**Acute HCV Infections, 2013, by State**

**Deaths From Heroin Overdose, 2014, by County**


Hepatic Fibrosis Staging: Do Not Miss F3 or Cirrhosis

**Liver Biopsy**
- Gold standard
- Rarely done

**Elastography**
- > 12.5 kPa = cirrhosis

**Axial CT/MRI**
- Cirrhotic morphology
- Portal hypertension

**Fibrosis Serum Biomarkers**
- APRI and FIB-4 have very good negative predictive value
- APRI < 0.5 and FIB-4 < 1.45 rule out cirrhosis
- Commercial serum fibrosis tests are also available in the US
  - F3/F4 fibrosis, screen for HCC
  - F4 fibrosis, may need to screen for esophageal varices

AASLD-IDSA. hcvguidelines.org.
HCV Treatment: Assessing Fibrosis

- Is used by some payers to determine urgency of therapy
- Identifies patients with cirrhosis in need of additional screening
  - Varices
  - Hepatocellular carcinoma
  - Decompensated cirrhosis (cannot use protease inhibitors)
- Allows for the selection of a proper treatment plan and duration of therapy

Child-Turcotte-Pugh Classification

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade 1-2 (or precipitant-induced)</td>
<td>Grade 3-4 (or chronic)</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild/Moderate (diuretic-responsive)</td>
<td>Severe (diuretic-refractory)</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2-3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>PT (see prolonged) or INR</td>
<td>&lt; 4</td>
<td>4-6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.7</td>
<td>1.7-2.3</td>
<td>&gt; 2.3</td>
</tr>
</tbody>
</table>

- CTP score: Obtained by adding the score for each parameter
- CTP class: A = 5-6 points; B = 7-9 points; C = 10-15 points

AASLD-IDSA. hcvguidelines.org.

Many Special Populations Are No Longer Special

<table>
<thead>
<tr>
<th>Population</th>
<th>SVR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black/Hispanic Race</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>HIV/HCV Coinfection</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>Post Orthotopic Liver Transplant</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>CKD/Dialysis</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>PWID/Opioid Agonist Treatment</td>
<td>&gt; 95%</td>
</tr>
</tbody>
</table>

• Those with decompensated cirrhosis who have failed therapy remain one of the few special populations in need of additional therapies
• Protease inhibitors cannot be given in decompensated cirrhosis

FDA-Approved DAAs From Multiple Classes

<table>
<thead>
<tr>
<th>5'UTR</th>
<th>Core</th>
<th>E1</th>
<th>E2</th>
<th>NS2</th>
<th>NS3</th>
<th>NS4B</th>
<th>NS5A</th>
<th>NS5B</th>
<th>3'UTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>NS3 Protease Inhibitors</td>
<td>NS5A Replication Complex Inhibitors</td>
<td>NS5B NUC Inhibitors</td>
<td>NS5B Non-NUC Inhibitors (NNI)</td>
<td>3'UTR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boceprevir (BOC)</td>
<td>Daclatasvir (DCV)</td>
<td>Sofosbuvir (SOF)</td>
<td>Dasabuvir (DSV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telaprevir (TVR)</td>
<td>Ledipasvir (LDV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir (SMV)</td>
<td>Ombitasvir (OMV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir (PTV)</td>
<td>Elbasvir (EBR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grazoprevir (GZR)</td>
<td>Velpatasvir (VEL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All First-Line Treatment Options Lead to SVR Rates Greater Than 95%

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis</th>
<th>Adverse Events (occurring in ≥ 10% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EBR/GZR³</td>
<td>EBR/GZR²</td>
<td>Fatigue, headache, nausea</td>
</tr>
<tr>
<td></td>
<td>GLE/PIB</td>
<td>GLE/PIB</td>
<td>Fatigue, headache</td>
</tr>
<tr>
<td></td>
<td>LDV/SOF</td>
<td>LDV/SOF</td>
<td>Fatigue, headache, nausea</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
<td>Fatigue, headache, nausea, anemia</td>
</tr>
<tr>
<td>2/3</td>
<td>GLE/PIB</td>
<td>GLE/PIB</td>
<td>Fatigue, headache</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
<td>Fatigue, headache, nausea, anemia</td>
</tr>
<tr>
<td>4</td>
<td>EBR/GZR</td>
<td>EBR/GZR</td>
<td>Fatigue, headache, nausea</td>
</tr>
<tr>
<td></td>
<td>GLE/PIB</td>
<td>GLE/PIB</td>
<td>Fatigue, headache</td>
</tr>
<tr>
<td></td>
<td>LDV/SOF</td>
<td>LDV/SOF</td>
<td>Fatigue, headache, nausea</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
<td>Fatigue, headache, nausea, anemia</td>
</tr>
<tr>
<td>5/6</td>
<td>GLE/PIB</td>
<td>GLE/PIB</td>
<td>Fatigue, headache</td>
</tr>
<tr>
<td></td>
<td>LDV/SOF</td>
<td>LDV/SOF</td>
<td>Fatigue, headache, nausea</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
<td>Fatigue, headache, nausea, anemia</td>
</tr>
</tbody>
</table>

*No NS5A RAS.

Recommended Assessments Prior to Starting Antiviral Therapy

- Patients scheduled to receive an HCV NS3 protease inhibitor should be assessed for a history of decompensated liver disease and for liver disease severity using the CTP calculator
  - Patients with current or prior history of decompensated liver disease or a current CTP score ≥ 7 should not receive treatment with regimens that contain NS3 protease inhibitors due to increased blood levels and/or lack of safety data
  - Similarly, patients with a CTP score of 5 or 6 who cannot be closely monitored for laboratory or clinical symptoms during treatment should not receive treatment with a regimen that contains paritaprevir/ritonavir
- Testing for the presence of RASs prior to starting treatment should be performed as recommended; rarely needed, but examples in which it would be warranted include:
  - In genotype 1a patients who are being considered for elbasvir, test for RAS at positions 28, 30, 31, or 93
  - For genotype 3 patients with cirrhosis who are being considered for velpatasvir, test for RAS at Y93
  - DAA failures

AASLD-IDSA. hcvguidelines.org
HBV Testing/Monitoring During HCV DAA Therapy

• Test all patients initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  – Vaccinate if no HBV markers present; follow flowchart below if HBV markers present

- HBsAg positive
  - HBV DNA detectable
    - HBV DNA meets criteria for treatment in AASLD HBV guidelines
    - Treat with HBV drug
  - Low or HBV DNA 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"
    - (Consider HBV reactivation if clinical symptoms or ALT rise)

Most Patients With HCV Viremia Should Be Considered Treatment Candidates if They Can Adhere to Therapy

AASLD-IDSA Treatment Guidelines:
• Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions
**C-EDGE CO-STAR: Study Design**

- Dedicated study in PWID
- Phase 3, randomized, parallel-group, placebo-controlled trial
- Patients:
  - Treatment naïve; genotypes 1, 4, and 6; ± cirrhosis (20%); ± HIV/HCV coinfection (7%)
  - On opioid agonist therapy for at least 3 months and consistently kept at least 80% of scheduled appointments while on opioid agonist therapy

![Study Design Diagram]

---

**C-EDGE CO-STAR: Efficacy Results (ITG)**

![Efficacy Results Chart]

Includes one subject with mixed infection (GT 1a and GT 1b) who achieved SVR12.

---

AASLD-IDSA HCV Treatment Guidelines: PWID

• “Recent and active IDU should not be seen as an absolute contraindication to HCV therapy”
• “Scale up of HCV treatment in PWID is necessary to positively impact the HCV epidemic in the United States and globally”

Recommended Monitoring During Antiviral Therapy

• Clinic visits or telephone contact is recommended as clinically indicated
  – Ensure medication adherence
  – Monitor for adverse events
  – Assess for potential drug-drug interactions with newly prescribed medications
• CBC, creatinine level, eGFR, and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated
• Quantitative HCV viral load testing is recommended 4 weeks after therapy initiation and 12 weeks after therapy completion
• Antiviral drug therapy should not be interrupted or discontinued if HCV RNA level evaluations are not performed or available during treatment
Follow-Up of Sustained Response (SVR or Cure)

- SVR is durable
- Liver complications and HCV-related complications will decrease, not disappear
- If ALT is still elevated post SVR, it must be explained (eg, NAFLD, alcohol, drug, reinfection)
- Risk of HCC decreases markedly, but does not disappear entirely; screen F3/F4 patients for HCC (ultrasound and AFP every 6 months)
- Reinfection is possible; educate those with high-risk behaviors about risk reduction (PWID/MSM)
- Do not dismiss F3/F4 patients from clinic

History and Evolving Landscape of HCV Therapy

HCV Therapy Has Paralleled *Helicobacter pylori* Therapy

**H. pylori**

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Duration</th>
<th>Eradication Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole (Prilosec)</td>
<td>14 days</td>
<td>80-86</td>
</tr>
<tr>
<td>Lansoprazole (Prevacid)</td>
<td>10-14 days</td>
<td>86</td>
</tr>
<tr>
<td>Bismuth subsalicylate (Pepto-Bismol)</td>
<td>14 days</td>
<td>80</td>
</tr>
</tbody>
</table>

**HCV**

All Oral Therapy

- Duration 8-24 Weeks
- Polymerase Inhibitor ± Protease Inhibitor ± NS5a ± Non-Nucleoside Inhibitor ± Ribavirin

---

HCV Can Be Eliminated

- No non-human reservoir exists
- Simple and accurate diagnostic tools are available
- Transmission can be prevented
- Infection can be cleared from host
- Highly effective, safe drugs exist that are given for a finite period
  - Most unique populations are now routinely treated
- We are entering the era of pan-genotypic therapies
- HCV elimination can be achieved but only with screening and linkage-to-care strategies that lead to treatment

© 2018

Unless otherwise indicated, photographed subjects who appear within the content of this activity or on artwork associated with this activity are models; they are not actual patients or doctors.