Hepatitis C for Primary Care: From Diagnosis to Cure and Beyond


28 MAY 2020
1245-1345 ET
Presenters

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Dr. Rife currently works as a Liver/Gastroenterology Clinical Pharmacist at the VA Northeast Ohio Healthcare System in a highly integrated interdisciplinary medical team. She sees patients in clinic and via telemedicine to initiate and follow-up on their HCV treatment regimens.

She has been highly involved in various research and quality improvement projects using Lean Six-Sigma methodology.

She additionally serves as the Clinical Program Manager of Academic Affairs to oversee education of pharmacists and trainees. Dr. Rife is a Clinical Instructor of Pharmacy Practice at Northeast Ohio Medical University and serves as a preceptor for pharmacy residents and students.
Dr. Kristina Pascuzzi Frangella earned her Bachelor of Science in Pharmaceutical Sciences in 1999, then her Doctorate of Pharmacy degree in 2001, both from the University of Toledo. Upon graduation, she completed her PGY1 Pharmacy Practice Residency with emphasis in Ambulatory Care at VA Connecticut Healthcare System in West Haven, CT. She earned her Board Certification in Pharmacotherapy in 2005, Certified Diabetes Educator certification in 2011, and her Board Certification in Ambulatory Care Pharmacy in 2015. Dr. Pascuzzi Frangella currently works as a PACT Clinical Pharmacist at the Wade Park campus of VA Northeast Ohio Healthcare System in Cleveland, OH. She sees patients in clinic and via telemedicine for chronic disease state management, with an emphasis on diabetes, hypertension, and dyslipidemia. Dr. Pascuzzi Frangella serves as a preceptor for pharmacy residents and students. She was the residency program director for the PGY2 Ambulatory Care Pharmacy residency program for nine years.
Disclosures

- Dr. Kelsey Rife and Dr. Kristina Pascuzzi Frangella have no relevant financial or non-financial relationships to disclose relating to the content of this activity.

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Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Assess patients at risk of Hepatitis C virus (HCV) and suggest appropriate testing for diagnosis.
2. Distinguish appropriate counseling and management options for patients with HCV.
3. Demonstrate the impact successful HCV treatment may have on patients’ diabetes.
Polling Questions

1. Who feels comfortable diagnosing hepatitis C?
2. Who feels comfortable treating hepatitis C?
Outline

- Hepatitis C (HCV) epidemiology
- Addressing the needs of your HCV patients
- HCV treatment and drug interactions
- Benefits beyond the Liver
Epidemiology – United States (US)

- Most common blood-borne infection
- Leading cause for end stage liver disease, hepatocellular carcinoma, and liver transplantation in US

http://www.cdc.gov/hepatitis
HCV Etiology

- Single-stranded RNA virus of Flaviviridae family
  - Lacks proofreading polymerase > frequent viral mutations

(Forns, X. et al, 1999)
HCV Screening

- All adults aged 18-70 years: one-time screening
  - Updated in 2020 from previous 1945-1965 “birth cohort” screening recommendation

- Additional risk factors
  - Blood transfusion before 1992
  - IV drug use
  - Blood exposure in job or military
  - Body piercing/tattoos in informal setting
  - High risk sexual behavior
  - History of hemodialysis
Prevent Spread of Virus

Safe
- Not transmitted through casual contact
  - Hugging
  - Kissing
  - Sharing a glass
  - Eating off the same plate

Avoid
- Do not share personal items
  - Razor
  - Toothbrush
  - Cuticle scissors
Natural History of HCV

Clinical Presentation: often asymptomatic prior to development of cirrhosis
Complications from HCV

**Hepatic**
- Cirrhosis
- End-stage liver disease
- Hepatocellular carcinoma
- #1 indication for liver transplantation in U.S.

**Extrahepatic**
- Cryoglobulins: immune complexes
  - Vasculitis
  - Glomerulonephritis
  - Dermatologic disorders-Sjögren’s syndrome
  - Arthritis
- Impaired glucose tolerance
- Fatigue
- Pain
Diagnosis

HCV Antibody

HCV Antibody screens for exposure to HCV

(-)

No Exposure to HCV

(+)

HCV RNA

HCV Ribonucleic Acid (RNA) detects active replicating HCV

Undetected

No Current Infection

Quantifiable

<6 months: Acute

≥6 months: Chronic

Additional Diagnostic Tests to guide regimen selection:

- Genotype (blood test)
- Cirrhosis status (variety of tests may determine degree of fibrosis)
Patient Counseling

- Avoid Alcohol
- Avoid sharing personal items
- Demonstrate good medication adherence
  - Goal 100% adherence to HCV regimen
  - Avoid break in therapy
- Maintain healthy diet and regular exercise routine
Alcohol = “Gasoline on a Fire”

- Clinical consequences

  - Increased rate of fibrosis and cirrhosis
  - Increased severity of HCV infection
  - Increased rates of Hepatocellular Carcinoma (HCC)

Harm Reduction Strategies

- Assessing for amounts/types of alcohol
- Not sharing needles
- Needle exchange programs
- Treatment groups
- Safe sex practices
- Removing patients from high risk settings
- Stable housing
HAV & HBV Immunizations

- Hepatitis A (HAV)
- Hepatitis B (HBV)

- Combination Hepatitis A/Hepatitis B vaccine
  - Standard
    - Day 0, month 1, and month 6
  - Accelerated
    - Day 0, 7, 21-30, booster at month 12

<table>
<thead>
<tr>
<th>Twinrix Dose</th>
<th>% Seroconversion for HAV</th>
<th>% Seroconversion for HBV</th>
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<tbody>
<tr>
<td>1</td>
<td>93.8</td>
<td>30.8</td>
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<td>2</td>
<td>98.8</td>
<td>78.2</td>
</tr>
<tr>
<td>3</td>
<td>99.9</td>
<td>98.5</td>
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</table>
Other Immunizations

- Influenza Vaccine
  - Indicated in chronic liver disease patients

- Pneumococcal Vaccine
  - Pneumococcus implicated in severe sepsis and SBP episodes
  - PneumoRecs Vax Advisor: [https://www2a.cdc.gov/vaccines/m/pneumo/pneumo.html](https://www2a.cdc.gov/vaccines/m/pneumo/pneumo.html)
  - Liver disease: Pneumovax 23 indicated < 65 years and 1 dose > 65 years
  - > 65 years old Prevnar 13 (PCV13) falls under shared decision making
Cirrhosis Identification

- Transient elastography
  - ≤ 9.5 kPa: rule out cirrhosis
  - ≥ 12.5 kPa: follow cirrhosis HCV treatment guidance
  - ≥ 19.5 kPa: screen for varices
- Radiographic
  - Surface nodularity
  - Hepatomegaly, splenomegaly
  - Ascites
- Biochemical
  - Platelet count < 150
  - ↑ bilirubin, ↓ albumin, ↑ Internal Normalized Ratio (INR)
- Clinical

(Lim J. K. et al., 2017)
Hepatocellular Carcinoma

Epidemiology
- 5th most common type of cancer in men, 9th in women
- Annual US incidence: 6 per 100,000 in 2010 (rates increasing)
  - Death rate is similar to incidence rate

HCC in chronic HCV
- Occurs in advanced liver disease
- HCV treatment decreases but does not eliminate risk

Current recommendations
- Screen at 6-month intervals using ultrasound ± alpha-fetoprotein (AFP)
  - AFP: low sensitivity
  - Ultrasound: sensitivity low in lesions < 1 cm
  - Triple phase CT scan: improved sensitivity when lesions unable to be characterized on ultrasound

Goal of Treatment for HCV

- Sustained virologic response (SVR):
  - Undetectable HCV RNA in serum ≥12 weeks post treatment using polymerase chain reaction (PCR) assay
Evolution of Hepatitis C Treatment

Interferon (IFN) x18-24months
SVR ~9%*

1991

Ribavirin (RBV) + Peg-interferon (PegIFN) x48wks
SVR 40-50%*

1998

Boceprevir/ Telaprevir
(1' gen direct-acting antivirals (DAAs))
+ RBV + PegIFN x36-48weeks
SVR ~70%*

2011

Sofosbuvir/ Simeprevir +
RBV + PegIFN
x12-24wks
SVR ~90%*

2013

Interferon-free regimens x8-12weeks
SVR >90%*

2014

*SVR rates reported for genotype (GT) 1
HCV DAA Targets

NS3/4A Protease Inhibitors (--previr)
- Boceprevir
- Telaprevir
- Simeprevir
- Paritaprevir
- Grazoprevir
- Voxilaprevir
- Glecaprevir

NS5A Inhibitors (--asvir)
- Ledipasvir
- Ombitasvir
- Daclatasvir
- Elbasvir
- Velpatasvir
- Pibrentasvir
- (Jameson, J. L. et al, 2017)

NS5B Polymerase Inhibitors (--buvir)
- Nucleoside analogs
  - Sofosbuvir
- Non-nucleoside analogs
  - Dasabuvir

Withdrawn
## DAA Products

<table>
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<tr>
<th>Generic</th>
<th>Brand Name</th>
<th>Genotype</th>
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<tbody>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>Harvoni®</td>
<td>1, 4, 5, 6</td>
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<tr>
<td>Elbasvir/grazoprevir</td>
<td>Zepatier™</td>
<td>1, 4</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>Epclusa®</td>
<td>1-6</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir/voxilaprevir</td>
<td>Vosevi®</td>
<td>DAA Retreatment: 1-6</td>
</tr>
<tr>
<td>Glecaprevir/pibrentasvir</td>
<td>Mavyret™</td>
<td>Naïve &amp; IFN-exp.: 1-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DAA Retreatment: 1</td>
</tr>
</tbody>
</table>

- Well-tolerated, all-oral medications
- Typical treatment durations 8-12 weeks
- SVR rates ~95%+
- Ribavirin still used as “booster” for patients with poor outcome predictors such as decompensated cirrhosis
Treatment Decisions

- **Genotype (GT)**
  - GT 1-6

- **HCV Genotypes in US**
  - Genotype 1: 76%
  - Genotype 2: 17%
  - Genotype 3: 7%

- **Treatment history**
  - Naïve or interferon experienced?
  - History of direct-acting antivirals?
    - Protease inhibitors v. NS5A inhibitors?

- **Cirrhosis determination**
  - Biopsy
  - Transient elastography >12.5 kPa
  - Aspartate Aminotransferase -to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) score
Additional Considerations in Regimen Selection

- Renal function
-Severity of cirrhosis
  - Compensated (Child-Pugh A) versus decompensated (Child-Pugh B or C)
- Cost-effectiveness
- Length of therapy
- Pill burden
- Drug interactions
- Comorbidities
Common Drug Interactions - PPIs and H2RAs

- Acid-reducing agents
  - Interacting regimens:
    - Ledipasvir/sofosbuvir
    - Sofosbuvir/velpatasvir (or sofosbuvir/velpatasvir/voxilaprevir)
    - Glecaprevir/pibrentasvir
  - Concern:
    - HCV antivirals require an acidic environment for absorption; acid-reducing agents may reduce absorption > levels > efficacy of HCV antivirals
  - Recommendations:
    - Proton Pump Inhibitors (PPIs): depending on regimen, may need avoided or limit to max equivalent dose of omeprazole 20mg
    - H2 antagonists (H2RA): max equivalent dose of famotidine 40mg q12h dosed at same time and/or 12 hours after HCV antiviral
    - Antacids: space four hours before or after HCV antiviral
Common Drug Interactions - Statins and P-gp Inducers

- Statins
  - Interacting regimens: ALL
  - Concern:
    - HCV antivirals increase levels/risk of adverse effects of statins
  - Recommendations:
    - Indication for statin 1' prevention: HOLD statin until end of treatment
    - Indication for statin 2' prevention: SWITCH to pravastatin (max dose varies by HCV DAA) until end of HCV treatment

- Potent P-glycoprotein (P-gp) inducers:
  - Interacting regimens: ALL
  - Concern:
    - Increase metabolism and decrease efficacy of HCV antivirals
  - Recommendations:
    - Phenytoin, carbamazepine, oxcarbazepine, etc.: consult to prescribing clinician if patient may be changed to alternative therapy to proceed with HCV treatment
Benefits of HCV Treatment Beyond the Liver

- May improve extrahepatic manifestations:
  - Cryoglobulins: may be severe, but uncommon (2-6%)
    - Vasculitis
    - Glomerulonephritis
    - Dermatologic disorders - Sjögren’s syndrome
    - Arthritis
  - Fatigue (50%+)
  - Depression (up to 28%)
  - Type 2 diabetes (~30%)
HCV and Diabetes

- Multifactorial:
  - Comorbid fatty liver disease
  - Fibrosis/cirrhosis
  - HCV core protein ↑phosphorylation of insulin receptor substrate-1
  - ↑Tumor necrosis factor alpha (TNF-α)
    - Effects on insulin receptor substrate-1
    - Mediate hepatic insulin resistance
    - Stimulate lipolysis
    - Down-regulate peroxisome proliferator-activated receptor-γ
    - Interfere with β-cell function
Objective: assess impact of HCV DAA treatment on glucose control in Veteran patients with Type 2 Diabetes Mellitus (T2DM) at a single center

Primary Endpoint: change in hemoglobin A1c \( (\text{HbA}_{1c}^{}) \) up to 4-months post-treatment in patients achieving sustained virologic response after 12 weeks (SVR12) from HCV treatment

Secondary Endpoints:
- Change in \( \text{HbA}_{1c}^{} \) up to 12- & 18-months post-treatment in patients achieving SVR12
- Change in antihyperglycemic regimen
- Change in \( \text{HbA}_{1c}^{} \) and antihyperglycemics in HCV treatment relapses vs. those who achieved SVR12

(Rife K. et al, 2019)
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Patients N = 157 (%)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean=62, SD=5.1, Range [45-86]</td>
</tr>
<tr>
<td>Male</td>
<td>151 (96%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>88 (56%)</td>
</tr>
<tr>
<td>Caucasian non-Hispanic</td>
<td>55 (35%)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Advanced Fibrotic Liver Disease</td>
<td>66 (42%)</td>
</tr>
<tr>
<td>SVR12 Achieved</td>
<td>147 (94%)</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>134 (85%)</td>
</tr>
<tr>
<td>Regimens</td>
<td></td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir +/- ribavirin</td>
<td>122 (78%)</td>
</tr>
<tr>
<td>Sofosbuvir + ribavirin +/- peginterferon</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- ribavirin</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Sofosbuvir + simeprevir</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Velpatasvir/sofosbuvir + ribavirin</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>No. of Antihyperglycemic Medications</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>64 (41%)</td>
</tr>
<tr>
<td>2</td>
<td>62 (39%)</td>
</tr>
<tr>
<td>3</td>
<td>27 (17%)</td>
</tr>
<tr>
<td>4</td>
<td>4 (3%)</td>
</tr>
</tbody>
</table>

(Rife K. et al, 2019)
HCV and DM: Outcomes

- Decreased HbA$_{1c}$ 0.67% at 4-months post-treatment in patients who achieved SVR12
  - 7.67% → 7.00% ($p < 0.001$)
- Larger decline in HbA$_{1c}$ for patients with higher HbA$_{1c}$ at baseline
  - Up to ~3% in patients with baseline HbA$_{1c}$ ≥10%
  - Sustained changes at 12- and 18-months post-treatment
- Antihyperglycemics decreased in 30% of patients achieving SVR12
- Comparison of relapsers limited by small numbers (n=8)

(Rife K. et al, 2019)
HCV and DM: Summary

- 80% patients on antihyperglycemics had either a decrease in their HbA$_{1c}$ or a de-escalation of their regimen after successful HCV treatment.
- Larger, sustained decline in HbA$_{1c}$ for patients with worse control at baseline.
- Warrants close follow-up for T2DM undergoing/recently completed HCV treatment.
- Potential significant benefits of HCV treatment for health outcomes, quality of life, and long-term cost avoidance beyond liver-related morbidity & mortality.

(Rife K. et al, 2019)
Key Takeaways

- Significant advancements in HCV treatment have led to well-tolerated, highly curative regimens.
- Identification and referral/management of cirrhosis remains an important role for primary care providers.
- HCV treatment may improve diabetes control in addition to its well-known ability to decrease liver-related morbidity & mortality.
References


Division of Viral Hepatitis Home Page. (2020, April 8). http://www.cdc.gov/hepatitis


Resources

www.cdc.gov/hepatitis/hcv/index.htm
www.hcvguidelines.org
www.hep-druginteractions.org
www.hepatitis.va.gov
Questions?

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