Hepatitis C
Screening and Treatment

October 11, 2018

A Department of Social Services
PCMH Presentation hosted by
Community Health Network of Connecticut, Inc.
Discussion Topics & Objectives

- **Hepatitis C Overview**
  - Provide important background information about hepatitis C
  - Review risk factors

- **Hepatitis C Screening**
  - Discuss significance of hepatitis C screening

- **Hepatitis C Testing and Diagnosis**
  - Understand test results and convey results to patients

- **Hepatitis C Treatment**
  - Review treatment strategies and current pharmacologic therapies

- **Hepatitis C Quality Improvement Project (QIP)**
  - Review goals and member and provider interventions
Hepatitis C Facts

- Hepatitis C is a liver infection caused by the hepatitis C virus (HCV)
- HCV is the most common blood-borne virus in the United States
- Hepatitis C can be either acute or chronic
  - 15% to 30% of cases are acute
  - 70% to 85% of cases become long-term, chronic infections
- An estimated 3.5 million people in the United States have chronic hepatitis C
- The majority of infected persons may not be aware of their infection

https://www.cdc.gov/hepatitis/hcv/index.htm
Risk Factors

- Current or former injection drug users
  - Even those who injected only once many years ago
- Recipients of clotting factor concentrates made before 1987 or blood transfusions/solid organ transplants prior to July 1992
  - This was before more advanced methods for manufacturing and testing of blood donors became available
- Chronic hemodialysis patients
- People with known exposure to HCV, such as:
  - Healthcare workers after needle sticks involving HCV-positive blood
  - Recipients of blood or organs from a donor who tested HCV-positive
- People with human immunodeficiency virus (HIV) infection
- Children born to HCV-positive mothers

*Injection drug use is currently the most common means of HCV transmission in the U.S.*
Risk Factors cont.

- Although infrequent, HCV can also be spread through:
  - Sex with an HCV-infected person
    - Generally an inefficient means of transmission
    - HIV-infected men who have sex with men (MSM) have increased risk of sexual transmission
  - Sharing personal items contaminated with infectious blood, such as razors or toothbrushes (also an inefficient means of transmission)
  - Other healthcare procedures that involve invasive procedures, such as injections (usually recognized in the context of outbreaks)
  - Unregulated tattooing

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm
Hepatitis C Screening

Why Screen?

- About half of those living in the United States that have HCV are unaware of their infection because they may not have any clinical signs or symptoms.

- Hepatitis C is a leading cause of liver transplants and liver cancer.
  - Annual HCV-associated mortality in the United States increased more than 50% from 1999 to 2007.
  - People born during 1945-1965 account for 73% of all HCV-associated deaths.

- New therapies, including interferon-free regimens, can halt disease progression and provide a virologic cure in most HCV-infected persons. These treatment options increase the effectiveness and reduce the duration of therapy for many patients.

- Testing people born between 1945 and 1965 and linking them to care can avert more than 120,000 HCV-related deaths and save $1.5 - 1.7 billion in liver disease related costs.

[https://www.cdc.gov/hepatitis/resources/professionals/pdfs/counselingandtestingpc.pdf](https://www.cdc.gov/hepatitis/resources/professionals/pdfs/counselingandtestingpc.pdf)
Hepatitis C Screening Recommendations

- The Centers for Disease Control and Prevention (CDC) recommends HCV screening for:
  - Adults born 1945-1965 (without prior ascertainment of HCV risk) “Baby Boomers”
    - National prevalence data show that people born during these years have a five times higher prevalence of hepatitis C than other adults
  - Current or former injection drug users, even if just once
  - Recipients of clotting factors made before 1987
  - Recipients of blood transfusions or solid organ transplants prior to July 1992
  - Chronic hemodialysis patients
  - Healthcare workers after needle sticks involving HCV-positive blood
  - Recipients of blood or organs from a donor who tested HCV-positive
  - People with HIV infection
  - Children born to HCV-positive mothers

- U.S. Preventive Services Task Force also recommends HCV testing for:
  - Incarcerated persons
  - People who use intranasal drugs
  - People who get an unregulated tattoo

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section3
Testing and Diagnosis for Hepatitis C

- Several blood tests are performed to test for HCV infection:
  - Screening tests for antibody to HCV (anti-HCV)
    - Enzyme immunoassay (EIA)
    - Enhanced chemiluminescence immunoassay (CIA)
  - Confirmatory tests for active HCV RNA
    - Qualitative tests to detect presence or absence of virus (HCV RNA polymerase chain reaction [PCR])
    - Quantitative tests to detect amount (titer) of virus (HCV RNA PCR)
- Testing should be initiated with anti-HCV. A reactive result should be followed by a nucleic acid test (NAT) for HCV ribonucleic acid (RNA).
- If the HCV RNA PCR test(s) is positive, this is indicative of a current, chronic HCV infection; testing for HCV genotype is subsequently performed to guide selection of appropriate medication regimen
- For anyone who may have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1
Testing for Hepatitis C Infection

Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

- **HCV antibody**
  - Nonreactive
    - No HCV antibody detected
    - STOP
  - Reactive
    - Not Detected
      - No current HCV infection
      - Additional testing as appropriate†
    - Detected
      - Current HCV infection
      - Link to care

† 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 is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† 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.

Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratories. MMWR 2015;64(18).
## Interpretation of Test Results

<table>
<thead>
<tr>
<th>TEST OUTCOME</th>
<th>INTERPRETATION</th>
<th>FURTHER ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody nonreactive</td>
<td>No HCV antibody detected</td>
<td>Sample can be reported as nonreactive for HCV antibody. No further action required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If recent exposure in person tested is suspected, test for HCV RNA.*</td>
</tr>
<tr>
<td>HCV antibody reactive</td>
<td>Presumptive HCV infection</td>
<td>A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA detected</td>
<td>Current HCV infection</td>
<td>Provide person tested with appropriate counseling and link person tested to care and treatment.†</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA not detected</td>
<td>No current HCV infection</td>
<td>No further action required in most cases.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In certain situations,§ follow up with HCV RNA testing and appropriate counseling.</td>
</tr>
</tbody>
</table>

* If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.
† It is recommended before initiating antiviral therapy to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.
§ If the person tested is suspected of having 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.


https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf
Providing Positive Test Results

- When first hearing the test result, the patient may have a strong emotional reaction
- The patient may want additional information immediately or may need some time to process what he/she has just heard. Take a cue from his or her reaction.
- Convey a positive message about the test result:
  - Many people with hepatitis C remain healthy throughout their lives
  - There are treatments available that can cure hepatitis C for many people
  - There is a lot you can do to keep yourself healthy
  - You can find out if you have liver damage
  - You can start doing things to take care of your liver and prevent more damage
  - You can prevent transmitting the virus to others

Counseling Patients

- Newly diagnosed patients should be informed about the effectiveness and benefits of new direct acting antivirals (DAAs) and referred for prompt assessment and treatment, if indicated.
- Patients should be advised to **avoid alcohol** because it can accelerate cirrhosis and end-stage liver disease.
- Patients should be counseled on measures to prevent transmission.
- Viral hepatitis patients should also check with a health professional before taking any new prescription pills, over-the-counter drugs (such as non-aspirin pain relievers/APAP), or supplements.
- Clinicians may wish to consider vaccinating HCV-positive patients against hepatitis A and hepatitis B even in the absence of liver disease.
- Vaccination against pneumococcal infection is recommended in all patients with cirrhosis.

**A guide to comprehensive HCV counseling and testing for primary care providers (PCPs) is available on the CDC website:**

[https://www.cdc.gov/hepatitis/resources/professionals/pdfs/counselingandtestingpc.pdf](https://www.cdc.gov/hepatitis/resources/professionals/pdfs/counselingandtestingpc.pdf)
Referral to Treatment for Substance Use

60% of HCV transmission in the U.S. is due to injection drug use

- People who inject drugs illicitly should receive screening and treatment for their substance use and alcohol use as well as education about reinfection with hepatitis C
- Reinfection is likely to occur among people who currently engage in high-risk practices that spread the virus
- The CDC recommends that all persons identified with HCV infection should receive brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment
- Studies have shown that prevention strategies including medication-assisted treatment with prevention counseling and/or supports for safe injection practices can reduce the incidence of HCV infection by 75% for people who had ever injected drugs
- Refer HUSKY Health members to CT Behavioral Health Partnership. Call 1.877.552.8247 for information on finding treatment options

https://store.samhsa.gov/shin/content/SMA15-4917/SMA15-4917.pdf
Further Testing

- The following additional tests are recommended within 12 weeks prior to starting therapy:
  - Complete blood count (CBC)
  - International normalized ratio (INR)
  - Hepatic function panel (i.e., albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels)
  - Calculated glomerular filtration rate (eGFR)

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

- Quantitative HCV viral load testing is recommended after 4 weeks of therapy and 12 weeks after completion of therapy

- Select other tests may be indicated depending on which therapy is initiated

Treatment

- HCV treatment administered independently by PCPs is safe and effective. This can significantly expand the scale of HCV therapy.

- Patients with a positive test result should be evaluated for chronic liver disease:
  - Assessment of liver function tests
  - Evaluation for severity of liver disease
  - Recommended HCV treatment
  - Determination of the need for hepatitis A and hepatitis B vaccination

Goal of Treatment

Why treat?
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)

- SVR is defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy
- Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation as reflected by improved aminotransferase levels (i.e., ALT and AST), and a reduction in the rate of liver fibrosis progression
- Among HCV-infected persons, SVR is associated with a >70% reduction in the risk of liver cancer, and a 90% reduction in the risk of liver-related mortality and liver transplantation
- Patients who achieve SVR have a substantially improved quality of life, which spans their physical, emotional, and social health

Who to treat?
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. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert.

- Patients with acute HCV should not be treated unless HCV RNA persists after 6 months

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1
Pharmacologic Therapies

- Older Therapies
  - PEGINTRON® (Peg-interferon alfa-2b) & PEGASYS® (Peg-interferon alfa-2a)
  - COPEGUS®/RIBASPHERE®/MODERIBA® (Ribavirin)

- Newer Therapies
  - SOVALDI® (Sofosbuvir)
  - HARVONI® (Ledipasvir-Sofosbuvir)
  - VIEKIRA® (Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir)
  - TECHNIVIE® (Ombitasvir-Paritaprevir-Ritonavir)
  - DAKLINZA® (Daclatasvir)
  - ZEPATIER® (Elbasvir-Grazoprevir)
  - EPCLUSA® (Sofosbuvir-Velpatasvir)
  - MAVYRET® (Glecaprevir-Pibrentasvir)
  - VOSEVI® (Sofosbuvir-Velpatasvir-Voxilaprevir)

Note: treatments that are no longer indicated or no longer on the market will not be discussed.
Pharmacologic Treatments: Older Therapies

PEGINTRON (Peg-interferon alfa-2b) & PEGASYS (Peg-interferon alfa-2a)

- FDA Approved 2001 & 2002
- **Mechanism of Action:** exert antiviral effects by augmenting the production and/or release of specific enzymes
- **Indications:**
  - Treatment of adults with chronic HCV with compensated liver disease as part of a combination regimen with other HCV antiviral drugs
  - Treatment of pediatric patients 5 years and older with chronic HCV and compensated liver disease in combination with ribavirin
  - Treatment (as a single agent) of chronic HCV in patients with compensated liver disease with contraindications or significant intolerance to other HCV antiviral drugs
    - Of note: monotherapy is no longer recommended per the HCV guidelines due to advent of newer agents, although an indication still exists

Pharmacologic Treatments: Older Therapies cont.

PEGINTRON (Peg-interferon alfa-2b) & PEGASYS (Peg-interferon alfa-2a)

- **Dosage:** injectable therapies administered in abdomen or thigh
  - 1.5 mcg/kg/week **SQ ONCE WEEKLY** x 24-48 weeks (Peg-interferon alfa-2b)
  - 180 mcg **SQ ONCE WEEKLY** x 24-48 weeks (Peg-interferon alfa-2a)

- Not specific to HCV, active against other RNA viruses
- Usually given in combination with oral *ribavirin* or other HCV antiviral drugs
- Bad side effects
  - Flu-like symptoms upon administration
  - Fatigue, alopecia, headache, rigors, insomnia, anxiety, depression, nausea/vomiting, myalgia, neutropenia, increased ALT
  - **Black box warning:** may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders

- Limited efficacy
- Long treatment course
Pharmacologic Treatments: Older Therapies cont.

**COPEGUS/RIBASPHERE/MODERIBA (Ribavirin)**

- **Mechanism of Action:** inhibits replication of RNA and DNA viruses
- Always used in combination with other therapies
- **Dosage:** TWICE DAILY dosing, with food
  - Weight-based dosing varies from 800-1400 mg/day
  - Up to 48 weeks of therapy, depends on regimen

<table>
<thead>
<tr>
<th>Weight</th>
<th>Ribavirin capsule daily dosage</th>
<th>Number of ribavirin capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 66 kg</td>
<td>800 mg/day</td>
<td>2 × 200 mg capsules in the morning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 × 200 mg capsules in the evening</td>
</tr>
<tr>
<td>66 to 80 kg</td>
<td>1,000 mg/day</td>
<td>2 × 200 mg capsules in the morning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 × 200 mg capsules in the evening</td>
</tr>
<tr>
<td>81 to 105 kg</td>
<td>1,200 mg/day</td>
<td>3 × 200 mg capsules in the morning</td>
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<tr>
<td></td>
<td></td>
<td>3 × 200 mg capsules in the evening</td>
</tr>
<tr>
<td>&gt; 105 kg</td>
<td>1,400 mg/day</td>
<td>3 × 200 mg capsules in the morning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 × 200 mg capsules in the evening</td>
</tr>
</tbody>
</table>
Pharmacologic Treatments: Older Therapies cont.

COPEGUS/RIBASPHERE/MODERIBA (Ribavirin)

- **Side effects:**
  - Primary clinical toxicity is hemolytic anemia
    - May result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions (MIs)
    - Do not use in patients with a history of significant or unstable cardiac disease
  - Other common side effects include but are not limited to:
    - Fatigue, alopecia, anorexia, nausea/vomiting, anxiety, dyspnea, emotional lability, headaches, myalgia

- **Contraindicated in:**
  - Women who are pregnant and the male partners of women who are pregnant
  - Sickle cell disease

- **Interactions:**
  - HIV antiretroviral drugs (NRTIs): *Didanosine, zidovudine*
  - *Azathioprine*
  - Select drugs metabolized by CYP450: patients should be closely monitored for treatment-associated toxicities
Pharmacologic Treatments: Newer Therapies

Direct Acting Antivirals (DAA)

- Affect various stages of the HCV life cycle that are essential for viral replication
  - HCV Nonstructural Protein 3/4A (NS3/4A) serine protein inhibitors
  - HCV Nonstructural Protein 5A (NS5A) protein inhibitors
  - HCV Nonstructural Protein 5B (NS5B) RNA-dependent RNA polymerase inhibitor
- Oral therapies
- Shorter duration of treatment
- Better tolerated
- Better cure rates
- Simplified regimens
- Compared to interferon-based therapy, DAAs are associated with an increased risk of drug-drug interactions with concomitant medications
- **Black box warning:** risk of hepatitis B virus reactivation in patients co-infected with HCV and HBV

*Today, over 90% of HCV infected persons can be cured of HCV regardless of genotype after 8-12 weeks of oral therapy*

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http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm
[Accessed May 14, 2018].
### Direct Acting Antivirals

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Genotype</th>
<th>Duration (weeks)</th>
<th>Daily Pill Burden</th>
<th>Use in Decompensated Cirrhosis</th>
<th>Use in Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOVALDI</strong> (Sofosbuvir)</td>
<td>NS5B</td>
<td>1,2,3,4(5,6 off-label)</td>
<td>12, or 24</td>
<td>1 tab QD</td>
<td>Yes- off label</td>
<td>Must ALWAYS be used with ribavirin or peg-interferon alfa + ribavirin</td>
</tr>
<tr>
<td><strong>HARVONI</strong> (Ledipasvir-Sofosbuvir)</td>
<td>NS5A+NS5B</td>
<td>1,4,5,6</td>
<td>8, 12, or 24</td>
<td>1 tab QD</td>
<td>Yes</td>
<td>May be used with ribavirin</td>
</tr>
<tr>
<td><strong>VIEKIRA</strong> (Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir)</td>
<td>NS5A+ NS3/4A +PK booster+ NS5B</td>
<td>1</td>
<td>12, or 24</td>
<td>3 tabs QD‡</td>
<td>No</td>
<td>May be used with ribavirin</td>
</tr>
<tr>
<td><strong>TECHNIVIE</strong> (Ombitasvir-Paritaprevir-Ritonavir)</td>
<td>NS5A+ NS3/4A + PK booster</td>
<td>4</td>
<td>12</td>
<td>2 tabs QD</td>
<td>No</td>
<td>Usually used in combination with ribavirin¹</td>
</tr>
<tr>
<td><strong>DAKLINZA</strong> (Daclatasvir)</td>
<td>NS5A</td>
<td>1,3 (2,4,5,6 off-label)</td>
<td>12</td>
<td>1 tab QD</td>
<td>Yes</td>
<td>Must ALWAYS be used with sofosbuvir or sofosbuvir + ribavirin</td>
</tr>
<tr>
<td><strong>ZEPATIER</strong> (Elbasvir-Grazoprevir)</td>
<td>NS5A+NS3/4A</td>
<td>1,4</td>
<td>12 , or 16</td>
<td>1 tab QD</td>
<td>No</td>
<td>May be used with ribavirin</td>
</tr>
<tr>
<td>*<strong>EPCLUSA</strong> (Sofosbuvir-Velpatasvir)</td>
<td>NS5B+NS5A</td>
<td>1,2,3,4,5,6</td>
<td>12</td>
<td>1 tab QD</td>
<td>Yes</td>
<td>May be used with ribavirin</td>
</tr>
<tr>
<td>*<strong>MAVYRET</strong> (Glecaprevir-Pibrentasvir)</td>
<td>NS3/4A +NS5A</td>
<td>1,2,3,4,5,6</td>
<td>8, 12, or 16</td>
<td>3 tabs QD</td>
<td>No</td>
<td>Used ALONE</td>
</tr>
<tr>
<td>*<strong>VOSEVI</strong> (Sofosbuvir-Velpatasvir-Voxilaprevir)</td>
<td>NS5B+NS5A+NS3/4A</td>
<td>1,2,3,4,5,6</td>
<td>12</td>
<td>1 tab QD</td>
<td>No</td>
<td>Used ALONE</td>
</tr>
</tbody>
</table>

- **VIEKIRA** and **TECHNIVIE** are scheduled to be discontinued by 12/31/18 due to advent of newer therapies

† Although included as an FDA-approved use, clinical practice guidelines do not recommend OLYSIO® in the treatment of chronic HCV genotype 4 infection
‡ This is dosing for **VIEKIRA XR**, there is also **VIEKIRA PAK** which contains a fixed dose tablet with ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg dosed at 2 tabs QAM co-packaged with dasabuvir 250 mg tablets dosed at 1 tab BID
¹ May consider use without ribavirin in treatment-naïve patients without cirrhosis unable to tolerate ribavirin
*Currently preferred agents on CT DSS formulary (verified on 7/12/18)
SOVALDI (Sofosbuvir)

- FDA Approved December 2013
- **Mechanism of Action:** inhibits HCV NS5B RNA-dependent RNA polymerase
- **Indication:**
  - Genotype 1, 2, 3, or 4 chronic HCV infection in adults
  - Genotype 2 or 3 chronic HCV infection in pediatric patients 12 years and older or weighing 35 kg or more, without cirrhosis or with compensated cirrhosis
  - OFF LABEL INDICATION: for the treatment of chronic HCV genotype 5 or 6 infection with compensated liver disease
  - **ALWAYS** as a component of a combination antiviral treatment regimen
    - With ribavirin (TWICE DAILY) or peg-interferon alfa (ONCE WEEKLY) + ribavirin (TWICE DAILY)
- **Dosage:** **ONE TABLET DAILY** (400 mg), with or without food
  - For 12 or 24 weeks of treatment dependent upon prior treatment history
SOVALDI (Sofosbuvir) cont.

- **Side effects as reported with combination therapy:**
  - **CNS:** fatigue (30% - 59%), headache (24% - 36%), insomnia (15% - 25%), chills (2% - 17%), irritability (10% - 13%)
  - **Dermatologic:** pruritus (11% - 27%), skin rash (8% to 18%)
  - **Gastrointestinal:** nausea (22% - 34%), decreased appetite (18%), diarrhea (9% - 12%)
  - **Hematologic:** decreased hemoglobin (<10 g/dL: 6% to 23%; <8.5 g/dL: ≤2%), anemia (6% - 21%)
  - **Neuromuscular:** weakness (5% - 21%), myalgia (6% - 14%)
  - **Respiratory:** flu-like symptoms (6% - 16%)

- **Notable Drug-Drug Interactions:**
  - Bradycardia with *amiodarone* co-administration
  - Anticonvulsants: *carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine* — not recommended due to reduced therapeutic effects of sofosbuvir
  - Not recommended with: *rifampin, tipranavir/ritonavir, St. John’s Wort*
HARVONI (Ledipasvir-Sofosbuvir)

- FDA Approved October 2014
- **Mechanism of Action:** Ledipasvir inhibits the HCV NS5A protein, sofosbuvir inhibits NS5B RNA-dependent RNA polymerase

**Indication:**
- Chronic HCV genotype 1, 4, 5, or 6 infection in adult and pediatric patients 12 years or older or weighing 35 kg or more, without cirrhosis or with compensated cirrhosis
- Chronic HCV genotype 1 in adult patients with **decompensated** cirrhosis, in combination with ribavirin
- Chronic HCV genotype 1 or 4 in adult liver transplant patients without cirrhosis or with compensated cirrhosis, in combination with ribavirin

**Dosage:** **ONE TABLET DAILY** (90 mg/400 mg), with or without food for 12 or 24 weeks
- May be considered for 8 weeks in treatment-naïve, genotype 1 HCV infection
- May be taken in addition to ribavirin in patients with genotype 1 HCV with decompensated cirrhosis, or genotype 4 HCV with a history of liver transplant
HARVONI (Ledipasvir-Sofosbuvir) cont.

- **Side Effects:**
  - CNS: fatigue & headache (> 10%)
  - Neuromuscular: weakness (18% - 31%), myalgia (9%)
  - Gastrointestinal: nausea (6% - 9%), insomnia (3% - 6%), depression (<5%)

- **Notable Drug-Drug Interactions:**
  - Serious symptomatic bradycardia when co-administered with *amiodarone*
  - Anticonvulsants: *carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine* — not recommended due to reduced therapeutic effects
  - Therapeutic concentration monitoring of *digoxin* is recommended when co-administered due to increased effects
  - Antacids (e.g., *aluminum* and *magnesium hydroxide*): separate antacid and HARVONI administration by 4 hours
  - H2-receptor antagonists (e.g., *famotidine*): H2-receptor antagonists may be administered simultaneously with or 12 hours apart from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily
  - Proton-pump inhibitors (e.g., *omeprazole*): doses comparable to *omeprazole* 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions
  - Not recommended with select HIV antiretrovirals, *rifampin, St. John’s Wort, rosuvastatin*
VIEKIRA
(Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir)

- FDA Approved December 2014, set to be discontinued by December 31, 2018
- **Mechanism of Action:** Ombitasvir inhibits HCV NS5A, paritaprevir inhibits HCV NS3/4A protease, dasabuvir inhibits HCV NS5B RNA-dependent RNA polymerase, ritonavir is not active against HCV, it is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure
- **Indication:**
  - Treatment of adults with chronic HCV infection genotype 1a and genotype 1b without cirrhosis or with compensated cirrhosis
- **Dosage:** take with food
  - **Viekira Pak** consists of a fixed dose tablet containing ombitasvir 12.5 mg, paritaprevir 75 mg, and ritonavir 50 mg, co-packaged with dasabuvir 250 mg tablets
    - 2 TABLETS EVERY MORNING of Ombitasvir/paritaprevir/ritonavir
    - 1 TABLET TWICE DAILY of Dasabuvir
  - **Viekira XR** is a fixed dose bilayer tablet; the immediate release layer contains ombitasvir 8.33 mg, paritaprevir 50 mg, and ritonavir 33.33 mg; the extended release layer contains dasabuvir 200 mg
    - 3 TABLETS ONCE DAILY
  - For 12 or 24 weeks depending on cirrhosis and/or prior treatment history
  - May be used with *ribavirin* in certain populations
VIEKIRA
(Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir) cont.

- **Side effects:**
  - Fatigue, nausea, pruritus, skin reactions, insomnia, asthenia

- **Many Drug-Drug Interactions:**
  - Many contraindications including:
    - Alfuzosin, clochicine, ranolazine, dronedarone, carbamazepine, phenytoin, phenobarbital, rifampin, lurasidone, St. Johns Wort, oral contraceptives containing ethinyl estradiol, atorvastatin, lovastatin, simvastatin, efavirenz, triazolam, tacrolimus, everolimus, sirolimus
  - Many drug-drug interactions requiring additional monitoring including:
    - antihypertensive agents, HIV antiretroviral, antidiabetic drugs, antiarrhythmics, antifungals, muscle relaxants, narcotics, immunosuppressants, salmeterol
  - **VIEKIRA** is contraindicated in patients with moderate to severe hepatic impairment
TECHNIVIE (Ombitasvir-Paritaprevir-Ritonavir)

- FDA Approved July 2015, set to be discontinued by December 31, 2018
- **Mechanism of Action:** Ombitasvir inhibits HCV NS5A, paritaprevir inhibits HCV NS3/4A protease, ritonavir is not active against HCV, it is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure
- **Indication:**
  - Genotype 4 chronic HCV infection without cirrhosis or with compensated cirrhosis, in combination with *ribavirin*
- **Dosage:** TWO TABLETS ONCE DAILY (12.5 mg/75 mg/50 mg), with food for 12 weeks
  - Used in combination with *ribavirin* which is TWICE DAILY with food
  - May consider use without *ribavirin* in treatment-naïve patients without cirrhosis unable to tolerate *ribavirin*
TECHNIVIE
(Ombitasvir-Paritaprevir-Ritonavir) cont.

- **Side Effects:**
  - Risk of hepatic decompensation and hepatic failure in patients with cirrhosis
  - Increased risk of ALT elevations
  - Common: asthenia, fatigue, nausea, insomnia, pruritus, anemia, weakness

- **Notable Drug-Drug Interactions:**
  - Many contraindications including:
    - *Alfuzosin, colchicine, ranolaznie, dronedarone, carbamazepine, phenytoin, phenobarbital, rifampin, lurasidone, St. Johns Wort, oral contraceptives containing ethinyl estradiol, atorvastatin, lovastatin, simvastatin, efavirenz, triazolam, tacrolimus, everolimus, sirolimus*
  - Many drug-drug interactions requiring additional monitoring including:
    - antihypertensive agents, HIV antiretroviral, antidiabetic drugs, antiarrhythmics, antifungals, muscle relaxants, narcotics, immunosuppressants, *salmeterol*
  - **TECHNIVIE** is contraindicated in patients with moderate to severe hepatic impairment

[https://www.hepatitisc.uw.edu/page/treatment/drugs/ombitasvir-paritaprevir-ritonavir](https://www.hepatitisc.uw.edu/page/treatment/drugs/ombitasvir-paritaprevir-ritonavir)
DAKLINZA (Daclatasvir)

- **FDA Approved July 2015**
- **Mechanism of Action:** inhibits HCV NS5A
- **Indication:**
  - Chronic HCV genotype 1 or genotype 3 infection in combination with *sofosbuvir*, with or without *ribavirin*
  - OFF LABEL INDICATION: Chronic HCV genotype 2, 4, 5, 6
  - *ALWAYS* as a component of a combination antiviral treatment regimen
    - With *sofosbuvir* or *sofosbuvir* + *ribavirin*
- **Limitations:** sustained virologic response rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving DAKLINZA in combination with *sofosbuvir* for 12 weeks
- **NS5A Resistance Testing in HCV Genotype 1a-Infected Patients with cirrhosis may be considered**
- **Dosage:** **ONE TABLET DAILY**, with or without food for 12 weeks
  - 30 mg, 60 mg, 90 mg: dose depends on concomitant therapies


[https://www.hepatitisc.uw.edu/page/treatment/drugs/daclatasvir](https://www.hepatitisc.uw.edu/page/treatment/drugs/daclatasvir)
DAKLINZA (Daclatasvir) cont.

- **Side Effects:**
  - **CNS:** fatigue (14% - 15%), headache (12% - 14%)
  - **GI:** nausea (8% - 15%)
  - **Hematologic:** anemia (20%)
  - 1-10%: drowsiness, insomnia, skin rash, diarrhea, increased serum lipase

- **Notable Drug-Drug Interactions:**
  - Contraindicated with: *phenytoin, phenobarbital, carbamazepine, rifampin, St. John's Wort*
  - Select HIV antivirals require dose-adjustment of DAKLINZA: Protease inhibitors, NNRTIs
  - **DAKLINZA** raises concentration of statins
  - Can increase effects of *buprenorphine/naloxone* — no dose adjustment necessary, just clinical monitoring for adverse events
  - Therapeutic concentration monitoring of *digoxin* is recommended when co-administered
ZEPATIER (Elbasvir-Grazoprevir)

- FDA Approved January 2016
- **Mechanism of Action:** Elbasvir inhibits HCV NS5A, Grazoprevir inhibits HCV NS3/4A protease

**Indications:**
- Genotypes 1 or 4 chronic HCV infection in adults; used with *ribavirin* in certain patient populations
- Additional testing is recommended before initiation of treatment in patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms in order to determine dosage regimen and duration

**Dosage:** **ONE TABLET DAILY** (50 mg/100 mg), with or without food
- For 12-16 weeks dependent prior treatment history and presence of polymorphisms
- May be used with *ribavirin* in certain populations
ZEPATIER (Elbasvir-Grazoprevir) cont.

- **Side Effects:**
  - **CNS:** fatigue (7% - 11%), headache (11%)
  - **Gastrointestinal:** nausea (5% - 11%)
  - 1-10%: increased ALT, increased bilirubin, insomnia, weakness, myalgia, pruritus, dizziness, irritability, anxiety, depression, night sweats, alopecia, GI symptoms

- **Notable Drug-Drug Interactions:**
  - **ZEPATIER** is contraindicated with the following:
    - Anticonvulsants: phenytoin, phenobarbital, carbamazepine
    - HIV medications: efavirenz, atazanavir, darunavir, lopinavir, saquinavir, tipranavir
    - Other: rifampin, St. John’s Wort, cyclosporine
  - There are other clinically significant drug-drug interactions present
    - **ZEPATIER** raises concentrations of statins
    - *Modafinil* may lead to reduced therapeutic effect of **ZEPATIER**, co-administration not recommended
EPCLUSA (Sofosbuvir-Velpatasvir)

- FDA Approved June 2016, first pangenotypic DAA
- **Mechanism of Action:** Sofosbuvir inhibits NS5B RNA-dependent RNA polymerase, velpatasvir inhibits the HCV NS5A protein
- **Indications:**
  - Treatment of chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection in adults without cirrhosis or with compensated cirrhosis
  - Treatment of chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection in combination with *ribavirin* in patients with *decompensated* cirrhosis
- **Dosage:** ONE TABLET DAILY (400 mg/100 mg), with or without food for 12 weeks
  - In decompensated cirrhosis: one tablet daily with concomitant twice daily *ribavirin* for 12 weeks
**EPCLUSA** (Sofosbuvir-Velpatasvir) cont.

- **Side Effects:**
  - **CNS:** headache (22%), fatigue (15%), asthenia (5%), and insomnia (5%)
  - **GI:** nausea (9%)
  - Less common (<5%): rash, depression

- **Notable Drug-Drug Interactions:**
  - Serious symptomatic bradycardia when *sofosbuvir* is co-administered with *amiodarone* and another HCV DAA
  - Anticonvulsants: *carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine* — not recommended due to reduced therapeutic effects
  - Antacids (e.g., *aluminum* and *magnesium hydroxide*): separate antacid and EPCLUSA administration by 4 hours
  - H2-receptor antagonists (e.g., *famotidine*): H2-receptor antagonists may be administered simultaneously with or 12 hours apart from EPCLUSA at a dose that does not exceed doses comparable to *famotidine* 40 mg twice daily
  - Proton-pump inhibitors (e.g., *omeprazole*): Co-administration of *omeprazole* or other proton-pump inhibitors is not recommended. If it is considered medically necessary to co-administer, EPCLUSA should be administered with food and taken 4 hours before *omeprazole* 20 mg. Use with other proton-pump inhibitors has not been studied.
  - Select HIV antivirals not recommended
  - EPCLUSA can increase concentrations of *rosuvastatin, atorvastatin* thus increased risk for myopathy
  - Therapeutic concentration monitoring of *digoxin* is recommended when co-administered with EPCLUSA due to increased effects
MAVYRET (Glecaprevir-Pibrentasvir)

- FDA Approved August 2017
- **Mechanism of Action:** Glecaprevir is an inhibitor HCV NS3/4A protease, Pibrentasvir is an inhibitor of HCV NS5A
- **Indication:**
  - Adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)
  - Adult patients with chronic HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both
- **Dosage:** THREE TABLETS ONCE DAILY (100 mg/40 mg), with food
  - For 8-16 weeks depending on extent of cirrhosis and prior treatment history
MAVYRET (Glecaprevir-Pibrentasvir) cont.

- **Side Effects:**
  - **CNS:** headache (9% - 17%), fatigue (11% - 14%)
  - **Gastrointestinal:** nausea (6% - 12%), diarrhea (3% - 7%), increased bilirubin (4%; 2 × ULN)

- **Notable Drug-Drug Interactions:**
  - Contraindicated with azatanavir, rifampin or in severe hepatic impairment
  - Carbamazepine, efavirenz, and St. John’s Wort may significantly decrease plasma concentrations of MAVYRET, and are not recommended
  - Oral contraceptives containing ethinyl estradiol may cause increased ALT when used in combination with MAVYRET and are not recommended
  - Therapeutic concentration monitoring of digoxin is recommended when co-administered
  - MAVYRET raises concentration of statins
  - Select HIV antiretrovirals not recommended
  - Co-administration of MAVYRET with cyclosporine is not recommended
VOSEVI (Sofosbuvir-Velpatasvir-Voxilaprevir)

- FDA Approved July 2017
- **Mechanism of Action:** Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, velpatasvir is an inhibitor of the HCV NS5A protein, voxilaprevir is a noncovalent, reversible inhibitor of the NS3/4A protease
- **Indication:**
  - Adults with chronic HCV infection without cirrhosis or with compensated cirrhosis who have genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor
  - Adults with chronic HCV infection genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor
    - Limitations of use: additional benefit of sofosbuvir/velpatasvir/voxilaprevir (VOSEVI) over sofosbuvir/velpatasvir (EPCLUSA) was not shown with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor
- **Dosage:** ONE TABLET ONCE DAILY (400 mg/100 mg/100 mg), with food for 12 weeks
VOSEVI (Sofosbuvir-Velpatasvir-Voxilaprevir) cont.

- **Side Effects:**
  - > 10%: Headache, fatigue, diarrhea, nausea, increased serum bilirubin
  - 1-10%: insomnia, depression, skin rash, increased serum lipase, weakness

- **Notable Drug-Drug Interactions:**
  - Serious symptomatic bradycardia when sofosbuvir is co-administered with amiodarone and another HCV DAA
  - Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine — not recommended due to reduced therapeutic effects
  - Therapeutic concentration monitoring of digoxin is recommended when co-administered with VOSEVI due to increased effects
  - Select HIV antiretrovirals not recommended
  - Antacids (e.g., aluminum and magnesium hydroxide): separate antacid and VOSEVI administration by 4 hours
  - H2-receptor antagonists (e.g., famotidine): H2-receptor antagonists may be administered simultaneously with or staggered from VOSEVI at a dose that does not exceed doses comparable with famotidine 40 mg twice daily
  - Proton-pump inhibitors (e.g., omeprazole): Omeprazole 20 mg can be administered with VOSEVI. Use with other proton pump-inhibitors has not been studied.
  - VOSEVI raises concentration of statins
  - Co-administration of VOSEVI with cyclosporine is not recommended
After Completion of Treatment

- Quantitative viral load with an HCV PCR test should be conducted ≥12 weeks after completion of treatment to confirm SVR.

- For patients who do not have advanced fibrosis (i.e., those with Metavir stage F0, F1, or F2), recommended follow-up is the same as if they were never infected with HCV.

- Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops.
  - In such cases, a quantitative HCV-RNA test rather than an HCV-antibody test is recommended to assess for HCV recurrence or reinfection.
Hepatitis C Quality Improvement Project (QIP)

- Community Health Network of Connecticut, Inc. (CHNCT) is committed to decreasing hepatitis C-related deaths in Connecticut.
- Increasing screening rates would lead to identification of previously undiagnosed cases and allow for early intervention.
- Implementation of the hepatitis C testing recommendations in primary care would help identify more individuals with hepatitis C, allowing them to get into care and treatment sooner.
QIP Goal

- Ensure HUSKY Health members born anytime from 1945 to 1965, as well as those with an increased risk of HCV infection are receiving needed screenings and appropriate follow-up care.
QIP Interventions

- Member Interventions:
  - Letter containing information encouraging members born anytime 1945-1965 and those at increased risk to schedule a well-visit and discuss screening with their PCP
  - HUSKY Health website enhancements to provide general information on hepatitis C and the importance of screening and diagnosis
    - A Hepatitis Risk Assessment Tool will be included to help members determine what they should discuss with their provider regarding testing
  - A phone call made to identified members to provide information on hepatitis C and encourage screening and offering Intensive Care Management (ICM) services
  - ICM outreach to members who are diagnosed with hepatitis C to monitor adherence to treatment protocols and follow-up appointments
  - Use of social media to educate members on hepatitis C screening and appropriate follow-up care
QIP Interventions

Provider Interventions:

- Assistance to practices in targeting members identified as at-risk and in need of hepatitis C screening
- Provide resources and education about the importance of screening for hepatitis C
- Provide portal reports for PCPs identifying members who are in need of hepatitis C screening
- HUSKY Health website enhancements to provide an educational resource for providers
- Emails will be sent to all Connecticut Medicaid Assistance Program (CMAP) providers about the importance of screening for hepatitis C
Chronic Hepatitis C is a serious disease that can result in severe long-term health problems, even death.

Today, with the advent of newer, simpler and more effective therapies, over 90% of HCV infected persons can be cured of HCV regardless of genotype after 8-12 weeks of oral therapy.

Screening patients for HCV and linking them to care sooner results in better health outcomes and decreased long-term healthcare costs.

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm
Resources

- A guide to comprehensive HCV counseling and testing for PCPs is available on the CDC website:
  - [https://www.cdc.gov/hepatitis/resources/professionals/pdfs/counselingandtestingpc.pdf](https://www.cdc.gov/hepatitis/resources/professionals/pdfs/counselingandtestingpc.pdf)

- Comprehensive and most up-to-date CDC information regarding HCV:
  - [https://www.cdc.gov/hepatitis/hcv/index.htm](https://www.cdc.gov/hepatitis/hcv/index.htm)

- American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). Recommendations for testing, managing, and treating hepatitis C. HCV Guidelines:
  - [https://www.hcvguidelines.org/](https://www.hcvguidelines.org/)

- Refer HUSKY Health members to CT Behavioral Health Partnership:
  - Call 1.877.552.8247 for information on finding treatment options
Contact Information

- By email: pathwaytopcmh@chnct.org
- By phone: 203.949.4194
- All webinars are located on the HUSKY Health website page at http://www.huskyhealthct.org/providers/provider_webinars.html#

- HUSKY Health Provider Website: http://www.huskyhealthct.org/providers.html#
- Provider Engagement Services: 1.800.440.5071
- Intensive Care Management: 1.800.859.9889 x2024
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Questions?