Hepatitis C Treatment Update: for the PCP

Jason Domagalski, MD, FAAFP

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Dr. Domagalski practices family medicine in Menomonee Falls, WI. He provides outpatient and inpatient services. Colon cancer screening, gastroesophageal reflux disease (GERD), and inflammatory bowel disease are his specialty topics. Dr. Domagalski believes that access to endoscopy through primary care is an important trend.
Learning Objectives

1. Follow current AAFP immunization schedules and preventive service recommendations for prevention of hepatitis A and B infection in patients with chronic hepatitis C.

2. Establish standardized protocols for identifying high-risk patients who should be screened for hepatitis C infection including risk-based and age-cohort screening.

3. Order appropriate laboratory and/or diagnostic tests to confirm diagnosis of chronic hepatitis C infection and rule out co-infection with HIV and HBV.

4. Be aware of current treatment recommendations plan for an adult patient with a confirmed chronic hepatitis C diagnosis using antiviral therapy, tailoring the treatment regimen for the individual, and considering patient-specific barriers to treatment, follow-up monitoring, and making an appropriate referral.

5. Monitor patients with chronic hepatitis C infection for sequelae including cirrhosis, hepatic failure and hepatocellular carcinoma.

Audience Engagement System

Step 1

Step 2

Step 3
Say Hello to “Dawn”

Background

- 185 million worldwide
  - 2 million in US alone
- 350,000 deaths annually
- Cost in US $6.5 billion in 2013
- Leading cause of liver-related mortality
  - Most common indication for transplant

Epidemiology

• 0.84% of US population
• Those born 1945-65 account for 75%
• Wisconsin statistics
  • Increase since 2006~2500 new cases/year
  • 57% men
  • People under 30 increase from 5% to 27%


Transmission

- Through blood and body fluids
- Mother to infant
- Organ transplant prior to 1992
- Blood-to-blood sexual transmission


<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>CDC</th>
<th>USPSTF</th>
<th>AASLD/IDSA</th>
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<tbody>
<tr>
<td>Born 1945-1965*</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>IV drug use*</td>
<td>x</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood transfusion before 1992</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Incarceration</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Unregulated tattoo</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HIV infection</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained liver disease</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Solid organ donor</td>
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<td></td>
<td>x</td>
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</table>
Pathophysiology

• 6 genotypes
  • 97% in US are 1a, 1b, 2 and 3
• Direct cell injury + local immune mechanism
• Chronic infection occurs in 80%
• Of chronic cases 20% develop sequela

Screening

• USPSTF /CDC
  • Periodic for high risk
  • once for adults born ‘45-65

• AASLD
  • Annual for IV drug use
  • Annual for HIV + men having unprotected sex with men
Testing

• HCV antibody screening
  • 97-100% sensitive/specific

• HCV RNA qualitative
  • Confirmatory test for chronic infection


Poll Question 1

Mr. Hye Risk is a 45-year-old male who presents to your practice with a history of incarceration as well as active heroin use. Based on current guidelines you order a hepatitis C antibody test which comes back positive, however the confirmatory HCV RNA is negative. What should you do now?

A. Nothing, he cleared his infection
B. Nothing, the screening test was a false +
C. Repeat RNA testing in 4 months because he may be acutely infected
D. Repeat RNA testing if symptoms develop
HCV Ab (+) RNA (-)

- Pt completely recovered and is in the 20%
- Antibody test was falsely positive
- Acutely infected without significant viremia yet


Screening Algorithm

**When to test simultaneously**

- Suspect acute exposure
  - Viremia in as little as 2 wks
  - Antibody 8-12 weeks
- Immunocompromised
- Hemodialysis
- HIV positive


**Known Exposure or Symptoms**

[Diagram showing HCV Antibody + HCV RNA Co-testing]

Diagnosis Confirmed, Now What?

- Assess for fibrosis/cirrhosis
  - Liver biopsy gold standard
  - Noninvasive measures
    - LFTs
    - Proprietary Tests (Fibrotest, PGAA index)
    - Specialized tests
    - Imaging
    - Transient elasticity


Transient Elasticity

Clinical Course

• Acute
  • Most have nonspecific symptoms
  • 50% have symptoms of acute infection
  • Flu like symptoms common
  • Jaundice, abd pain, dark urine


Poll Question 2

Mrs. Peggy Prognosis is a 58-year-old female presents to your practice with a recent diagnosis of hepatitis C and is concerned what her risks for disease complications are. Which of the following is a true statement regarding the clinical progression of chronic Hepatitis C infection?

A. Up to 20% progress to cirrhosis
B. Up to 10% develop decompensated cirrhosis
C. The annual incidence of hepatocellular carcinoma is 10%
D. Upper GI bleeds occur in 5%
Clinical Course

- Chronic
  - Asymptomatic
  - Myalgias/arthralgias most common
  - 10-20% develop cirrhosis (20-30 yrs)
    - 1-4% develop HCC
    - 20% decompensated cirrhosis

Progression

• Variable
• Prediction model for future burden
  • Peak HCV prevalence in 1994
  • Peak for compensated cirrhosis 2015
  • Peak for decompensated cirrhosis 2019
  • Peak in Hepatocellular Carcinoma 2020


Secondary Prevention

• Abstinence from alcohol
• Evaluate for HIV/HBV
• Hepatitis A & B vaccines
• Counsel IV Drug users on safe practices
• Educate on safe sex practices

Surveillance

- Assess cirrhosis patients
  - For Hepatocellular Carcinoma
    - AASLD Recommend US + α-fetoprotein*
    - every 6-12 months
    - Data Lacking
  - For varices
    - Upper Endoscopy every 1-2 years


Treatment

- Based on genotype, extent of fibrosis, prior treatment, comorbidities, side effects
- Candidates 18+, elevated ALT, adhere to tx
- Metavir Scoring System
  - Grades fibrosis 0-4
  - Treatment for anyone 2 or above
- Sustained Viral Response (SVR) goal of 12-24 wks

Metavir Scoring System

<table>
<thead>
<tr>
<th>Score</th>
<th>Level of Fibrosis</th>
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<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Minimal Scarring</td>
</tr>
<tr>
<td>2</td>
<td>+Scarring extending beyond blood vessels</td>
</tr>
<tr>
<td>3</td>
<td>Bridging fibrosis</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis/Advanced Scarring</td>
</tr>
</tbody>
</table>


Achieving SVR

• Reduce progression of fibrosis/cirrhosis
• Reduce incidence of HCC
• Reduced liver-related complications
  • Ascites, encephalopathy, GI bleeding
• Reduce Liver-Related Deaths
• Reduce all-cause mortality

Poll Question 3

Mr. Hardy Too-Treat is a 55-year-old African American Male with chronic hepatitis C who is undergoing evaluation for treatment. He has advanced fibrosis and genotype 1 HCV. His current viral load is 550,000 IU/ml and has Past Medical history of Type 2 Diabetes. Which of the following is associated with a higher rate of Sustained Viral Response?

A. African American Race  
B. Age >50  
C. Viral Load< 800,000  
D. History of Insulin Resistance

Predictors of SVR

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Age</td>
<td>Higher rates of SVR in those &lt;40</td>
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<tr>
<td>Fibrosis</td>
<td>Lower rates of SVR in advanced fibrosis/cirrhosis</td>
</tr>
<tr>
<td>Genotype</td>
<td>SVR rates highest for type 2/3 and lowest for 1</td>
</tr>
<tr>
<td>Race</td>
<td>African Americans have lower SVR rates</td>
</tr>
<tr>
<td>Statin use</td>
<td>Higher rate of SVR in statin users</td>
</tr>
<tr>
<td>IL288 polymorphism</td>
<td>Involved in viral resistance; genotype CC and TT assoc with higher SVR rates</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Insulin resistance associated with lower SVR rates</td>
</tr>
<tr>
<td>Low viral load</td>
<td>Viral loads &lt;800,000IU/ml associated with higher SVR rate</td>
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</tbody>
</table>

Treatment History

• Standard Interferon (early 1990s)
  • SVR 6% w/ 6 mos and 12% w/ 12 mos
• Interferon + Ribavirin (mid-1990s)
  • SVR 34% at 6 mos and 42% at 12 months
• Pegylated Interferon (2000)
  • SVR 39% at 12 mos alone/55% w/ ribavirin


NS3/4a Inhibitors

• Telaprevir and Boceprevir
  • First on market
  • Co-administered with RBV and peg interferon
  • Discontinued due to lower SVR and side effects
• Simeprevir (Olysio)
  • Genotypes 1,4,5,6
  • Anemia, fatigue, flu like symptoms
  • 80-92% SVR at 12 wks

NS5B Inhibitors

- Sofosbuvir (Sovaldi)
  - Effective on all genotypes
  - Anemia, fatigue, nausea
  - SVR 59%-93%

Recommended Interferon free Regimens

- Harvoni (12 weeks)
  - Ledipasvir+Sofosbuvir
  - Genotypes 1, 4, 5, 6
  - Headache and fatigue
- Mavyret (8-12 weeks)
  - Glecaprevir+Pibrentasvir
  - Genotypes 1-6
  - Good for patients with CKD or ESRD

Recommended Interferon free Regimens

• Epclusa (12 wks)
  • Sofosbuvir/Velpatasvir
  • Genotypes 1-6
  • Reactivation of Hepatitis B, fatigue, headaches
• Zepatier
  • Elbasvir/Grazoprevir
  • Headache, fatigue, nausea
  • Genotypes 1 & 4


Alternative Regimens

• Viekira Pak (12 wks)
  • Ombitasvir+Paritaprevir+Ritonavir+ Dasabuvir
  • Fatigue, weakness, nausea, insomnia
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<tr>
<th>FDA Approval</th>
<th>Medications</th>
<th>SVR %</th>
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<td>November 2013</td>
<td>Simeprevir (Olysio)*</td>
<td>59-100%</td>
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<tr>
<td>December 2013</td>
<td>Sofosbuvir (Solvadi)*</td>
<td>59-93%</td>
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<td>October 2014</td>
<td>Ledipasvir/sofosbuvir (Harvoni)</td>
<td>94-99%</td>
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<tr>
<td>November 2014</td>
<td>Sofosbuvir+simeprevir</td>
<td>92%</td>
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<tr>
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<td>Ombitasvir/paritaprevir/ritonavir+dasabuvir (Viekira Pak)</td>
<td>91-100%</td>
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<tr>
<td>March 2017</td>
<td>Sofosbuvir/Velpatasvir (Epclusa)</td>
<td>95-99%</td>
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<td>March 2017</td>
<td>Elbavirt/Grazoprevir (Zepatier)</td>
<td>95-99%</td>
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<tr>
<td>September 2017</td>
<td>Glecaprevir/Pibrentasvir (Mavyret)</td>
<td>92%</td>
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* Indicates need for co-administered ribavirin+/-peginterferon


SVR and Outcomes

- SVR only a surrogate marker
- 20% developed advanced disease
  - DA Antivirals increase SVR by 26%
  - 0.26x0.20=0.05 or 5% benefit
- Balance with 5-8% risk of side effect

Ta K, ZehtabiS. Efficacy of Direct-Acting Antivirals Compared with Older Agents for Hepatitis C. Am Fam Physician. 2017 Jun 1; 95(11):696A-B.
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Regimen</th>
<th>Cost</th>
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<tbody>
<tr>
<td>1a</td>
<td>Harvoni for 12 wks</td>
<td>$93,000</td>
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<tr>
<td></td>
<td>Vekira Pak+RBV 12 wks</td>
<td>$94,000</td>
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<tr>
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<td>Mavyret 8 to 12 wks</td>
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<td></td>
<td>Epclusa for 12 wks</td>
<td>$75,000</td>
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<td></td>
<td>Zepatier for 12 to 16 wks</td>
<td>$60-80,000</td>
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<tr>
<td>1b</td>
<td>Harvoni 12 wks</td>
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<td></td>
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<tr>
<td></td>
<td>Mavyret 8 to 12 wks</td>
<td>$26-39,000</td>
</tr>
</tbody>
</table>

Insurance Coverage

- Prior Authorization criteria:
  - Presence of advanced fibrosis or cirrhosis
  - HCC present
  - Failure of Peg interferon + ribavirin
- Written by: GI, hepatologist, ID, transplant
- Exclusions for pt with advanced renal disease

Poll Question 4

Mr. Nat Ural is a 58-year-old male with chronic hepatitis C preparing to initiate a course of Direct Acting Antiviral medication. He has a viral load of 500,000 and no objective signs of cirrhosis. Which of the following would be contraindicated to take during his treatment?

A. Acetaminophen  
B. Ginseng  
C. Aspirin  
D. St. John’s Wort

Over the Counter/Herbal Therapies

• Tylenol, Aspirin, NSAIDs SAFE*  
  • If no signs of cirrhosis  
• St. John’s Wort contraindicated  
  • Strong CYP3A inducer  
  • Decreases medication effect  
• Red Yeast Extract contraindicated  
  • May induce hepatitis  
• Ginseng, Vitamin D, Licorice Root  
  • No clear evidence

Monitoring

• Baseline labs
  • CBC, INR, LFTs, GFR, HCG, Genotype, Viral Load

• Monitoring
  • CBC, Creatinine, GFR, LFTs 1 month after
  • Viral load 4 wks, 12 wks and 24 wks


Best Practice Recommendations

• Periodic Screening in all high-risk patients and one time screening for adults born 1945-1965. (SOR B)

• Quantitative HCV RNA and genotype assessment prior to treatment. (SOR A)

• Vaccination against Hepatitis A and B for susceptible patients (SOR C)
Contact Information

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• Jason.Domagalski@froedtert.com

Questions
References