Management of Hepatitis C in Primary Care

BABAFE MI ONABANJO, MD & BEN ALFRED, FNP
UMASS FAMILY HEALTH CENTER WORCESTER
Objective

Epidemiology
Screening criteria
Appropriate work up
Treatment Guidelines
HCC screening
Follow up post treatment
Background

Hepatitis C virus infection is the most common blood borne infection in the US

70-85% will become chronically infected with HCV after initial infection

CDC estimates 2.4 million persons are living with HCV infection in the US
- Compared to 2.2 million persons living with HBV infection in the US
- Compared to 1.24 million persons 13yrs and older living with HIV in the US

- In 2016, a total of 2,967 cases of acute hepatitis C were reported to CDC from 42 states
Background

Gentotype 1: 75%
  • 1a: 55%; 1b: 35%

Genotype 2 & 3: 15-20%

Genotype 3, 4, 5: 5%
RISK FACTORS

Ivdu
Transfusions prior 1992
Solid organ transplant
Hemophilia
MSM
Body tattoos
Intranasal cocaine use
Hemodialysis: Prevalence increases to 8% (5x the general population)
PERINATAL- about 5%
Background

HCV prevalence is highest among persons born during 1945 to 1965
Background
Morbidity/Mortality

ALL cause mortality 2x> than in HCV negative patients
Attributes to about 15,000 deaths per year
Mortality rate 12x than general population
8x> than HBV related deaths
20% if not treated will develop cirrhosis after 20yrs of infection
1/3 of all persons on liver transplant list have HCV associated liver disease
Morbidity/Mortality

*Mortality Rates = HBV, HCV, HIV listed as cause of death
Because of decedent can have multiple causes of death, a record listing more than 1 type of infection was counted for each type of infection
Morbidity/Mortality
Natural History

Factors associated with viral clearance
- Younger age
- Female gender
- Nonblack race
- Symptomatic acute infection
- Normal immune status
Natural History

Factors impacting rate of progression of fibrosis
- Older age: Acquisition after 40 associated with more rapid fibrosis progression
- Gender: MALE
- Coinfection with HIV:
- Coinfection with HBV
- Metabolic Factors: obesity, insulin resistance, steatosis
- Alcohol use
- Marijuana use

No impact
- HCV RNA VL or Genotype unlike HIV

![Graph showing rate of fibrosis progression per year by age at time of initial HCV infection.](source: Paynard T, Bedossa P, Opolon P, Lannes, Natural history of liver fibrosis progression in patients with chronic hepatitis C. The METAVIR, METAVIR, CLINVAR, and DOGVIR groups. Lancet. 1997;349:35-32.)
Background
Natural History

Time

Normal Liver

Chronic Hepatitis

Cirrhosis

20-25 years

25-30 years

HCC ESLD Death

HCV Infection
Natural History

The Path to Fibrosis

- Dynamic scarring process with chronic inflammation
- Accumulation of collagen and ECMP
- Remodeling and regression of fibrous tissue via breakdown of matrix proteins
Natural History

![Graph showing the natural history of HCV and HCV + HIV over different durations of HCV (in years)].
Natural History

*Excessive alcohol defined as > 40 g/day for women and > 60 g/day for men*
Natural History
SCREENING

CDC, USPSTF, AASLD/IDSA

Routine Screening

- Active or Prior IDU
- People who have intimate contact with persons with HCV
- Medical Conditions
  - Received clotting factors prior 1987
  - Chronic hemodialysis
  - Persons with persistently abnormal ALT
  - HIV+
- Prior recipient of transfusion or organ transplant
  - Received transfusion of blood/blood products before 7/1992
  - Received organ transplant before 7/1992
  - Pts who received blood from a donor who was later tested Hep C Ab+
SCREENING

Screen based on exposure
- Healthcare, emergency medical, public safety worker after needle stick, sharps, or mucosal exposure to HCV+ blood
- Children born to HCV+ women
- Hx of incarceration
- Intranasal drug use
SCREENING-BABY BOOM

2012: CDC recommends screening for those born between 1945-1965

2013-USPSTF recommended 1 time screening for baby boomers

About 75% of persons living with HCV are in this cohort

Baby boomers make up about 23% of population, they account for 70% of Hep C related deaths
Diagnosis

ACUTE HEP C- within 6 months of initial acquisition

- Clinical Criteria: an illness with discreet onset of any signs or symptom consistent with acute viral hepatitis (fever, headache, anorexia, n/v/d/abd pain)

- Jaundice OR peak ALT>200 IU/L during the period of acute illness

- Laboratory Criteria
  - Hep C Ab+: develops after 8-12wks of infection
  - Hep C RNA Detected
    - NAT(Quantitative, qualitative, or genotype testing)
  - Documented negative HCV Ab within 12 months
Diagnosis

Chronic Hep C

- Clinical criteria: none; possible evidence of chronic liver disease

- Laboratory criteria
  - Hep C Ab+ > 6 months
  - Hep C RNA detected
Diagnosis

Recommended Testing Sequence for Identifying Current HCV Infection

[Diagram showing decision points and test outcomes]

- **Nonreactive**
  - No HCV antibody detected
  - **STOP**

- **Reactive**
  - **Not Detected**
    - No current HCV infection
  - **Detected**
    - Current HCV infection
    - Additional testing as appropriate†
    - 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 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.
Diagnosis

New Diagnosis of Hepatitis C Infection: Post-Test Counseling Messages

Persons infected with HCV can benefit from the following messages

- **Contact a health-care provider (either a primary-care clinician or specialist [e.g., in hepatology, gastroenterology, or infectious disease]),** for
  - medical evaluation of the presence or development of chronic liver disease;
  - advice on possible treatment options and strategies; and
  - advice on how to monitor liver health, even if treatment is not recommended.

- **Protect the liver from further harm by,**
  - considering hepatitis A and B vaccination if susceptible and if liver disease is present;
  - reducing or discontinuing alcohol consumption;
  - avoiding new medicines, including over-the-counter and herbal agents, without first checking with their health-care provider; and
  - obtaining HIV risk assessment and testing.

- **For persons who are overweight (BMI ≥25kg/m²) or obese (BMI ≥30kg/m²),**
  - consider weight management or losing weight and
  - follow a healthy diet and stay physically active.

- **To minimize the risk for transmission to others,**
  - do not donate blood, tissue, or semen and
  - do not share appliances that might come into contact with blood, such as toothbrushes, dental appliances, razors, and nail clippers.
Staging Fibrosis

Liver Biopsy: gold standard
- May incorrectly stage fibrosis in 20% of people; invasive
- Use if conflicting non-invasive results (FibroSure/Fibrotest/APRI)
- When suspecting concurrent liver disease (AIH, hemochromatosis)
- When non-invasive test aren’t available (Fibroscan)
- Determine whether to continue surveillance on HCC
FIBROSIS Staging

Aspartate Aminotransferase-to-Platelet ratio index (APRI):

FIB-4:

FibroIndex:

Forns Index

HepaScore:

FibroSure, FibroTest-ActiTest:
FIBROSIS Staging

\[
\text{APRI} = \frac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}} \times 100
\]

\[
\text{Platelet Count (10}^9/\text{L)}
\]
FIBROSIS Staging

\[
\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count (10}^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}
\]
FIBROSIS Staging

<table>
<thead>
<tr>
<th>Score</th>
<th>IASL</th>
<th>Batts-Ludwig</th>
<th>Metavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Fibrosis</td>
<td>No Fibrosis</td>
<td>No Fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Mild fibrosis</td>
<td>Fibrous portal expansion</td>
<td>Periportal fibrotic expansion</td>
</tr>
<tr>
<td>2</td>
<td>Moderate fibrosis</td>
<td>Rare bridges or septae</td>
<td>Periportal septae (&gt; 1 septum)</td>
</tr>
<tr>
<td>3</td>
<td>Severe fibrosis</td>
<td>Numerous bridges or septae</td>
<td>Portal-central septae</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>
FIBROSIS Staging

FibroSure

Contraindications for use of the FibroSure method for fibrosis staging include Gilbert’s disease, acute hemolysis, extrahepatic cholestasis, post transplantation, or renal insufficiency, all of which may lead to inaccurate quantitative predictions.
Radiologic Evaluation

Hepatic Ultrasound-used to confirm overt cirrhosis and/or portal hypertension, and screen for hepatocellular carcinoma.

Fibroscan-correlates directly with liver stiffness
- hepatic inflammation, obesity, ascites, and elevated central venous pressure and can influence the transient elastography result

Magnetic Resonance Elastography:
FIBROSIS Staging

Castera Transient Elastography Breakpoints

- **2.5**
  - Metavir: Absent or mild fibrosis
  - F0-F1: Absent or mild fibrosis

- **7.0**
  - Metavir: Significant fibrosis
  - F2: Significant fibrosis

- **9.5**
  - Metavir: Severe fibrosis
  - F3: Severe fibrosis

- **12.5**
  - Metavir: Cirrhosis
  - F4: Cirrhosis

- **75 kPa**
CASES
Patient Evaluation

Medical History
- Asses for Alcohol Use,
- Illicit Drug use
- Medication Use
- Comorbidities: HIV, Hepatitis B, DM, Obesity, Steatosis
- Psychiatric History
- ROS: abdominal swelling, edema, hematemesis, melena, AMS
Patient Evaluation

Physical Exam
- BMI: BMI>25 at risk for NAFLD
- Wasting
- Scleral icterus
- Lower extremity edema
- Spider angiomata, Palmar erythema, gynecomastia, testicular atrophy
- Assess for Ascites: fluid wave and shifting dullness
- Mental status
- Asterixis and hepatic encephalopathy
### Child-Turcotte-Pugh Classification for Severity of Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
</tr>
</tbody>
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*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

**Class A** = 5 to 6 points (least severe liver disease)

**Class B** = 7 to 9 points (moderately severe liver disease)

**Class C** = 10 to 15 points (most severe liver disease)
3-Month Mortality Based on Child-Turcotte-Pugh Score

- < 7-9: 4.3%
- 10-12: 11.2%
- 13-15: 40.1%
Work UP

CBC
LFT
INR
BMP
HCV genotype
HCV RNA (viral load)
Baseline Ultrasound
HIV
Hep B sAg/sAb/cAb: If negative Vaccinate
Hep A tAB: if negative vaccinate
Treatment Contraindications

Absolute Contraindications
- Short life expectancy
- Pregnancy

Relative Contraindication
- Active severe substance abuse
- Uncontrolled psychiatric condition
- Social issues that hinders adherence to therapy, monitor treatment safety, schedule office visits
Management

Welcome to HCVGuidelines.org

The AASLD and IDSA in partnership with the panel have created an updated web experience to facilitate easier and faster access to this important resource. Please select a patient profile from the menu above, click on a guidance section below, or use the search box to begin.
Management

### Treatment-Naive

- **Genotype 1**: GT1a: No Cirrhosis
- **Genotype 2**: GT1a: Compensated
- **Genotype 3**: GT1b: No Cirrhosis
- **Genotype 4**: GT1b: Compensated
- **Genotype 5 or 6**: TELC

A telocytome includes patients with chronic hepatitis C who have not been previously treated with interferon, peginterferon, ribavirin, or any HCV direct-acting antiviral (DAA) agent, whether experimental, investigational, or US Food and Drug Administration (FDA) approved.
Management

### Treatment-Naive Genotype 1a Without Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
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<tbody>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs&lt;sup&gt;*&lt;/sup&gt; for elbasvir</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>8 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (60 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (60 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is &lt;0 million IU/mL</td>
<td>8 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

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<tr>
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<th>DURATION</th>
<th>RATING</th>
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<tr>
<td>Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dosabuvir (600 mg) as part of an extended-ribavirin regimen or plus twice-daily dosabuvir (250 mg), with weight-based ribavirin</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily simeprevir (150 mg) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
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</tr>
<tr>
<td>Daily dasabuvir (60 mg)+ plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
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<tr>
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<td>16 weeks</td>
<td>IIA, B</td>
</tr>
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## Management

<table>
<thead>
<tr>
<th>Treatment-Naive</th>
<th>Treatment-Experienced</th>
<th>Unique Populations</th>
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<tbody>
<tr>
<td>Genotype 1</td>
<td>GT1a : P/R : No Cirrhosis</td>
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<tr>
<td>Genotype 5 or 6</td>
<td>GT1 : NS3 : No Cirrhosis</td>
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</tr>
<tr>
<td>Genotype 5 or 6</td>
<td>GT1 : NS3 : Compensated</td>
<td></td>
</tr>
<tr>
<td>Genotype X</td>
<td>GT1 : Non-NSSA : No Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Genotype Y</td>
<td>GT1 : Non-NSSA : Compensated</td>
<td></td>
</tr>
<tr>
<td>Genotype Z</td>
<td>GT1 : NS5A</td>
<td></td>
</tr>
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### Retreatment

This section provides guidance for patients whose treatment therapy failed. The level of evidence and strength of the recommendation vary, and are rated specific (R) and strong (S). Specific recommendations are given when treating different viral genotypes. Recommended regimen group, based on optimal efficacy, favorable tolerability, and cost-effectiveness, is outlined for each patient (Table 2). In general, retreatment regimens for patients with treatment failure are similar to the initial regimen for most patients, but may include additional complexity, and nucleoside/nucleotide inhibitors. Alternative regimens are those that are effective with clear advantages, limitations for use in certain patient situations, an alternative regimen may be optimal in specific situations. However, these regimens, lack well-substantiated data.
Management

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

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<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
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<td>Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), and weight-based ribavirin</td>
<td>12 weeks</td>
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<td>Daily simeprevir (150 mg) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily daclatasvir (60 mg)* plus sofosbuvir (400 mg)</td>
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<td>I, B</td>
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<td>16 weeks</td>
<td>IIa, B</td>
</tr>
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</table>

* Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 53 known to confer aRNA resistance.
* This is a 3-tablet formulation. Please refer to the prescribing information.
* The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
Management

HCV RNA Monitoring in Patients Receiving Antiviral Therapy

HCV RNA (IU/ml)

-8 -4 0 4 8 12 16 20 24 28 32 36 40

Baseline | Treatment Period | Follow-Up

Undetectable

Treatment Week
Management

Patient who do not achieve SVR
- Monitor LFT, CBC, INR q6-12month
- Consider re-treating
- IF F3-F4
  - HCC q6 months screening with US
PERINATAL TRANSMISSION

Approximately 5%-15% will transmit HCV (MTCT)
- CDC 4-7%
- Depends on HCV RNA viral load at time of delivery
- Co-infected with HIV and HCV - 2x higher risk
- Rare: Hep C Ab+ and HCV RNA –

Breastfeeding is not contraindicated in women with HCV

Screen infant at 18 months for HCV Ab and if + again after age 3

Women with HCV should be re-evaluated after delivery to assess for spontaneous clearance
- 10% with clearance

Treatment is contraindicated in Pregnancy
HCC Screening

Worldwide, hepatocellular carcinoma (HCC) is the sixth most common malignancy
2nd leading cause of cancer-related death

In 2012, there was an estimated 24,696 new cases of HCC diagnosed

1973: incidence was 1.51 cases per 100,000 persons
2011: incidence 6.20 cases per 100,000 persons
HCC Screening

![Graph showing survival rates after diagnosis of HCC for screening and control groups.](image-url)
HCC Screening

all adults with cirrhosis of any etiology

any patient with chronic HCV who has developed advanced fibrosis or cirrhosis (Metavir stage 3 or 4) even if treated and cured
  ◦ Rates decrease by 79% once cured but risk is still not 100% eliminated

recommend using a surveillance interval of 6 months.

If Coinfected with HBV
  ◦ Asian men 40 years of age or older
  ◦ Asian women 50 years of age or older
  ◦ Black men 40 years or older
  ◦ Patients with cirrhosis
  ◦ First degree family history of HCC
  ◦ Hepatitis D virus
HCC Screening

AFP is no longer recommended as a routine surveillance test

Hepatic US: sensitivity of 60 to 80% and specificity > 90% for detecting HCC at any stage
HCC Screening

Liver nodule

< 1 cm
- Repeat US at 3 months
  - Growing/changing character
  - Stable
    - Investigate according to size

> 1 cm
- 4-phase MDCT/dynamic contrast enhanced MRI
  - Arterial hypervascularity AND venous or delayed phase washout
    - Other contrast enhanced study (CT or MRI)
      - Arterial hypervascularity AND venous or delayed phase washout
        - Yes
          - HCC
        - No
          - Biopsy
    - No
Acknowledgement

Phil Bolduc, MD- Community Based HIV/Viral Hepatitis Fellowship Program Director
Gicauri Colon: Hepatitis Team MA
Alicia Gonzalez, RN and OBOT team

Team work makes the Dream Work!
References

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