HCV: FROM DIAGNOSIS TO CURE TO ELIMINATION

Jorge Mera, MD, FACP
Cherokee Nation Infectious Diseases
HCV: OUTLINE

- HCV 101
  - What you really need to know

- Workflow
  - Diagnosis
  - Lab/Imaging workup
  - Fibrosis Staging
  - Critical Information that guides treatment

- Treatment Plan and follow-up
“Everything Should Be Made as Simple as Possible, But Not Simpler”

Albert Einstein
HCV 101

What you really need to know
GOOD AND BAD NEWS

- The good news
  - Hepatitis C can be cured
  - Curing HCV reduces morbidity, mortality and TRANSMISSION

- The bad news
  - The HCV epidemic still remains **INVISIBLE**
    - Public/Medical providers/Policy makers
  - It is the infectious diseases with the highest mortality¹
  - AI/AN are the most affected compared to other races or ethnicities

- Good news again
  - YOU ARE HERE TODAY TO CAN CHANGE THIS

Holmberg SD, et al ID Week 2015 San Diego
What We Are Trying To Prevent

Ascites

End Stage Liver Disease

Esophageal Varices
HCV-ASSOCIATED DISEASE BURDEN (2015–2050)

Chhatwal et al. 2016 Hepatology 64:1442-1450
**HCV-ASSOCIATED DISEASE BURDEN (2015–2050)**

**Disease Burden (2015–2050)**

- **Liver-related Death**
  - No Treatment: 767,000
  - Pre-DAA Era: 578,000
  - DAA Era: 407,000
- **HCC**
  - No Treatment: 407,000
  - Pre-DAA Era: 299,000
  - DAA Era: 651,000
- ** Decomp. Cirrhosis**
  - No Treatment: 458,000
  - Pre-DAA Era: 63,000
  - DAA Era: 52,000

**20–30% reduction in HCV-associated disease burden**

Chhatwal et al. AASLD 2015 Abstract
50–70% reduction in HCV-associated disease burden

Chhatwal et al. AASLD 2015 Abstract 104
Patients with Chronic HCV

Specialist Providers

3,500,000

20,000

Lack of Specialist Availability Limits Access to HCV Treatment
NO DIFFERENCE IN CURE RATES BETWEEN PROVIDER TYPES
N=304

94.9% 96.7% 92.1% 93.8%

NP PCP Specialist Overall

75/79 58/60 152/165 285/304

HCV 101

Ascend Study Investigators
CROI 2016
NO DIFFERENCE IN HCV CURE RATES BETWEEN PROVIDER TYPES AT CNHS

N = 365

90.0% 92.1% 89.5% 90.6%

NP  PCP  Specialist  Overall

CNHS: Cherokee Nation Health Services
2014-2016
More people are dying of HCV than all 60 other nationally notifiable infectious diseases combined.
HCV – RELATED MORTALITY
RACE/ETHNICITY 2007 COMPARED TO 2011

Per 100,000 persons

AI/AN  Black  Hispanic  White

2007  2011

Byrd KK, et al Pub Hlth Rep 2011
250% INCREASE IN REPORTED HCV 2010-2014

Reported number of acute hepatitis C cases 2000-2014

CDC, National Notifiable Diseases Surveillance System
Incidence of Acute Hepatitis C, by Race/Ethnicity – United States, 2000-2013

American Indian/Alaska Native  Asian/Pacific Islander
Black, Non-Hispanic  White, Non-Hispanic
Hispanic

Year

Source: National Notifiable Diseases Surveillance System (NNDSS)
WHAT IS DRIVING THE HCV EPIDEMIC TODAY IN THE USA

Time Magazine, June 15, 2015
200% increase in acute HCV in 17 states from 2007-2012

Recent studies show:
- ~ 70% PWID
- Many used prescription opioids
- Many 18 to 29 years old
- Predominantly white
- Equally female and male
- More non-urban and suburban

Sources: MMWR 2011; MMWR 2014; www.cdc.gov/hepatitis
Blood
- IVDU is the leading cause in the United States
  - Snorting
- Percutaneous injuries
- Dental
- Tattooing
- Blood transfusion (Before 1992)

Sexual contact
- Rare in heterosexual
- More frequent in HIV + MSM

Mother-to-child
- The rate is 1.7% - 4.3%
- Increased in IVDU, HIV co-infection, VL (?)

*Nosocomial; Health-care work; Perinatal
TODAY > 80% OF HCV TRANSMISSION OCCURS IN PWID
Paraphernalia is important in transmission
Dear Baby Boomers: Hep C Isn’t Your Fault, According to New Study

The spread of hepatitis C virus genotype 1a in North America: a retrospective phylogenetic study

Medical practices, not lifestyle choices, are actually behind the generation’s high HCV rates, so now will you go get tested?
**TOWARD A MORE ACCURATE ESTIMATE OF THE PREVALENCE OF HEPATITIS C IN THE UNITED STATES**

- **Addition of Groups**
  - Incarcerated
  - Homeless
  - Nursing Home Residents
  - Hospitalized Persons
  - Active Military Duty

- **Recalculation of Groups**
  - Healthcare Workers
  - Chronic Hemodialysis
  - Veterans

4.6 (Range 3.4-6.0) million Antibody Positive for HCV

3.5 (Range 2.5-4.7) million living with chronic HCV

**Edlin et al. HEPATOLOGY, 2015. 62,5;1353-1363**

Adapted from Hepatitis Web Study & the University of Washington Hepatitis C Online Course
Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

Rationale

- 45%-85% of infected persons are undiagnosed
- Limitations of current risk-based strategies
- 75% of chronic infections are in persons born from 1945-1965
Patients who were evaluated for treatment at CNHS (2012)
Natural History of HCV Infection.

HCV INFECTION
NATURAL HISTORY IN A 30 YEAR PERIOD

Acute HCV
- Incubation: 2-26 wks.
  - Resolved 15%
  - Extrahepatic manifestations

Chronic HCV 85%
- Cirrhosis 40%
- Slowly progressive 75%
- HCC 4%
- Liver failure 25%

HCC, hepatocellular carcinoma
NATURAL HISTORY OF CHRONIC LIVER DISEASE

Chronic liver disease

Compensated cirrhosis

Development of complications:
- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

 Decompensated cirrhosis

Death
<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>1-year mortality</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Compensated <strong>without varices</strong></td>
<td>1%</td>
<td>&gt;12 years</td>
</tr>
<tr>
<td>2</td>
<td>Compensated <strong>with varices</strong></td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Decompensated with ascites <strong>without variceal hemorrhage</strong></td>
<td>20%</td>
<td>~2 years</td>
</tr>
<tr>
<td>4</td>
<td>Decompensated without ascites <strong>with variceal hemorrhage</strong></td>
<td>57%</td>
<td></td>
</tr>
</tbody>
</table>
HEPATITIS C: PROGRESSION OF DISEASE

HCV Infection

Normal Liver

Chronic Hepatitis

Cirrhosis

20-25 years

25-30 years

HCC
ESLD
Death
HCV IS NOT JUST A LIVER DISEASE
Approximately 40% of HCV patients will develop at least one extrahepatic manifestation.

Often not clinically recognized.

Many patients may not have concurrent evidence of liver disease.
EXTRAHEPATIC MANIFESTATIONS

- Renal Disease
- Peripheral Neuropathy
- Dermatologic Manifestations
- Diabetes
- Lymphomas
COMMON SYMPTOMS OF HCV IN THE ABSENCE OF CIRRHOSIS

- Fatigue
- Impaired cognitive function (brain fog)
- Migratory arthralgia or myalgia
  - Many patients equivocally diagnosed with rheumatoid arthritis or other autoimmune diseases (personal communication)
- Depression
PORPHYRIA CUTANEA TARDA (PCT)

HCV Extrahepatic Manifestation
LEUKOCYTOCLASTIC VASCULITIS

HCV Extrahepatic Manifestation
- Risk increased by 70% compared to non-infected controls (OR 1.7)

- Successful HCV treatment associated with decrease in insulin resistance and reduction in incidence of diabetes mellitus

Patients with extrahepatic manifestations should be prioritized for treatment.

Successful treatment of HCV reduces risk of DM and lymphoma.

Successful treatment of HCV has benefit for vasculitis and renal disease.
IDENTIFYING PRIORITIES TO IMPROVE OUTCOMES

HCV Care Cascade

- Total US Population with Chronic HCV: 100%
- HCV Detected: 50%
- Referred to Care: 32–38%
- HCV RNA Test: 20–23%
- Underwent liver fibrosis staging: 12–18%
- Treated: 7–11%
- Successfully treated: 5–6%

HCV Workflow

- Confirm Diagnosis
- Lab/Imaging workup
- Fibrosis Staging
- Critical Information
- Treatment
THE SCREENING CASCADE

HCV antibody

Nonreactive

No HCV antibody detected

STOP*

Reactive

Not detected

HCV RNA

Detected

Current HCV infection

Link to care

No current HCV infection

Additional testing as appropriate**

* 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.

**VIRAL LOAD**

- *Number of virus particles* (RNA) per mL of blood
- Confirms active infection
  - 20% of acutely infected patients spontaneously resolve
- *Defines the duration of treatment*
  - For genotype 1 (when treating it with Sofosbuvir/Ledipasvir)
- *It defines cure* when the viral load is not detected
  - 12 weeks after treatment is discontinued, sustained virological response (SVR 12)

*Does not predict liver disease progression*
### LAB/IMAGING WORKUP

<table>
<thead>
<tr>
<th>Test Description</th>
</tr>
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<tbody>
<tr>
<td>Hepatitis A Antibody (R)</td>
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<tr>
<td>Hepatitis B Surface Antibody (R)</td>
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<tr>
<td>Hepatitis B Core Antibody (R)</td>
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<tr>
<td>Hepatitis B Surface Antigen (R)</td>
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<tr>
<td>Complete Blood Count with Differential (CBC w/ Diff.)</td>
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<tr>
<td>Comprehensive Metabolic Panel (CMP)</td>
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<tr>
<td>Alpha Fetoprotein Tumor Marker (R)</td>
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<tr>
<td>Vitamin D Total (R)</td>
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<tr>
<td>HIV Screen 4th Generation wRfx (R)</td>
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<tr>
<td>Iron Profile</td>
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<td>PT/INR</td>
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<tr>
<td>PTT</td>
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<tr>
<td>Thyroid Stimulating Hormone (TSH)</td>
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<tr>
<td>Hemoglobin A1c</td>
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<tr>
<td>Drug Screen Urine</td>
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<tr>
<td>Hepatitis C Genotyping (R)</td>
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<tr>
<td>Hepatitis C RNA PCR Quantitative (R)</td>
</tr>
<tr>
<td>US Abdomen Limited</td>
</tr>
<tr>
<td>US Hep C FIBROSCAN shear wave, Liver elastography</td>
</tr>
</tbody>
</table>
LAB WORK UP

- **Genotype** determines treatment
  - Three main genotypes in the US: GT1, GT2, and GT3

- **Hep A** serology is important for Immunization
  - Order total Hep A total antibody or IgG antibody

- **Hep B** serology is important for
  - Immunization and to monitoring reactivation
  - Order HBsAg, HBcAb (total or IgG) and HBsAb

- **HIV** serology
  - Important to treat HIV
  - Important to treat HCV (interaction with some HIV medications)
LAB WORK UP

- **CBC:**
  - Hg important to determine if ribavirin can be used
  - Platelets are critical for liver fibrosis staging

- **Comprehensive metabolic pannel**
  - ALT/AST are important for liver fibrosis staging
  - Bilirubin is Important for Child Pugh Score if necessary
  - Creatinine:
    - Will determine treatment drugs if GFR < 30 ml
    - May point to urgent treatment if it is due to HCV related nephropathy

- **Urinary Drug Screen**
  - Important to address issue and refer to
    - Behavioral health
    - Needle exchange program if available
    - Opioid substitution program if pertinent and available
**Ultrasound**
- Specific for advanced liver disease but *not sensitive*
  - Nodular liver
  - Ascites
  - Splenomegaly
  - Portal vein flow
- Screens for liver cancer
- May find other comorbidities such as fatty liver

**Fibroscan**
- Used for liver fibrosis staging
Histologic Features of HCV Infection According to Different Scoring Systems

A Portal tract

B Stage 2: Portal and periportal fibrosis

C Stage 3: Bridging Fibrosis

D Stage 4: Regenerative nodules

**LIVER FIBROSIS STAGING**

- **F0:** No fibrosis
- **F1:** Scattered portal fibrosis
- **F2:** Diffuse periportal fibrosis
- **F3:** Bridging fibrosis
- **F4:** Cirrhosis

**Cirrhosis**
- Compensated
- Decompensated
  - History or presence of ascitis
  - Hx of esophageal bleeding due to esophageal varices
  - Hx or presence of hepatic encephalopathy
HOW DO WE STAGE LIVER FIBROSIS

- **Non Invasive**
  - AST Platelet Ratio Index
  - FIB-4
  - Fibrosure
  - Fibroscan

- **Invasive**
  - Liver biopsy

Calculators found at www.hepatitisc.uw.edu
An APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. APRI score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis.

University of Washington: Hepatitis C Online www.hepatitisc.uw.edu/
A FIB-4 score <1.45 has a negative predictive value of 90% for advanced fibrosis. A FIB-4 >3.25 has a 97% specificity and a positive predictive value of 65% for advanced fibrosis.

University of Washington: Hepatitis C Online www.hepatitisc.uw.edu/
The probe of the Fibroscan device is positioned in an intercostal space near the right lobe of the liver, and a 50-MHz wave is passed into the liver from a small transducer on the end of the probe. The device then measures the velocity of the shear wave (in meters per second) as this wave passes through the liver, and this measurement is converted to a liver stiffness measurement.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3594956/
FIBROSCAN
(TRANSIENT ELASTOGRAPHY)

Castera Transient Elastography Breakpoints

2.5  |  7.0  |  9.5  |  12.5  |  75kPa

Metavir  |  F0-F1  |  F2  |  F3  |  F4

Absent or mild fibrosis | Significant fibrosis | Severe fibrosis | Cirrhosis
HCV FIBROSURE™ is a noninvasive blood test that combines the quantitative results of six serum biochemical markers:

- α2-macroglobulin
- Haptoglobin
- apolipoprotein A1
- Bilirubin
- gamma glutamyl transpeptidase (GGT)
- ALT

with a patient’s age and gender in a patented artificial intelligence algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver.
**FIBROSIS STAGING ALGORITHM**

**Chronic HCV**

- Obvious Signs of Cirrhosis
- Screen for Varices and HCC

**Non-Invasive Staging (2 tests)**

- Concordant
  - Treat

- Discordant
  - Fibroscan/Fibrosure

FS: Fibrosis Score
Adapted from Boghal H, Sterling RK, Infect Dis Clin N Am 26 (2012) 839-847
- Treatment *may be different between* cirrhotic and non cirrhotic patients

- Treatment *will be different* between those patients with decompensated and NOT decompensated cirrhosis

- **All patients** with liver fibrosis (F3 or F4) will need screening for
  - hepatocarcinoma
  - Esophageal varices
  - Hepatic encephalopathy

- Patients with decompensated cirrhotic *need* to be referred to a liver transplant center

- **STAGING IS NOT TO DECIDE IF YOU SHOULD TO TREAT HCV**
  - **BECAUSE EVERYONE SHOULD BE OFFERED TREATMENT**
HCV Workflow

Confirm Diagnosis

Lab/Imaging workup

Fibrosis Staging

Critical Information

Treatment
Compliance
- Untreated psychiatric illness/Active drug use/Active alcohol abuse

Renal Function
- GFR < 30
  - Determines type of antivirals and dosing of RBV if needed
  - Dialysis (only one antiviral FDA approved)

Other medications
- Antacids, anti seizure medications and others
  - Drug interaction should be done on all patients prior to determine treatment

For those with decompensated cirrhosis
- Child Pugh score / Meld score

Previous antiviral treatment
Pregnancy risk
**DATA COLLECTION**

**Coordination of Care**
- Nurse Case Manager: ____________________________
- HCV Clinic Location: ____________________________
- HCV Evaluating Provider: _________________________
- Treatment Provider: _____________________________
- Pharmacy to send Rx: ____________________________
- Rx Insurance Co: _______________________________

**HCV Evaluation**
- GT: ____________  APRI: ____________  FIB-4: ____________
- Fibroscan: ____________  Fibrosis Stage: ____________  Initial Eval Date: ____________
- Previously Treated: Y / N  Regimen: _________________
- Cirrhosis: Y / N  If yes, MELD: ____________  Child Pugh Class: ____________

**Treatment Data**

<table>
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<th>Week __</th>
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**Demographics**
- Name: ____________________________
- MRN: ____________________________
- DOB: ____________  Age: ____________
- Phone: ____________________________
- Gender: ____________  BMI: ____________
- Ht(cm): ____________  Wt(kg): ____________

**Hemoglobin**
- Platelets
- ALT
- AST
- Total Bilirubin
- Creatinine/GFR
- INR
- Albumin
- AFP
- Hepatitis A Total Ab
- Hepatitis B Surface Ag
- Hepatitis B Surface Ab
- Hepatitis B Core Ab
- HCV RNA quant
- HIV status

**Treatment Regimen:** ____________________________
- Start Date: ____________________________  End Date: ____________________________  SVR Due: ____________________________
- Date of last IVDU: ____________________________  Reorder meds: ____________________________

**Hep A**  **Hep B**
- #1
- #2
- #3
NOW WHAT?

Lets Treat HCV !!!!!!
HCV Workflow

1. Confirm Diagnosis
2. Lab/Imaging workup
3. Fibrosis Staging
4. Critical Information
5. Treatment