HCV: 101

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DISCLOSURES

- I have participated on advisory board meetings for Gilead and Abbvie Pharmaceuticals.

- Cherokee Nation receives Grant funding from the following institutions:
  - Oklahoma University
  - Aids Education and Training Center (AETC)
  - Indian Health Services
HCV: OUTLINE

- HCV 101
  - What you really need to know

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

- Treatment basics
HCV 101

What you really need to know
HCV Treatment: What We Are Trying To Prevent

Ascites

End Stage Liver Disease

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

50–70% reduction in HCV-associated disease burden

Chhatwal et al. AASLD 2015 Abstract 104
Lack of Specialist Availability Limits Access to HCV Treatment

Patients with Chronic HCV

Specialist Providers

3,500,000

20,000
NO DIFFERENCE IN HCV CURE RATES BETWEEN PROVIDER TYPES AT CNHS
N= 365

CNHS: Cherokee Nation Health Services, PCP: Primary Care Physician,
NP: Nurse Practitioner
More people are dying of HCV than all 60 other nationally notifiable infectious diseases combined.
HCV – RELATED MORTALITY
RACE/ETHNICITY 2007 COMPARED TO 2011

Byrd KK, et al Pub Hlth Rep 2011

Per 100,000 persons

AI/AN  Black  Hispanic  White

2007  2011
Incidence of Acute Hepatitis C by Race/Ethnicity - USA, 2000-2013

What is driving the HCV epidemic today in the USA?

Source: National Notifiable Diseases Surveillance System (NNDSS)

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
HCV: TRANSMISSION

- **Blood**
  - IVDU is the leading cause in the United States
    - Snorting
  - Percutaneous injuries
  - Dental
  - Tatooing
  - 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
Medical practices, not lifestyle choices, are actually behind the generation’s high HCV rates, so now will you go get tested?
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)
HEPATITIS C: PROGRESSION OF DISEASE

- **HCV Infection**
- **Normal Liver**
- **Chronic Hepatitis**
- **20-25 years**
  - **Cirrhosis**
  - **85%**
- **25-30 years**
  - **HCC**
  - **ESLD**
  - **Death**
  - **30% - 40%**
  - **4% per year**
NATURAL HISTORY OF CHRONIC LIVER DISEASE

Chronic liver disease

Compensated cirrhosis

Medium Survival > 12 years

Development of complications:

• Variceal hemorrhage
• Ascites
• Encephalopathy
• Jaundice

Decompensated cirrhosis

Medium Survival ~ 2 years

Death

HCV IS NOT JUST A LIVER DISEASE
~40% of HCV patients will develop at least one extrahepatic manifestation

Often not clinically recognized

Many don’t have concurrent evidence of liver disease

- Renal Disease
- Peripheral Neuropathy
- Dermatologic
- Lymphomas
- Diabetes (OR 1.7)¹

Successful HCV treatment is 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.
HCV Workflow

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

* 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.

- **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*
HCV Workflow

- Confirm Diagnosis
- Lab/Imaging workup
- Fibrosis Staging
- Critical Information
- Treatment
LAB/IMAGING WORKUP

- Hepatitis A Antibody (R)
- Hepatitis B Surface Antibody (R)
- Hepatitis B Core Antibody (R)
- Hepatitis B Surface Antigen (R)
- Complete Blood Count with Differential (CBC w/ Diff...)
- Comprehensive Metabolic Panel (CMP)
- Alpha Fetoprotein Tumor Marker (R)
- Vitamin D Total (R)
- HIV Screen 4th Generation w/Rfx (R)
- Iron Profile
- PT/INR
- PTT
- Thyroid Stimulating Hormone (TSH)
- Hemoglobin A1c
- Drug Screen Urine
- Hepatitis C Genotyping (R)
- Hepatitis C RNA PCR Quantitative (R)

Tests
- US Abdomen Limited
- US Hep C FIBROSCAN shear wave, Liver elastography
**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 panel**
  - 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
HCV Workflow

1. Confirm Diagnosis
2. Lab/Imaging workup
3. Fibrosis Staging
4. Critical Information
5. Treatment
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 with septa
- 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**
  - **Laboratory**
    - AST Platelet Ratio Index
    - FIB-4
    - Fibrosure
  - **Imaging**
    - Transient Elastography (Fibroscan)/MRE

- **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/
FIBROSIS STAGING ALGORITHM

Chronic HCV

Obvious Signs of Cirrhosis

Screen for Varices and HCC

Non-Invasive Staging (2 tests APRI/FIB-4/Fibrosure/Fibroscan)

Concordant

Treat

Discordant

Use a 3rd test (Fibroscan/Fibrosure)

CNHS Workflow Algorithm
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
Confirm Diagnosis

Lab/Imaging workup

Fibrosis Staging

Critical Information

Treatment

HCV Workflow
OTHER CRITICAL INFORMATION

- 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
HCV Workflow

Confirm Diagnosis

Lab/Imaging workup

Fibrosis Staging

Critical Information

Treatment
“The goal of treatment of HCV-infected persons is 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 an SVR”

SVR: sustained virological response
SVR (cure) of HCV is associated with:

- 70% Reduction of Liver Cancer
- 50% Reduction in All-cause Mortality
- 90% Reduction in Liver Failure

Lok A. NEJM 2012; Ghany M. Hepatol 2009; Van der Meer AJ. JAMA 2012
DIRECT ACTING ANTIVIRAL AGENTS (DAAS): KEEPING THEM STRAIGHT

**Protease**
- NS3
- NS5A
- NS5B

**Non-Enzyme Target**
- NS4A
- NS4B

**Polymerase**
- p7

**Ribavirin**

**NS3 Protease Inhibitors**
- Boceprevir (BOC)
- Telaprevir (TVR)
- Simeprevir (SMV)
- Paritaprevir (PTV)
- Grazoprevir (GRZ)

**NS5A Replication Complex Inhibitors**
- Daclatasvir (DCV)
- Ledipasvir (LDV)
- Ombitasvir (OMV)
- Elbasvir (ELB)
- Velpatasvir (VEL)

**NS5B NUC Inhibitors**
- Sofosbuvir (SOF)

**NS5B Non-NUC Inhibitors**
- Dasabuvir (DSV)
# HCV THERAPIES - DAAS

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<th>NS5A Inh</th>
<th>NS3 PI</th>
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* Need to be combined with sofosbuvir +/- ribavirin
# HCV Treatment by Genotype

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</table>

* Need to be combined with sofosbuvir + ribavirin
65 year old HCV positive female with a hx of a post partum blood transfusion 40 years ago

- Genotype 1a
- VL 8.8million/ML
- Treatment naïve
  - Fibrosis Stage F3-F4
  - No history of
    - Esophageal varices/ encephalopathy or ascitis
  - Labs: GFR of 28 ml/min, Hg 13 Platelets 109
  - Other medical conditions
    - Barrett's esophagus (on omeprazole 40 mg once a day)

What are your options?
Hepatitis C: Genotype 1a Cirrhotic Treatment Regimen

Does the patient have decompensated cirrhosis?

Yes →

No →

Treatment experienced?

No →

Check NSSA RAVs

EBR/GZR 12 weeks

Alternative DCE/ADV

(+) RAVs

(+) RAVs

ELB/GZR and PrOD are contraindicated with CTP Class B or C cirrhosis

Alternative choice
WHO TO TREAT, AND WHEN? WHO TO PRIORITIZE?

Who to treat?
- All patients with chronic HCV should be treated, unless:
  - Life expectancy is < 1 year that cannot be remediated by treating HCV or liver transplantation (AASLD)
  - Uncontrolled comorbidities that can cause HCV treatment discontinuation (Dr. Mera’s Opinion)

When to Prioritize
- Limited resources for medication procurement
- Limited clinical capacity to treat
SUMMARY: WHAT DO YOU NEED TO KNOW TO SELECT THE BEST TREATMENT OPTION

- Genotype
- Viral load for GT1a (< 6 million ?)
- Liver Fibrosis Staging
  - Cirrhosis vs no Cirrhosis
  - If Cirrhotic
    - Compensated vs Decompensated
- Previous treatment status
- Kidney function
  - CrCl < or > 30
  - Dialysis
- Drug interaction check
  - Anti seizure meds, PPI, etc.
- Check Hepatitis B status to monitor reactivation
WHAT NOW?

Join the ECHO Community and start Paving the Road to HCV Elimination in Native America
THE ECHO MODEL IMPROVES CAPACITY AND ACCESS SIMULTANEOUSLY
MOVING KNOWLEDGE INSTEAD OF PATIENTS
SHARING EVIDENCE BASED BEST MEDICAL PRACTICES
Benefits to Rural Clinicians

• Professional interaction with colleagues with similar interest
  – Less isolation with improved recruitment and retention
• A mix of work and learning
• Obtain HCV certification
• Access to specialty consultation with GI, hepatology, psychiatry, infectious diseases, addiction specialist, pharmacist, patient educator
IMPACT OF ECHO IN CNHS HCV PROGRAM

CNHS: Cherokee Nation Health Services
HELPFUL RESOURCES

- http://www.hcvguidelines.org/

- http://www.hepatitisc.uw.edu/
  - On-line curriculum on liver disease and HCV, includes clinical studies, clinical calculators, slide lectures

- ECHO guidelines
REFERENCES

1. Sovaldi® [package insert]. Gilead Sciences, Foster City, CA
2. Harvoni® [package insert]. Gilead Sciences, Foster City, CA
7. Project ECHO. University of New Mexico. http://echo.unm.edu/