HCV: 101

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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 TREATMENT: WHAT WE ARE TRYING TO PREVENT

Ascites

End Stage Liver Disease

Esophageal Varices
WHY DO WE NEED TO TREAT HCV

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
HCV-ASSOCIATED DISEASE BURDEN (2015–2050)

Disease Burden (2015–2050)

Liver-related Death
- No Treatment: 767,000
- Pre-DAA Era: 317,000
- DAA Era: 154,000

HCC
- No Treatment: 407,000
- Pre-DAA Era: 198,000
- DAA Era: 63,000

Decomp. Cirrhosis
- No Treatment: 651,000
- Pre-DAA Era: 198,000
- DAA Era: 31,000

Liver Transplants
- No Treatment: 0
- Pre-DAA Era: 63,000
- DAA Era: 31,000

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 HCV CURE RATES BETWEEN PROVIDER TYPES AT CNHS

N= 365

NP: 90/100 (90.0%)
PCP: 130/141 (92.1%)
Specialist: 111/124 (89.5%)
Overall: 331/365 (90.6%)

CNHS: Cherokee Nation Health Services 2014-2016
More people are dying of HCV than all 60 other nationally notifiable infectious diseases combined.
ACUTE HEPATITIS C INCIDENCE
USA, 2000 – 2013

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)
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

Paraphernalia is important in transmission

Needle
Syringe
Mixing container
Table
tourniquet

EDUCATE YOUR PATIENTS
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
CNHS HCV: AGE DISTRIBUTION (N=263)

Patients who were evaluated for treatment at CNHS (2012)
HCV SCREENING IN CHEROKEE NATION*
8/2015 - 5/2017

Patients tested

Expanded Age Targeted Screening (Ages 20-69)
Lab Triggered Screening discontinued

Lab Triggered Screening Initiated

*preliminary data
HCV “LAB TRIGGERED” SCREENING *
WW HASTINGS HOSPITAL

Patients Screened 11/15 - 2/16

- HCV Negative (4908)
- New HCV Positive
- Known HCV Positive

New HCV Positive Patients

Non Babyboomers: 60
Baby Boomers: 37

*preliminary data
LAB TRIGGERED SCREENING: LOCATION PATIENTS WERE SCREENED

97 patients with new HCV antibody screen at WW Hastings Hospital

- 34% Urgent Care
- 33% Emergency Department
- 14% Primary Care
- 8% Women's Clinic
- 3% Podiatry Clinic
- 2% Orthopedic Clinic
- 1% Surgery Clinic
- 1% Behavioral Health
- 3% Infectious Diseases
- 3% Dental Clinic

67% of the HCV seropositive patients were detected in the Urgent Care/Emergency Department
HEPATITIS C: PROGRESSION OF DISEASE

HCV Infection

- Normal Liver
- Chronic Hepatitis
- Cirrhosis
- HCC
- ESLD
- Death

85% of HCV infections progress to Chronic Hepatitis within 20-25 years.

30-40% of patients with Chronic Hepatitis develop Cirrhosis within 25-30 years.

4% per year of patients with Cirrhosis develop HCC.

Death from HCC and ESLD occurs in 30-40% of patients.
NATURAL HISTORY OF CHRONIC LIVER DISEASE

Chronic liver disease

Compensated cirrhosis

Median Survival ~ 12 years

Median Survival ~ 2 years

Decompensated cirrhosis

Development of complications:

- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

Death

HCV IS NOT JUST A LIVER DISEASE
COMMON SYMPTOMS OF HCV IN THE ABSENCE OF CIRRHOSIS

- Fatigue
- Impaired cognitive function
  - “Brain fog”
- Migratory arthralgia or myalgia
  - Misdiagnosed Rheumatoid Arthritis
- Depression
Approximately 40% of HCV patients will develop at least one extrahepatic manifestation

- Often not clinically recognized

- Many patients do not have concurrent evidence of liver disease
EXTRAHEPATIC MANIFESTATIONS

- Diabetes
- Dermatologic Manifestations
- Lymphomas
  - Other cancers
- Renal Disease
- Peripheral Neuropathy
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

PORPHYRIA CUTANEA TARDA (PCT)
LEUKOCYTOCLASTIC VASCULITIS
EXTRAHEPATIC MANIFESTATIONS

- 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: OUTLINE

- HCV 101
  - What you really need to know

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

- Treatment basics
HCV WORKFLOW

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

- Cure
- Surveillance
**THE SCREENING CASCADE**

**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**

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* 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**
  - 15-30% 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 complete - sustained virological response (SVR 12)
- **Does not predict liver disease progression**
HCV WORKFLOW

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

- Cure
- Surveillance
LABORATORY WORKUP

- Hepatitis C RNA and genotype
- Hepatitis Serology
  - Hep A Total antibody
  - Hep B surface antibody, Hep B surface antigen, Hep B core antibody
- HIV serology
- CBC with differential
- Comprehensive metabolic panel
- Iron profile (Fe, TIBC, Ferritin)
- 25 OH Vitamin D
- Urinary drug screen
- PT/INR
- Alpha Fetoprotein Tumor Marker (AFP)
- Fibrotest
**Genotype**
- determines treatment
- Three main genotypes in the US: GT1, GT2 and GT3

**Hep A serology**
- Order total Hep A total antibody or IgG antibody
- If non-reactive, patient needs vaccination

**Hep B serology**
- 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**
  - HgB 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
  - GFR
    - Will determine treatment (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
Stage 1: Mild inflammation

Stage 2: Portal and periportal fibrosis

Stage 3: Bridging Fibrosis

Stage 4: Regenerative nodules
LIVER FIBROSIS STAGING

- **F0**: No fibrosis
- **F1**: Scattered portal fibrosis
- **F2**: Diffuse periportal fibrosis
- **F3**: Bridging fibrosis
- **F4**: Cirrhosis
  - Compensated
  - Decompensated
    - History or presence of ascites
    - 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**
    - Fibroscan/MRE

- **Invasive**
  - Liver biopsy
APRI: AST TO PLATELET RATIO INDEX

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.

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)

Concordant

Discordant

Concordant

Treat

Fibroscan/Fibrosure

FS: Fibrosis Score
Adapted from Boghal H, Sterling RK, Infect Dis Clin N Am 26 (2012) 839-847
Why is it important to stage?

- 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 cirrhosis **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

- Cure
- Surveillance
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 (Two antivirals FDA approved)

- Other medications
  - Antacids, PPIs, anticonvulsants and others
    - Drug interaction should be done on all patients prior to determining treatment

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

- Previous antiviral treatment

- Pregnancy risk
Confirm Diagnosis
Lab/Imaging workup
Fibrosis Staging
Critical Information
Treatment

- Cure
- Surveillance
Treatment of HCV

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GOAL OF 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
IMPACT OF TREATMENT COMPARED TO OTHER COMMON DISEASES

- HCV cirrhosis risk = 40% over 30 years
- Hepatocellular carcinoma (HCC) risk in HCV Cirrhosis = 17% over 5 years
- When we cure 30 patients with HCV we will prevent:
  - 12 cases of HCV related cirrhosis
  - 2 case of HCV related HCC

If we treat 104 patients with hypercholesterolemia with statins (For 5 years), we will prevent 1 first time heart attack and $\frac{3}{4}$ of a stroke

www.thennt.com
DIRECT ACTING ANTIVIRAL AGENTS (DAAS): KEEPING THEM STRAIGHT

Protease

**NS3**
- Ribavirin
- **NS3 Protease Inhibitors**
  - Boceprevir (BOC)
  - Telaprevir (TVR)
  - Simeprevir (SMV)
  - Paritaprevir (PTV)
  - Grazoprevir (GRZ)
  - Voxilaprevir (VOX)
  - Glecaprevir (GLE)
- Daclatasvir (DCV)
- Ledipasvir (LDV)
- Ombitasvir (OMV)
- Elbasvir (ELB)
- Velpatasvir (VEL)
- Pibrentasvir (PIB)

Non-Enzyme Target

- NS5A Replication Complex Inhibitors
- Sofosbuvir (SOF)
- Dasabuvir (DSV)

Polymerase

**NS5A**
- NS5A NUC Inhibitors

**NS5B**
- NS5B Non-NUC Inhibitors
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
73 year old HCV positive male with no risk factors

- Genotype 2
- VL 3.4 million/ML
- Treatment naïve
- ALT 72, AST 65
- No history of ascites, variceal bleed or encephalopathy
- Labs: GFR of 69 ml/min, Hg 13.4, Platelets 88
- (Fibrosis score ?)
- Other medical conditions
  - Prediabetes/40 pack/year smoking/HTN on amlodipine
  - Hypercholesterolemia on atorvastatin

What are your options?
What are his Drug - Drug Interactions with Epclusa or Mavyret?
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
  - ALT 38, AST 61
  - No history of
    - Esophageal varices/ encephalopathy or ascites
  - Labs: GFR of 28 ml/min, Hg 13 Platelets 109
  - Other medical conditions
    - Barrett's esophagus (on omeprazole 40 mg once a day)

(Fibrosis score ?)

What are your options?
CLINICAL CASE #3

- 55 year old HCV positive male with a hx of IVDU 10 years ago
- Genotype 1a
- VL 2.4 million/ML
- Treatment naïve
- AST 24, ALT 38 Labs: GFR of 65 ml/min, Hg 13
- Platelets 245
- (Fibrosis score ?)
- Other medical conditions
  - HTN on amlodipine

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

Is patient treatment experienced?

- yes

- no

LDV/SOF 8 weeks

May consider:
- IF HCV RNA ≤ 6 million
- Ø black
- Ø HIV

G/P 8 weeks

Check for NS5A RASs

(-) RASs

LDV/SOF 8 weeks
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
  - GFR < 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
TELEMEDICINE IMPROVES ACCESS BY USING TECHNOLOGY TO BRIDGE DISTANCE

Specialist

Primary Care Clinician OR Patient

Treatment
THE ECHO MODEL IMPROVES CAPACITY AND ACCESS SIMULTANEOUSLY
MOVING KNOWLEDGE INSTEAD OF PATIENTS
Benefits of ECHO® model to Health System

- Quality and Safety
- Rapid Learning and best-practice dissemination
- Reduce variations in care
- Access for Rural and Underserved Patients, reduced disparities
- Workforce Training and Force Multiplier
- De-monopolize Knowledge
- Improving Professional Satisfaction/Retention
- Supporting the Medical Home Model
- Cost Effective Care- Avoid Excessive Testing and Travel
- Prevent Cost of Untreated Disease (e.g.: liver transplant or dialysis)
- Integration of Public Health into treatment paradigm
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
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