Update on Hepatitis C virus infection

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Disclosures:

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Hepatitis C Virus:

- Structure of the virus
- Historical facts
- Prevalence
- Diagnosis
- Clinical manifestations
- Natural history
- Treatment
Hepatitis C Virus

- Nucleic Acid: 9.6 kb ssRNA
- Classification: *Flaviviridae, Hepacivirus*
- Genotypes: 1 to 9
- Enveloped
- In vitro model: primary hepatocyte and T cell cultures; replicon system
- In vivo replication: in cytoplasm, hepatocyte and lymphocyte; human and other primates
Hepatitis C Virus

**Genome and Gene Products**

- **5' UTR**
- **3' UTR**

**Structural protein coding region**
- C
- E1
- E2
- NS2

**Nonstructural protein coding region**
- P7
- NS4A
- NS4B
- NS5A
- NS5B

**Host signal peptidase**

**Serine Protease**

**Core**
- Protease
- Cofactor
- Protease
- Helicase
- RNA polymerase

**Envelope**
- Serine protease
HCV historical facts:

- 1970-80’s a chronic type of hepatitis associated with transfusion was recognized
- 1989 the HCV virus was identified
- 1990 blood banks start screening but tests were not perfected until 1992
- 1991 FDA approved first Interferon alpha
- 1998 FDA approved Interferon plus Ribavirin
- 2001 FDA approved Pegylated Interferon
- 2011 FDA approved first direct anti viral agent for HCV
HCV - Epidemiology

Prevalence

Worldwide

170 million (3%)

United States

Anti-HCV positive
3.9 million (1.8%)

HCV RNA positive
2.7 million (1.4%)

Lavanchy D & McMahon B, In: Liang TJ & Hoofnagle JH (eds.)
HCV - Epidemiology

Worldwide Prevalence

Heintges, T., Hepatology 1997; 26:521
Distribution of hepatitis C genotypes
By 2007 hepatitis C-associated deaths had overtaken HIV as a cause of mortality in the United States. To achieve declines in mortality similar to those seen with HIV will require new policy directions and commitment to detect and link infected persons to care and successful treatment.

DCC, decompensated cirrhosis
Most Americans With Chronic HCV Have Not Been Diagnosed and Few Have Been Treated

- Limited response to treatment with Interferon
- Severe side effect profile
- Multiple contra indications

Overall: 3.2 million of U.S. population with chronic HCV

- 50% (1.6M) Diagnosed
- 32-38% (1.0-1.2M) Referred to Care
- 7-11% (220,000-360,000) Treated
- 5-6% (170,000-200,000) Successfully Treated

HCV - Epidemiology

Risk Factors for Hepatitis C

- Clotting Factor Treatment Prior to 1987
- Blood Transfusion or Organ Transplant Prior to 1992
- Injection Drug Use
- Birth from Infected Mother
- Mass Injections and Traditional Practices
- Multiple Sexual Partners
- Long-Term Hemodialysis
- Mass Injections and Traditional Practices
- Birth from Infected Mother
- Clotting Factor Treatment Prior to 1987
- Blood Transfusion or Organ Transplant Prior to 1992
- Injection Drug Use
- Birth from Infected Mother
- Mass Injections and Traditional Practices
- Multiple Sexual Partners
- Long-Term Hemodialysis
The CDC and USPSTF recommend offering 1-time screening for HCV infection to adults born between 1945 and 1965.

BORN FROM 1945 TO 1965?

Americans born during these years have the highest rates of Hepatitis C.

Talk to your doctor about getting tested. Early detection can save lives.

www.cdc.gov/knowmorehepatitis
Who should be tested for hepatitis C

- Risk factors for HCV
- Elevated ALT
- Extra-hepatic
- Test for HCV antibody

Baby boomers
HCV Antibody test

If positive, test HCV RNA

HCV RNA negative = False positive or past infection

HCV RNA positive = current HCV infection

If negative

No HCV infection
Diagnostic Tests

- Hepatitis C antibody test: screening
- Qualitative HCV RNA test: confirmatory
- Quantitative HCV RNA test: monitor treatment
- Genotype: how to treat and for how long
- Liver biopsy: when to treat*

HCV - Diagnosis
Acute HCV Infection

- **HCV RNA positive**
- **Anti-HCV**
- **Symptoms**

**ALT (IU/L)**

- **0**
- **200**
- **400**
- **600**
- **800**
- **1000**

**Time After Exposure**

- **Weeks**
- **Months**

**Hoofnagle JH, Hepatology 1997; 26:15S**
Acute hepatitis C

- **Signs and symptoms:**
  - Asymptomatic (79% of cases)
  - Anorexia, right upper quadrant abdominal pain, with or without jaundice, arthralgia, myalgia, fatigue, weight loss, skin rash and fever.

- **Laboratory tests:**
  - CMP: increased AST, ALT up to thousands, mild increase in ALK phosphatase and GGT, variable increase in bilirubin, decreased albumin
  - Coagulation: prolonged prothrombin time in severe cases.

- **Natural history:** 55 to 85% of the patients will progress to chronic HCV
Chronic hepatitis C

• Signs and symptoms:
  • Asymptomatic
  • Fatigue, joint pain, dull right upper quadrant abdominal pain, anorexia, nausea, pruritus, memory loss

• Laboratory tests:
  • 1/3 of patients have normal ALT/AST.
  • Mildly increased AST/ALT (50-low hundreds), with typical fluctuation over time.
  • Increased PT and bilirubin, low albumin is seen as the disease progresses to cirrhosis.

• Natural history:
  • Remain as chronic hepatitis
  • Progress to cirrhosis and liver failure
  • Patients may develop liver cancer.
Extra hepatic Disorders Associated with Chronic HCV

<table>
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<th>Hematological</th>
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<tr>
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<td>Diabetes mellitus</td>
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<td>Idiopathic thrombocytopenic purpura</td>
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*Gumber SC and Chopra S., Ann Intern Med 1995;126
HCV - Natural History

Outcome Following Hepatitis C Infection

- Acute hepatitis C: 55 - 85% chance of chronic infection
- Chronic infection: 70% chance of chronic hepatitis
  - Chronic hepatitis: 1 - 4%/yr risk of HCC
  - Cirrhosis: 20% chance of decompensation
  - Cirrhosis: 4 - 5%/yr risk of HCC

Time (yr)

- 10
- 20
- 30
Stages of Fibrosis In Chronic Hepatitis

HCV - Natural History

Portal

Periportal

Septal

Cirrhosis
Liver biopsy or image modalities

- Degree of fibrosis is most important predictor of prognosis
- Useful in determining need for anti-viral therapy
- Advanced cirrhosis is associated with reduced response to treatment
Liver Biopsy
Factors Associated With Fibrosis

- Duration of infection
- Alcohol > 50 gm per day
- Age > 40 years at infection
- Male gender
HCV Genotypes

- Six major genotypes found throughout the world (1 to 6).
  - In Europe and U.S., 60-70% of patients have genotype 1 infection, followed by genotypes 2 and 3.
  - Treatment is different for G1 and G2 and 3.
Goals of Hepatitis C Treatment

Primary
- Eradicate the virus

Secondary
- Prevent progression to cirrhosis
- Reduce incidence of HCC
- Reduce need for transplantation
- Enhance survival
HCV - Natural History

Outcome Following Hepatitis C Infection

- **Acute hepatitis C**: 55 - 85%
- **Chronic infection**: 70%
- **Chronic hepatitis**: 20%
- **Cirrhosis**: 1 - 4%/yr
- **HCC**: 4 - 5%/yr
- ** Decompensation**
HCV - Treatment

Patterns of Response to Treatment in Hepatitis C

HCV RNA

Baseline

Treatment

Nonresponder

Sustained Responder

Relapser

HCV RNA Negative

Time
Progress in the Treatment of Hepatitis C

- IFN: 6% (1989)
- PEG-IFN: 18% - 23%
- IFN+RBV: 35% - 43%
- PEG-IFN+RBV: 47% - 63%
- DAAs: 70% - 90% (2012 - 2015)
Current HCV therapy Genotype 1:

- Sofosbuvir and Ledipasvir for 12 weeks or 24 weeks if patients is treatment experienced with cirrhosis.
- Sofosbuvir and Simeprevir combination for 12 weeks if treatment naïve, for 24 weeks if treatment experienced.
- Ombitasvir/Paritaprevir/Ritonavir without Ribavirin for Genotype 1b and with Ribavirin for Genotype 1a. Treat for 12 weeks if treatment naïve and 24 if treatment experienced.
HCV therapy for Genotypes 2 and 3:

• Sofosbuvir and Ribavirin for 12 weeks (Genotype 2)
• Sofosbuvir and Ribavirin for 24 weeks (Genotype 3)
HCV treatment special populations:

- HIV co-infected patients (pts) can be treated with similar response rate
- Pts with GFR no less than 30 can be treated safely
- Post liver and post kidney transplant pts can be treated with excellent response rate
- On going trials for treatment of pts on dialysis
- DAA awaiting FDA approval for pts on dialysis
Current HCV therapy:

- Response rate is similar regardless of genotype
- Response rate is similar regardless of the presence of cirrhosis
- Response rate is similar in different ethnic groups
- Overall response rates are 70 to 90%
- Interferon free regimens are well tolerated with mild adverse effects (headache, nausea, diarrhea and anemia)
Resources for DDIs

• AASLD treatment guidelines with regular updates
• Outstanding – University of Liverpool (David Back, Editorial Board, EASL reps); sponsored by Janssen, MSD, Roche, Vertex:
  – http://www.hep-druginteractions.org

• FDA:

• Other Online Resources –
  – Epocrates
  – Micromedex, Lexicomp and Others
What is in the pipeline?

- Even more effective direct anti-viral agents
- Shorter duration of therapy
- Therapy for pts on HD
HCV summary

• HCV infection is common and can be silent
• In addition to the classic risk factors all baby boomers MUST be tested
• Normal AST and ALT does not exclude HCV
• Untreated HCV may progress to cirrhosis and HCC
• Treatment is no simpler, better tolerated and shorter duration
• Response to therapy is seen in 70 to 90% of the treated patients
Thank you!