Update on Hepatitis C virus infection

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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 P7 3'UTR

Structural protein coding region

Nonstructural protein coding region

Host signal peptidase

Serine Protease

Core

Protease

Cofactor

Protease

Envelope

Serine protease

Helicase

RNA polymerase
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
HCV - Epidemiology

Worldwide: 170 million (3%)

United States:
- Anti-HCV positive: 3.9 million (1.8%)
- HCV RNA positive: 2.7 million (1.4%)

Distribution of hepatitis C genotypes
United States: Increased Morbidity and Mortality Due to HCV Now and in the Future

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
Recent Trend in Acute HCV Incidence in the US

Source: National Notifiable Diseases Surveillance System (NNDSS)
Most Americans With Chronic HCV Have Not Been Diagnosed and Few Have Been Treated

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

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

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

Risk Factors for Hepatitis C

HCV - Epidemiology

- Clotting Factor Treatment Prior to 1987
- Blood Transfusion or Organ Transplant Prior to 1992
- Long-Term Hemodialysis
- Multiple Sexual Partners
- Injection Drug Use
- Mass Injections and Traditional Practices
- Birth from Infected Mother
Birth Cohort Screening for HCV

Age-specific HCV Prevalence in US General Population (National Health and Nutrition Examination Surveys)

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

Baby boomers

Test for HCV antibody
Diagnostic Tests for HCV

HCV Antibody test

If positive, test HCV RNA

HCVRNA negative = False positive or past infection

HCV RNA positive = current HCV infection

If negative

No HCV infection
HCV - Diagnosis

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*
Acute HCV Infection

HCV - Diagnosis

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>
<thead>
<tr>
<th>Category</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>Essential mixed cryoglobulinemia, Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Renal</td>
<td>Membranoproliferative glomerulonephritis, Membranous nephropathy</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Porphyria cutanea tarda, Leukocytoclastic vasculitis, Lichen planus</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Diabetes mellitus *, Idiopathic thrombocytopenic purpura</td>
</tr>
</tbody>
</table>

*Gumber SC and Chopra S., Ann Intern Med 1995;126*
*Cacoub P, et al., Medicine 2000; 79:47*
Liver biopsy or image modalities

HCV as a risk factor for cardiovascular diseases

- Several small studies and a meta-analysis (Gastroenterology 2016; 150:145-55)
- Increased risk of cardio-vascular related mortality, carotid plaques and cerebrovascular diseases
Outcome Following Hepatitis C Infection

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

Time (yr): 10 20 30
Factors Associated With Fibrosis

- Duration of infection
- Alcohol > 50 gm per day
- Age > 40 years at infection
- Male gender
- Co-infection (HBV, HIV)
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 (?)
Stages of Fibrosis In Chronic Hepatitis

HCV - Natural History

1. Portal
2. Periportal
3. Septal
4. Cirrhosis
Liver Biopsy
Evaluation of fibrosis:

- Fibro sure test
- US elastography
- MRI elastography
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 G 1 and G 2 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
Progress in the Treatment of Hepatitis C

- **1989**
  - IFN: 6 - 16%
  - PEG-IFN: 18 - 23%

- **2011**
  - IFN + RBV: 35 - 43%
  - PEG-IFN + RBV: 47% - 63%

- **2012 - 2015**
  - DAAs: 70% - 90%
Gane EJ, Agarwal K. Am J Transplant 2014;14:994-1002.
Multiple Classes of Direct-Acting Antiviral Agents

- Ribavirin
- NS3 Protease Inhibitors
  - Simeprevir
  - Paritaprevir
  - Grazoprevir
- NS5A Replication Complex Inhibitors
  - Daclatasvir
  - Ledipasvir
  - Ombitasvir
- NS5B NUC Inhibitors
  - Sofosbuvir
- NS5B Non-NUC Inhibitors (NNI)
  - Dasabuvir

- Combinations of different classes of DAAs:
  - Provide near-universal cure
  - Are generally safe and well-tolerated
Current therapy for HCV Genotype 1 and 4

1) Daclatasvir and Sofosbuvir with and w/o Ribavirin for 12 or 24 weeks
2) Ledipasvir and Sofosbuvir with and without Ribavirin for 12 or 24 weeks
3) Sofosbuvir and Velpatasvir with and w/o Ribavirin for 12 weeks*
4) Ombitasvir, Paritaprevir/Ritonavir and Dasabuvir for 12 or 24 weeks, with or w/o Ribavirin
5) Simeprevir and Sofosbuvir, with or w/o Ribavirin
6) Elbasvir and Grazoprevir with and w/o Ribavirin**
Current HCV therapy: Genotypes 2 and 3

- Sofosbuvir and Ribavirin for 12 weeks or 24 weeks for G 2 and G 3 respectively.
- Sofosbuvir and Daclatasvir for Genotypes 2 and 3 *
  - Sofosbuvir and Velpatasvir **
General Concepts About Selecting HCV Regimens to Optimize SVR and Safety

- Choice of regimen, treatment duration, and use of ribavirin depends on:
  - Genotype
    - Genotype 1a vs 1b
    - Genotypes 2-6
  - Prior treatment experience (Naïve vs Experienced)
    - PEG-RBV failure
    - Prior protease inhibitor failure
    - Prior NS5A inhibitor failure
    - Prior sofosbuvir failure
  - Presence of cirrhosis
    - Compensated (CP-A) vs Decompensated (CP-B, CP-C)
    - Presence of baseline resistance-associated variants (NS5A)
  - Potential for drug-drug interactions
Principles of All Oral Regimens for HCV

• Combine drugs from different classes:
  • Hit multiple targets to increase efficacy
  • Diminish risk of viral resistance

• Possible strategies:
  • Backbone/Anchor drug plus additional agent(s)
  • Multiple drugs: When combined achieve superior efficacy than might be predicted by individual drug characteristics

• If done properly:
  • Near universal efficacy
  • Shortened duration of therapy
  • Adverse events have minimal impact on QOL
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
HCV treatment special populations:

- HIV co-infected patients (pts) can be treated with similar response rate
- Pts with renal failure including those on dialysis can be treated
- Post liver and post kidney transplant pts can be treated with excellent response rate
Hepatitis C in 2016: Treatment Recommendations

- Patients with HCV infection will achieve near universal cure with currently available regimens
- Treatment is safe and well tolerated
  - Caution when treating patients with decompensated cirrhosis (protease inhibitors)
  - Caution with drug-drug interactions (amiodarone)
- Optimizing SVR rates for different clinical scenarios includes lengthening duration of therapy, adding ribavirin, or performing baseline resistance testing
- Access to treatment remains the major barrier to improving health outcomes for all patients with HCV
What is in the pipeline?

- More pan genotypic direct anti-viral agents
- Shorter duration of therapy
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 now simpler, better tolerated and shorter duration
- Response to therapy is seen in 70 to 90% of the treated patients
Thank you!