Hepatitis C

New Hopes, .....but a long tale

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Chronic Liver Disease

Primary Causes of Chronic Liver Disease*

- Hepatitis C Virus (26%)
- Alcohol (24%)
- Unknown (17%)
- Other (5%) and Alcohol (3%)
- Hepatitis B Virus (11%)

*Jefferson County, Alabama, USA
Case #1

- 61 M- CPA
  - Abnormal LFTs found at a routine physical
  - HCV antibody +
    - PCR RNA +
    - Liver biopsy- mild inflammation and 2-3+ fibrosis
      - Mild to moderate fibrosis
      - Decision to actively treat his HCV
  - When was he likely infected?, and which genotype?
  - How did he likely contract the virus?
Natural history of HCV

Natural History of HCV Infection

- **Exposure (Acute Phase)**
  - Resolved: 15% (15)
  - Chronic: 85% (85)
  - HIV and Alcohol

- **Stable**: 80% (68)
  - Cirrhosis: 20% (17)
  - 75% (13)
  - HCC Transplant Death: 25% (4)

- **Slowly Progressive**
Prevalence of Hepatitis C

- Worldwide ~ 3%
  - About 170 million are infected with hepatitis C
  - Since the identification of hepatitis C virus (HCV) in 1989
    - The number of acute HCV cases has fallen 80%

- U.S.
  - About 3.2 million estimated to be infected
  - 1.6% of the population living with HCV
    - About 76% were born between 1945 and 1965
HCV a global prevalence

HCV Has Broad Global Prevalence
HCV Incidence since 1989

Incidence of acute Hepatitis C, by year
United States, 1982-2008

Estimated number of cases

Year


Hepatitis C. Centers for Disease Control & Prevention, 2011.
Prevalence of Hepatitis C

• U.S. continued
  • 3 of 4 seropositive persons are also viremic

• HCV accounts for
  • 20% of all acute cases of hepatitis
  • ~ 30,000 new acute HCV infections a year
  • 8000-10,000 deaths per year - 75% of those in ages 45 to 64
  • The death rate now exceeds that of HIV

• Most infected with HCV are unaware of their diagnosis
HCV in the U.S.

More than 3 million Americans have chronic hepatitis C. Up to 75% don't know it.
Prevalence of Hepatitis C

• In the U.S.
  • HCV is the leading cause of liver transplantation without treatment

• 15-40% of HCV positive patients will develop
  • Cirrhosis
  • Hepatic cancer

• ~50-60% of the new cases of HCV occur in people with histories of injection drug abuse
Future of HCV in the U.S.

- Magnitude of HCV complications in the next 10-20 years
  - 60% increase in cirrhosis
  - 68% increase in hepatocellular carcinoma
  - 280% increase in the incidence of liver failure
  - 500+% increase in need for liver transplantation
    - Currently 40% are done for HCV
  - 225% increase in death rate from liver disease
Prevalence leading to screening

- U.S. Preventive Services Task Force (USPSTF) has issued new screening recommendations
  - Those at high risk
    - H/o injection drug use
    - Sex with an injection drug user
    - Transfusion before 1992
  - All people born between 1945 and 1965 should undergo one-time HCV screening
  - Parallels a CDC recommendation
HCV screening

Hepatitis C

Testing baby boomers saves lives

3 Million
About 3 million adults in the US are infected with the hepatitis C virus, most are baby boomers.

3 in 4
Up to 3 in 4 people who are infected don’t know they have hepatitis C so they aren’t getting the necessary medical care.

1945–1965
Baby boomers, anyone born from 1945 through 1965, should get tested for hepatitis C.
Etiology of HCV

• Hepatitis C
  • A spherical, enveloped single-stranded RNA virus
  • Closely related to viruses of
    • Hepatitis G
    • Dengue
    • Yellow fever

• HCV can produce 10 trillion new viral particles each day
  • Worsened by daily alcohol consumption
Hepatitis C Virus

Structure of Hepatitis C Virus
- Envelope glycoproteins
- Core
- Viral RNA
- Approx 60 nm
- Structure of Hepatitis C Virus
Etiology of HCV

• HCV has

  • 6 genotypes, with numerous subtypes
    • Genotype 1 the major form worldwide, 40-80% of all HCV
      • Genotype 1a and 1b occurs in 74% of U.S. cases

    • Genotypes 2a, 2b, 2c occur in 10-15% of U.S. cases
      • Most responsive to treatment

    • Genotypes 3a and 3b in 4-6% of cases
      • Most prevalent in India, Pakistan, SE Asia, and Scotland

    • Genotypes 4, 5, and 6 < 5% of U.S. cases
Transmission of HCV

- Those at highest risk
  - Injection illegal drug users
    - In developed countries, most HCV cases ~60% are related to IV drug abuse
  - Shared straw, cocaine snorting
  - Less than 20% of new cases through sexual exposure

- Other exposures of lower risk
  - Needle-stick injuries - ~3%
  - Maternal-fetal transmission - less than 5%
Transmission of HCV

• Other exposures of lower risk, cont.
  • Via tattooing, sharing razors, acupuncture

• Transfusion-associated HCV, 1 case in 103,000 units
  • Blood pool screened since 1990

• Using polymerase chain reaction (PCR) as an assay
  • Transfusion risk is 1 in 230,000 donations
  • Window after infection, to detection can be 1 to 2 weeks with PCR
HCV Sources of Infection

Sources of Infection for Persons with Hepatitis C

- **Injecting Drug Use**: 60%
- **Sexual**: 15%
- **Transfusion (before screening)**: 10%
- **Other (Hemodialysis; health-care work; perinatal)**: 5%
- **Unknown**: 10%
Incidence of HCV demographics

• In U.S.
  • HCV more common in minority populations
    • Impact of lower socio-economic and educational levels
  • No sex preponderance

• 65% of persons with HCV are 30-49 years
  • Being infected while younger, has a somewhat better prognosis
  • Infection uncommon in those 20 and younger
HCV Prognosis

- HCV is *self-limited* in only a small minority

- Chronic infection
  - Develops in 70-80%
  - Cirrhosis develops within 20 years in 20%
  - ~10% develop hepatocellular carcinoma- HCC

- Hepatitis B infection, iron overload, and alpha 1-antitrypsin def. with HCV may promote a more rapid progression to cirrhosis
HCV Prognosis

• Chronic infection cont.
  • Cirrhosis and HCC higher when HCV acquired by transfusion
  • Likelihood of progression influenced by
    • Alcohol use
    • Immunosuppression, or HIV co-infection
    • Male sex
    • Age at acquisition (>40-55 years) impact of hepatic toxin exposure over time
    • Concomitant hepatitis, or conditions with iron excess
    • BMIs > 30
Detecting HCV

• Antibodies to HCV (anti-HCV Ab) are detectable after 2-4 weeks
  • 3rd generation anti-HCV enzyme immunoassays (EIA)
    • Presence of antibodies supports HCV infection has occurred,
      …..but not whether it has resolved

• Confirmation tests
  • RIBA (recombinant immunoblot assay)
    • Detects 4 different antigen areas, if 2 or more are +
      considered a positive test
HCV immune response
DX of HCV

Diagnostic Algorithm for HCV: Modified NIH Algorithm

- Consider other causes of ↑ ALT
  - PCR to confirm
    - Monitor and repeat as necessary
  - Low-risk patients: EIA-2
    - RIBA-2
      - PCR
        - Consider treatment
  - High-risk patients: EIA-2
    - Monitor and repeat as necessary

Detecting HCV

• Viral HCV-RNA
  • Qualitative and quantitative assays for HCV-RNA
    • Based on a polymerase chain reaction (PCR)
      • Quantitative PCRs measure *actual number of RNA copies*
      • Qualitative PCRs indicate, HCV-RNA present or absent (+ or -)
    • Identifies those HCV-RNA positive applicants who remain infected
      • HCV-RNA is only detected intermittently, a single negative test is *not* conclusive and warrants verification by repeat testing
      • HCV-RNA via PCR has largely replaced the use of RIBA
  • Used commonly to monitor response to HCV treatment
ALT and HCV

- Fluctuations in serum ALT are frequent but not an invariable feature of acute and chronic hepatitis
  - Peak levels of ALT tend to be lower with HCV
    - Infrequently exceed 120, and are < 48 in ~ 50%
    - Variability in ALT probably reflects waves of liver cell destruction
  - 10 years post-infection average ALTs may be normal or only slightly elevated
    - ALT levels do not correlate with the amount of damage
Liver Biopsy

• Only reliable way to assess current condition
  • Still may not be predictive of the future course

• The biopsy evaluates the extent of hepatic damage
  • Two important features (Batt’s – Ludwig scoring)
    • The severity of inflammation
      • Represented by “Grade” on a scale of “0” to “4”
    • Extent of fibrosis or cirrhosis
      • Represented by “Stage” with a scale of “0 to 4”
      • Stage 0 no fibrosis
      • Stage 4 is cirrhosis
Liver Biopsy in HCV

• Numerous staging and grading scoring systems
  • Batt’s and Ludwig
    • Referenced in Swiss Re Life Guide

• Knodell Histologic Activity Index Score (HAI)
  • Referenced in Hannover’s Ascent manual
  • Numerical score given to degree of inflammation and fibrosis
  • The higher the score the more severe the inflam./fibrosis
  • Scores of 4 or less = mild inflammation/fibrosis

• Regardless of the system used, when fibrosis worse than “mild” the prognosis worsens
Signs and Symptoms of HCV

• Acute hepatitis C
  • For ~75% initial symptoms are nonspecific or absent
    • Fatigue and malaise
    • Generally, acute Hep C goes completely unnoticed

• When symptomatic, often extra hepatic
  • Commonly involving the joints, muscle or skin
    • Arthralgias, myalgias
    • Paresthesias
    • Pruritis
Signs and Symptoms of HCV

- Commonly symptoms arise when HCV is advanced in stage....or associated with:
  - De-compensated chronic liver disease
    - Hepatic synthetic and metabolic dysfunction
    - Portal hypertension resulting from cirrhotic damage
    - Mental status changes, edema, hematemesis,

- When symptoms present, there is cause for genuine concern
Treatment of Hepatitis C

- Acute Hepatitis C
  - Most go undetected (75%.. or more)
  - When identified in first 1-3 months of infection
    - Response to pegylated interferon + Ribavirin may be very favorable in > 90%
      - Length of treatment can also be shorter ~ 6 months
  - Unfortunately, early discovery is quite rare and explains the burden of chronic Hepatitis C
Treatment of Chronic HCV

• Main goal
  • Achieve a sustained viral response (SVR)
    • Defined as an absence of HCV-RNA at least 6 mo after discontinuation of therapy
  • HCV-RNA assessed by PCR
    • Preferably should have a repeat PCR in follow up for validation
    • Overcomes issue of HCV RNA being intermittently detectable
Case #2

- 48 F RN needle stick
  - HCV+ genotype 2
  - Completes 48 weeks of Peginterferon + Ribavirin
    - LFTs and PCR negative after 12 weeks
    - Anemic and depressed but finishes Tx while continuing to work
    - PCR HCV-RNA (-) at Tx completion and again at 6 mo
    - Considered an SVR 1 year out, when HCV-RNA remains undetectable
- Do you offer, and at what rate?
Treatment response in HCV

• Three types of response to therapy
  • SVR
    • HCV-RNA levels become undetectable in 4-24 wks and remain negative for the duration of treatment
    • ALT normalizes, and bx improves if done in f/u
      • Including many with cirrhosis
  • Relapse or breakthrough
    • 10-20% HCV RNA reappears usually a few weeks after end of treatment
Treatment responses in HCV

• Response types, cont.
  • Non-response
    • HCV-RNA never becomes undetectable
  
  • If HCV-RNA doesn’t decrease significantly by 12 weeks, SVR is unlikely in > 98%
    • Initial response to treatment
      • Therapeutic milestone and decision point at 3 months
  
  • Decision to stop treatment impacted by
    • Costs, 48 weeks of therapy can cost $50 to 70K
    • Avoiding side-effects when therapeutic benefit very low
Treatment of Chronic HCV

• Decision to treat considerations

  • HCV-RNA is detectable
  • Elevated ALT levels
    • Remember ALT levels don’t correlate with disease severity
    • May regularly oscillate around normal
  • Liver biopsy suggestive of progressive disease
    • Generally more than “mild” fibrosis present
  • Absence of any serious co-morbid conditions
Treatment of Chronic HCV

• Remember, there are no useful predictors of HCV severity of disease

• Favorable factors influencing a response to therapy
  • Younger age
  • Shorter duration of infection
  • Absence of cirrhosis or advanced liver disease
  • Lower levels of HCV-RNA in serum
    • < 2 million viral copies/ml
Treatment of Chronic HCV

• Therapy options have improved substantially
• Interferon (INF)-alpha
  • Monotherapy holds a 5-15% SVR response rate
  • Adding
    • A polyethylene glycol (auto antifreeze) moiety
      • INF becomes more biologically active, has a better tissue distribution, and increased half-life
      • Pegylated interferon = peginterferon

• Peginterferon and Ribavirin is now the standard of care
The evolution of efficacy with interferon-based therapy over the last 10 years:

- Interferon a-2b 24 weeks: 0%
- Interferon a-2b 48 weeks: 18%
- Interferon a-2b tiw + Ribavirin: 41%
- PEG-Interferon: 24% - 36%
- PEG-Interferon a-2b qw + Ribavirin: 54%
- PEG-Interferon a-2b qw + weight dosed Ribavirin: 61%
Treatment of Chronic HCV

• Combination PegINF and ribavirin
  • Duration of therapy is commonly 48 weeks
    • 70-80% of those with genotypes 2 or 3 achieve a SVR
    • Up to 45% with genotype 1 achieve a SVR
Triple therapy for HCV

- Direct-acting antiviral protein agents
  - Telaprevir
  - Boceprevir

- Triple-therapy regimens for Genotype 1
  - PegInterferon + ribavirin + one of the new agents
  - Approved only for genotype 1
  - More side effects (SEs) and complex to take
    - Must be taken every 8 hrs
Triple therapy for HCV

- Genotype 1 (3 drug) regimens with
  - Either Boceprevir + Ribavirin + PegInf
    - Common SEs: anemia, neutropenia, dysgeusia
  - or... Telaprevir
    - Common SEs: anemia, rash, anorectal pain

- Drugs cannot be used alone in genotype 1 due to early antiviral resistance

- Triple therapy of genotype 1 improves response rate ~ 70% vs. the prior 45%
Figure 2. Adverse Events and Side Effects Noted as Reasons for Alfa Discontinuation, Stratified by Genotype (N = 252)^a

*Categories are not mutually exclusive. 30% of patients with "other" adverse events also had ≥ one additional adverse event noted.
Newer oral therapies for HCV

• Treatment without PegInterferon
  • Avoids the SEs associated with interferon as well as the need for parenteral administration

• Sofosbuvir (NEJM May 2013)
  • A polymerase inhibitor used with ribavirin in genotypes 2 and 3
    • In patients who were intolerant of PegInf
    • Patients to failed on 2 drug therapy to achieve a SVR
  • 12 weeks of therapy showed a 100% rate of SVR
Interferon-free therapies of HCV

- Expect them to dominate HCV therapy the next 5 years
  - Simeprevir (FDA review 10-13)
    - Oral therapy with ribavirin, 80% response rates

- A simple oral regimen that becomes a reality will
  - Significantly reduce HCV morbidity and mortality
Underwriting HCV

• Maintain our current approach
  • Underwriting manuals are valid
    • Impact of a SVR after treatment
      • After 1-2 years STD to T2 for most age 40 and above
    • Respect shown for regular ethanol use with HCV
    • Respect for HCV duration and impact of age
    • Recognize the impact of more than mild fibrosis on bx

• Remember cirrhosis and hepatocellular cancer risks in those with chronic Hep C
Case #1

• 61M CPA
  • HCV found after abNL LFTs and specific HCV testing
  • Moderate fibrosis found on biopsy
    • How does that risk stratify him?
  • Decision made to treat him

• Expected response rate to Peginterferon+ Ribavirin?
  • Genotype impact on response rate
Case #3

• 52 M
  • MVA in 1986 warranting multiple transfusions
  • Social amount of alcohol
  • HCV+ when he attempts to donate blood in 2011
  • LFTs 1.5 to 2 x normal, ALT 89, AST 76, GGT 201
  • Liver bx = moderate fibrosis
  • Treatment begins in May of 2011
    • Lots of side-effects from Rx
    • 12 wks into Tx
      • LFTs remain abnormal
      • PCR-RNA still > 3.5 million copies/ml
Case #3

• 52M with Hep C
  • Stops treatment d/t SEs
  • Feels well, and continues 2-3 alcoholic beverages
  • Gains 20lbs to 255lbs, while height is 5’9”

• Risk profile?
  • Is he high SS?
  • What influences his risk?
Hepatitis C

Questions?
Resources

- eMedicine.com: Hepatitis C, July 2013
- NIH.gov Hepatitis C: a clinical review
- Swiss Re Life Guide
- Liang TJ, Ghany MG. Current and Future Therapies for Hepatitis C Virus Infection: NEJM 2013; 368; 1907-17
- Jacobson IM, Gordon SC, Dowdley KV et al. Sofosbuvir for Hepatitis C genotype 2 and 3 in Patients without Treatment Options. NEJM 2013;368; 1867-77