Hepatitis C

Update for Public Health Professionals
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Hepatitis C Talk Aims

- Epidemiology and Testing Review
- Discuss Variability of Natural History
- Discuss Variability of Treatment Response
  - Variable intensity and duration of therapy
- Discuss Success with Acute Hepatitis C
- Discuss Rising Numbers of HCC
Hepatitis C Virus

- RNA virus identified 1988
  - Several genotypes, many quasispecies
- Causative agent: transfusion-associated NANB hepatitis

**Hypervariable region**

5' core E1 E2 NS2 NS3 NS4 NS5 3'

capsid envelope protein protease/helicase RNA-dependent RNA polymerase
HCV: Background

- Currently <40,000 infections/year
  - < 20% of acute hepatitis cases
  - 70% of chronic hepatitis cases
  - 25-30% of advanced liver disease
  - 40-50% of liver transplantation

- Infection not uncommon
  - Nearly 4,000,000 Americans (1.8%)
    - estimated 90,000 Tennesseans
  - 5-8% of users of VA healthcare system
HCV: Prevalence of Infection Among Blood Donors*

Anti-HCV Prevalence

- >5% - High
- 1.1%-5% - Intermediate
- 0.2%-1% - Low
- <0.1% - Very Low
- Unknown

* Anti-HCV prevalence by EIA-1 or EIA-2 with supplemental testing; based on data available in January, 1996
Hepatitis C Virus: Transmission

- High Risk: Primarily Bloodborne
  - Transfusion
  - Injection Drug Use
- Lower Risk
  - Sexual contact, Incarceration, Cocaine
  - Perinatal
Estimated Incidence Acute HCV

Source: Hepatology 31:777-82, 2000
Post-transfusion Hepatitis C

Adapted from HJ Alter and Tobler and Busch, Clin Chem 1997
Age Distribution 1988-94

NHANES III Data

Percent Anti-HCV Positive vs. Age in Years for different age groups:
- 6-11
- 12-19
- 20-29
- 30-39
- 40-49
- 50-59
- 60-69
- 70+

NHANES III Data
Age Distribution: Time Shift

Source: CDC, NHANES III
Hepatitis C Virus Infection

<table>
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<tr>
<th>Time after Exposure</th>
<th>Titer or IU</th>
<th>Symptoms</th>
<th>ALT</th>
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<td>0</td>
<td>Anti-HCV</td>
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<tr>
<td>Years</td>
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HCV: Framing the Issue

- **Personal Health Issues**
  - Many patients feel poorly
  - Some are at risk for advanced liver disease
  - Premature death and hepatoma (HCCa)

- **Public Health Issues**
  - Transmission
  - Cost of care, limited organs for transplantation
  - Increasing death rate from HCCa
HCV: Whom to Test

- Prior Injection Drug Use
  - Even once
- Persons with selected medical conditions, including
  - Persistently/intermittently abnormal (ALT/SGPT)
  - Unexplained liver disease
  - Hemodialysis patients
    - Difficult to test
HCV: Whom to Test

- Transfusion / Transplantation
  - Receipt of clotting factor concentrates produced before 1987
  - History of blood products prior to 1992
  - History of organ transplant prior to 1992

- Recognized exposure
  - Healthcare workers (percutaneous/cutaneous)
  - Neonates of HCV moms
HCV: Whom to Test ????

- Recipients of transplanted tissue
  - e.g., corneal, musculoskeletal, skin, ova, sperm
- Intranasal cocaine, other non-injecting drug users.
- History of tattooing or body piercing.
- High Risk Sex
  - Multiple sex partners
  - HCV Positive partner
- Incarceration
HCV: How to Test

- Antibody detection
  - ELISA / EIA
  - RIBA

- Virus detection
  - Qualitative
    - RT-PCR
  - Quantitative
    - Variably sensitive technology
## HCV: Antibody Testing

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<tr>
<th>Assay</th>
<th>ELISA</th>
<th>RIBA</th>
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<td>C100-3</td>
<td>C-100-3</td>
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*Medina et al., Semin Liver Dis 15:33*
## HCV Ab Testing: How Good?

<table>
<thead>
<tr>
<th>Assay</th>
<th>Sensitivity*</th>
<th>Predictive Value†</th>
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<tr>
<td></td>
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<td>Low Prev</td>
</tr>
<tr>
<td>Elisa-1</td>
<td>70-80%</td>
<td>30-50%</td>
</tr>
<tr>
<td>Elisa-2</td>
<td>92-95%</td>
<td>50-61%</td>
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<tr>
<td>Elisa-3</td>
<td>97%</td>
<td>25%</td>
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* c/w clinical and PCR
† c/w RIBa

*Gretch et al., Hepatology 26:43S*
Antibody Testing Problems

- **False Negatives**
  - Patients with antibody deficiency
    - Hematological diseases
  - Dialysis patients
  - Immunosuppressed patients
    - Transplant recipients

- **False Positives**
  - Hypergammaglobulinemia (Autoimmune)
  - Low risk patients
HCV: Virus Testing

- **Qualitative**
  - RT-PCR
    - Most sensitive, gold standard

- **Quantitative**
  - Many technologies
  - Must pay attention to sensitivity limits
HCV: Testing Issues

- Confirming positive ELISA / EIA
  - At risk, recommended but may not be needed
  - Normal ALTs, low risk: RIBA
  - Abnormal ALT, high risk: Sensitive PCR

- Negative Ab test: at risk
  - Sensitive PCR, properly handled

- Quantitative viral testing
  - Sensitivity and comparability
  - Only very sensitive quants ok for monitoring therapy
HCV: Genotype Testing

- Genotypes: differ by 30-25% bp
- Quasispecies: differ by 1-9% bp
- Genotypes 1-6
- Genotype 1 (60-70% US)
- Implications for:
  - Success therapy
  - Length and intensity of therapy
HCV: Natural History

- Acquisition usually **not** symptomatic
- 50-90% develop chronic disease
  - Most have little evidence of disease
  - Cirrhosis and hepatoma develop in some
- Progression of disease can be enhanced
  - Lifestyle factors (e.g. Alcohol, Obesity)
  - Genetics
- Treatment can be beneficial
HCV: Variable Complication Risk

- Estimated 10-20% over 20-30 years
- Hepatoma risk 1-4% per year after cirrhosis
- Aggravating Factors
  - Alcohol
  - > 40 yo at acquisition
  - Gender and race
  - Hemochromatosis and AA1T heterozygotes
  - Immunosuppression / HIV poorly controlled
  - Obesity / steatohepatitis
- NOT Viral load - this is not HIV
HCV Nat Hx Study: Anti-D IgG

- Irish woman getting Rh neg prophylaxis 1977
  - 17 year follow up
- Mass screening due to HCV+ donor
  - 704 Ab+ / 390 RNA+ = 55%
  - 376 systematically evaluated
    - 55% elevated ALT
  - 363 had liver biopsy
    - 98% inflammation (52% >min)
    - 51% some fibrosis, 2% cirrhosis (2/7 with alcohol use)
HCV: Role of Liver Biopsy

- Not Required
- Confirm Diagnosis
  - Assess for additional diagnoses
- Stage Disease (fibrosis)
- Assess risk of progression
  - More severe fibrosis, higher risk
  - Adjust therapeutic aggressiveness
- Assess Probability of Response
HCV Positive: Evaluation

- Physical Examination
- Biochemical Disease Markers
  - Bilirubin, AP, ALT, AST, Albumin
- CBC with platelets, PT
- Hep B sAg, cAb total, sAb, Hep A Ab total
  - Hepatitis A and B vaccination
- HIV testing
- Encourage lifestyle modification
HCV Positive: Clinical Pearls

- **CBC with platelets**
  - Low counts c/w portal hypertension

- **Biochemical Disease Markers**
  - Bili ≥ 3, Albumin ≤ 3 and PT ≥ 3 sec - - all bad

- **Transaminases can be deceptive**
  - Correlate poorly with fibrosis
  - Change with time
    - Follow up IVDU: 2 y, ≥ 4 testings (Hepatology 29:590)
      - ALT stayed normal 42%, ever abnormal 43%
      - 15% persistently abnormal
HCV: Treatment Goals

- Classical ID Model
  - Eliminate virus, eliminate disease?
  - Increasing evidence
    - Responses are durable
    - QOL increases
    - Progression risk decreased
    - Decreased risk of hepatoma?

- "HIV" Model: suppress hepatitis
  - Possibly beneficial, data conflicting
  - Potential option for some patients
HCV: Treatment

- Drug Choices: all expensive
  - An Interferon and Ribavirin (6 - 18 mo)
    - First line therapy
  - An Interferon alone (min 12 mo)
    - Relapse rate too high
- Classic Interferons - short half-life
  - Intron, Roferon, Imfergen
- PEGylated Interferons - long half-life
  - PEG-Intron (Shering)
  - PEGASYS (Roche)
HCV: Treatment Side Effects

- **Interferons**
  - Low WBC and Platelets
  - Fatigue, mood swings
  - Thyroid abnormalities

- **Ribavirin**
  - Hemolytic anemia
  - Teratogenicity

- Increased difficulty with HIV therapy
- Growth factor support
HCV: Treatment Variability

- **Response Variable (10-70%)**
  - Poor predictors
    - Genotype 1, high viral load
    - Afroamerican and Hispanic ethnicity
    - Obesity

- Response to interferon is key

- Evaluate return on investment

- Some patients not candidates in 2007
  - Consistently normal ALT/AST?
  - Advanced disease
  - Alcohol, drug abuse, severe psychiatric disease
  - Other “Life-limiting” illness
# HCV: Treatment Responses

<table>
<thead>
<tr>
<th></th>
<th>PEG-Intron 1.5 µg/kg</th>
<th>Intron A 3 MU</th>
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<tr>
<td></td>
<td>QW</td>
<td>TIW</td>
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<tr>
<td>Overall Response</td>
<td>52% 264/511</td>
<td>46% 231/505</td>
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<tr>
<td>Genotype 1</td>
<td>41%</td>
<td>33%</td>
</tr>
<tr>
<td>Genotype 2-3</td>
<td>75%</td>
<td>73%</td>
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</table>

PEG-Intron: 1.5 µg/kg QW
Ribavirin: 800 mg QD
Intron A 3 MU: 1000/1200 mg QD

Ribavirin: 1000/1200 mg QD
HCV: Refining Strategies

- **New Medications Still in Development**
- **Primary Therapy Interferons and Ribavirin**
  - Discontinuation parameters
- **Strategies**
  - Adjusting length of therapy to rapidity of viral clearance
    - Genotype 2 or 3: 3-4 months if VL = 0 at 4 weeks
    - Genotype 2 or 3: ? Longer with delayed response or prior relapse
    - Genotype 1: lengthen or intensify therapy if VL not 0 at 12 weeks.
HCV: Maintenance Therapy

- Usually interferon monotherapy
  - After failure to eradicate virus, but
  - Biochemical/histological response, and
  - Tolerance to interferon side effects

- Indications
  - Bridging fibrosis and compensated cirrhosis
    - Reduce progression and hepatoma?
  - Symptomatic cryoglobulinemia
  - Disabling "HCV symptoms"
  - Transplant and HIV patients
HCV: Acute Hepatitis C

- Infrequently Recognized with IDU
- Occupational Needle Sticks
- Iatrogenic Transmissions
- Treatment
  - Highly successful if treated in first year (>90%)
    - Related to treatment adherence
    - Not genotype dependent
  - Probably only 6 months required
Hepatocellular Carcinoma (HCC)

- Most Common Primary Liver Tumor
  - Adults
- Traditionally Rare in North America
  - Incidence has > doubled over last 10-20 years
    - 20,000 cases per year
  - Mortality nearly equals incidence
- Fourth Leading Cause of Cancer Death Worldwide
  - Leading cancer in areas of Africa and Asia
HCV: Major Contributor to NA HCC

- Hepatocellular Carcinoma Risk
  - Increased by most forms of cirrhosis
  - Risk rises dramatically after cirrhosis in HCV (4%/y)

- Screening Strategies Argued
  - Start after fibrosis significant
  - Alphafetoprotein (AFP) poor but done
  - US inadequate in my opinion
  - CT multiphase contrast or MRI with contrast

- Treatment Options Poor
  - Transplant for limited disease
HCV: Hepatoma Numbers Rising

Male
All
Female
**HCV: Summary**

- **HCV: Still a Large Burden of Disease**
  - Wave will pass in 20 years or so
  - Will be replaced by fatty liver disease
- **Progression Variable**
- **Treatment Response Variable**
  - Genotype, VL and Ethnicity important
  - Acute Disease with excellent response
- **Successful Treatment Halts/Reverses Disease**
- **Hepatocellular Carcinoma Rates Rising due to HCV**
  - Fatty liver disease will continue the trend