The Changing Landscape of Hepatitis C Testing and Therapy

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9-30-2015

Hepatitis C Virus (HCV)

- Flaviviridae family
- Recent widespread human transmission
  - Transfusion services
  - ID drug use
- Chronic HCV Infection
  - 3.8 million U.S.
  - >130 million worldwide
- Most chronic infection undiagnosed

Discovery HCV

- Search for basis of non-A, non-B hepatitis
  - 85% of blood transfusion hepatitis
  - DNA or RNA virus?
- Purify nucleic acid from infected chimpanzee
- Copy and clone into bacteriophage λgt11
- Identify clones expressing viral proteins using antibodies from non-A, non-B patient

“It is not unrealistic to expect that other elusive agents may now be recognized using similar approaches”

Harvey Alter, Annals of Internal Medicine 1991
- Genome ssRNA
- Replicates in hepatocytes
- HCV genome does not integrate into host genome allowing spontaneous clearance and therapeutic cures

**Viral load tests**
- Genotyping (low resolution)
- Interferon sensitivity pro-protein
- Genotyping (high resolution)

**5' UTR**
- Genotyping (high resolution)
- Serine protease inhibitors
- RNA polymerase NS3/4A

**HCV Genotypes 1-7**

- Multiple Subtypes (a,b,c,...)
- Type 1 virus most common in the US and most challenging to treat
- Assays and therapies optimized to type 1 virus

![HCV Genotype Pie Chart]

**Genotype and subtype used to inform:**

- Selection of therapy
- Length/duration of therapy
- Likelihood of resistance mutations

<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>SUBTYPE (total=64)</th>
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<tbody>
<tr>
<td>1</td>
<td>a,b,c,d,e,f,g,h,l,j,k,m (13)</td>
</tr>
<tr>
<td>2</td>
<td>a,b,c,d,e,f,g,h,l,j,k,l,m,n,o,p,q,r (18)</td>
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<tr>
<td>3</td>
<td>a,b,c,d,e,f,g,h,l,k (10)</td>
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<tr>
<td>4</td>
<td>a,b,c,d,e,f,g,h,l,j,k,l,m,n,o,p,q,r,s,t,u (21)</td>
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<tr>
<td>5</td>
<td>a (1)</td>
</tr>
<tr>
<td>6</td>
<td>a,b,c,d,e,f,g,h,l,j,k,l,m,n,o,p,q,r,s,t (20)</td>
</tr>
<tr>
<td>7</td>
<td>a (1)</td>
</tr>
</tbody>
</table>

**Confirmed subtypes**
**Provisional subtypes**
**Provisional subtypes added since 2006**
Natural History of Hepatitis C

- Acute Hepatitis C (rarely diagnosed)
- Chronic Hepatitis C: 85%
- Cirrhosis: 20%
- Liver cancer: 1-5%

- #1 cause of cirrhosis
- #1 cause of liver failure
- 10,000 death per year
- #1 cause for liver transplant in the US

The Changing Face of HCV in the US


Natural History of Chronic HCV Progression

- Chart review of 485 plasma donors infected in Austria during 1970s (mean follow-up: 33 yrs)
- First liver transplant: 18 yrs after infection
- First death: 28 yrs after infection

Recent Increase in HCV Infection

- Between 2007 to 2012
  - 50% increase in case reporting
  - 200% increase in 17 states
- Risk factors
- ~70% persons who inject drugs
- Previous oral prescription narcotic use
- Equally male to female
- Young, ages 18-29 years
- Rural and suburban
- White

Source: [CDC.gov/hepatitis](http://www.cdc.gov/hepatitis)

Transmission Among Persons Who Inject Drugs

- Transmission risks
  - injection duration
  - Injection frequency
  - Equipment sharing
- HCV prevalence
  - 27 to 51%
- Incidence declined in response to HIV harm reduction (syringe access programs)


Other Modes HCV Transmission

- Accidental needle stick in healthcare setting
  - HCV risk is 1.3%, HIV risk is 0.3%
- 18 healthcare-associated outbreaks from 2008 to 2013
  - 223 cases involving over 90,550 at risk persons notified
- Non-injecting drug use (e.g., intranasal cocaine use)
- Perinatal-infants born to HCV infected mothers
  - ~4% risk if mother infected with HCV
  - ~25% risk if mother co-infected with HCV and HIV
- Sexual transmission is rare
  - HIV infected MSM at highest risk
- Miscellaneous reported
  - Unregulated tattooing


Bending the HCV Outcomes Curve

- Estimated 45% to 85% of HCV persons with chronic HCV are unaware of infection
- Screening strategies have been based on risk*
  - Blood transfusion before 1992, IV drug exposure
  - Many in highest risk cohort do not identify themselves
- Recent treatments only ~ 50% effective, expensive
  - Many identified persons have elected to wait for better drugs which are now available (Combination DAAs)

• In 2012 the CDC issued guidelines recommending a one-time anti-HCV antibody test for all baby boomers (those born during 1945 through 1965), although those at high risk should be tested regularly. MMWR Recomm Rep. 2012;61(RR-4):1-32.

Other Screening Indications
• Persons who have injected drugs (once)
• Persons with conditions associated with HCV – HIV
• Elevated aminotransferase (ALT)
• Hemodialysis
• Transfusions/organ transplants prior to 1992
• Children of HCV infected mothers
• Exposed healthcare workers
• Sexual partners of HCV infected individuals *

Laboratory Testing for HCV Infection
• Serology - anti-HCV antibodies screening test (EIA or CIA)
  
  RIBA

  Virus Detection - HCV RNA qualitative PCR or TMA quantitative real-time PCR
HCV Immunoassay (IA)

HCV IA detects antibodies to 3 or more viral proteins

**Signal to Cutoff Ratios (S/Co)**

<table>
<thead>
<tr>
<th>Screening Test Kit Name</th>
<th>Manufacturer</th>
<th>Signal-to-cut-off of the time</th>
<th>S/CO predicts HCV viremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ortho HCV Version 3.0 EIA</td>
<td>Ortho EIA</td>
<td>&gt; 3.8</td>
<td>S/CO guide to choosing screening confirmation</td>
</tr>
<tr>
<td>Abbott HCV EIA 2.0</td>
<td>Abbott EIA</td>
<td>&gt; 3.8</td>
<td>(RIBA vs PCR) testing algorithm now obsolete</td>
</tr>
<tr>
<td>VITROS Anti-HCV</td>
<td>Ortho CIA</td>
<td>&gt; 8.0</td>
<td>S/CO predicts HCV viremia</td>
</tr>
<tr>
<td>AxSYM Anti-HCV</td>
<td>Abbott MEIA</td>
<td>&gt; 10.0</td>
<td>S/CO guide to choosing screening confirmation</td>
</tr>
<tr>
<td>Architect Anti-HCV</td>
<td>Abbott CMIA</td>
<td>&gt; 5.0</td>
<td>S/CO predicts HCV viremia</td>
</tr>
<tr>
<td>Advia Centaur HCV</td>
<td>Siemens CIA</td>
<td>&gt; 11.0</td>
<td>S/CO guide to choosing screening confirmation</td>
</tr>
</tbody>
</table>

**anti-HCV RIBA 3.0**

Reagent manufacture discontinued 2013
HCV Algorithm (2013)

- Nonreactive
  - HCV Ab
    - Reactive
      - HCV RNA
        - Not Detected
          - STOP
        - Detected
          - No current HCV Infection
          - Current HCV Infection
      - STOP
    - HCV RNA
      - Not Detected
      - STOP

Result Interpretation

<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV RNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Acute or chronic HCV depending on clinical context</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Past, resolved HCV infection; False Positive Screen</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Early acute HCV infection; chronic HCV in setting of immunosuppressed state; false positive HCV RNA test</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Absence of HCV infection</td>
</tr>
</tbody>
</table>

HCV Molecular Confirmation Issues

- Confirm with “sensitive” HCV RNA test
  - COBAS AmpliPrep/COBAS Taqman, quantitative (Roche)
  - RealTime HCV, quantitative (Abbott)
  - APTIMA HCV RNA, qualitative (Hologic) FDA approved for diagnosis HCV
- Both HCV Viral Load tests are very sensitive but none are FDA approved for diagnosis (still confirmation standard)
- Confirmation with quantitative assay is both process and cost efficient (baseline for therapeutic monitoring)
Issues for Timely Confirmatory Testing

• Time gap in Screening vs PCR confirmation
  — Patients at risk for follow up.
• Re-testing screening sample by PCR condoned by CDC, however, potential contamination risk?
  — Reflex PCR testing of 2nd tube for sero-positives?
  — Pre-aliquoting samples prior to serologic and potential molecular testing?
• Unmet need: Rapid, unified screening/assay process (POC?)

Candidates for Therapy and Outcome Predictors

• >18 years
• Antibody & RNA +
• Liver bx (chronic hepatitis), not required
• Stage of disease appropriate
• No Rx contraindications

- VL < 400,000 IU/ml
- Age
- Sex
- Race
- Weight
- Fibrosis
- Steatosis
- Insulin resistance
- Alcohol consumption
- All less predictive than IL28 (traditional interferon Rx)?
- New treatment options (DAAs) effective for previous difficult to treat patients

HCV Treatment:
Goal is Sustained Viral Response (SVR)

0 12 18
EHFED Therapeutic Response SVR Sustained Viral Response
SVR = Improved Outcomes!

- SVR – virologic "cure"
  - Durable
  - Leads to improved histology
  - Leads to clinical benefits
    - Decreases decompensation
    - Decreases risk of hepatocellular carcinoma
    - Decreases mortality

Sofosbuvir (Pre-2011)


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Treatment of Chronic Hepatitis C (Pre-2011)


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HCV Therapies Continue to Evolve:
Unmet needs driving drug development
Direct Acting Antivirals (DAA) Basis for New Therapies

DAA Class Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protease inhibitors</th>
<th>Nucleoside Polymerase inhibitors</th>
<th>Nonnucleoside Polymerase inhibitors</th>
<th>NS5A inhibitors</th>
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<tbody>
<tr>
<td>Potency</td>
<td>High, Variable among HCV genotypes</td>
<td>Moderate-high, Consistent across genotype, subtype</td>
<td>Variable, Variable among HCV genotypes</td>
<td>High, multiple HCV genotypes</td>
</tr>
<tr>
<td>Barrier to Resistance</td>
<td>Low: 1a &lt; 1b</td>
<td>High: 1a &gt; 1b</td>
<td>Very Low: 1a &lt; 1b</td>
<td>Low: 1a &lt; 1b</td>
</tr>
<tr>
<td>Drug Interaction Potential</td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
<td>Low to moderate</td>
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<tr>
<td>Toxicity</td>
<td>Rash, Anemia</td>
<td>Mitochondrial Navi interactions (AHT, PBO)</td>
<td>Variable</td>
<td>Variable</td>
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<tr>
<td>Pharmacokinetics</td>
<td>Variable, OD to TID</td>
<td>QD</td>
<td>Variable, OD to TID</td>
<td>QD</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd (or 1st PIs): better barrier, pan-genotype</td>
<td>Single target Active site</td>
<td>Allosteric, Many targets</td>
<td>Multiple antiviral MCA</td>
</tr>
</tbody>
</table>

New Therapies (Post-2011)

- Greatly increased likelihood of sustained viral response (SVR)
- Better Tolerated
- Shorter Treatment Regimens
- Simpler Treatment and Monitoring Algorithms
- More Drug Options
- Expensive
HCV Treatment: Tests for Selection and Guidance of Therapy

- **Selection**
  - Genotype and subtype
  - Stage of disease
  - Past treatment history
- **Guidance**
  - Genotype and subtype guided
    - how long to treat
  - Response guided
    - How long to treat/when to stop

Two Approaches to Guided Therapy

- **Genotype Guided Therapy**
  - Rx some genotypes shorter (GT2,3 interferon ribavirin therapy)
  - Rx other genotypes longer (GT1, 4, 5, 6 interferon ribavirin therapy)
- **Response Guided Therapy**
  - Rx based on rate VL decline
  - Treatment duration
  - Stopping rules

Response-Guided Therapy

“First Generation Direct Acting Antivirals”
**Recommended Regimens for Treatment-Naive GT1 HCV Pts**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Noncirrhotic</th>
<th>Cirrhotic</th>
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<tbody>
<tr>
<td>GT1</td>
<td>DSV + DAS + RBV</td>
<td>DSV + DAS + RBV</td>
</tr>
<tr>
<td></td>
<td>12*</td>
<td>12</td>
</tr>
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</table>

*Shorter course can be considered in pts with pretreatment HCV RNA < 6 million IU/mL at provider’s discretion but should be done with caution.

**Recommended Regimens for Treatment-Naive GT1 HCV Pts**

- **DSV** dasabuvir
- **ABT-333** NS5AI
- **LDV** ledipasvir
- **GS-5885** NS5AI
- **OMV** ombitasvir
- **ABT-267** PI
- **PTV** paritaprevir
- **ABT-450 PI**
- **RBV** ribavirin
- **RTV** ritonavir
- **SMV** simeprevir
- **TMC435 PI**
- **SOF** sofosbuvir

**Genotype 1 HCV Ledipasvir (LDV) and Sofosbuvir (SOF)**

**HCVCurrent Recommendations, New All Oral Therapies:**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Week</th>
<th>4</th>
<th>6</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>SVR12</th>
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<td>4</td>
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<tr>
<td>2, 3, 4</td>
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<td>3, 4, 5, 6</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SOF=sofosbuvir; PIF=paritaprevir; OMB=ombitasvir; DAS=dasabuvir; RTV=ritonavir; SPV=simeprevir; RBV=ribavirin; gl = genotype PEG-INF = pegylated interferon

*Note: For genotype 5, PEG-INF can be used as an alternative

**From Sulkowski Clinical Care Opinions 2015**
Evolving Landscape of HCV
Updated 2014 AASLD Guidelines

- Establish starting point: determine treatment duration
- Identify adherence: treatment failure
- Assess viral suppression in response to therapy
- Detect treatment relapse

* If quantitative HCV viral load has increased by greater than 10-fold (>1 log_{10} IU/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended.

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HCV Genotyping Considerations

- Patients with HCV genotype 1a tend to have higher relapse rates than patients with HCV genotype 1b with certain regimens.
- Genotype 1a patients may receive more aggressive therapy
- Genotype 1 HCV infection that cannot be subtyped should be treated as genotype 1a infection

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HCV Genotyping Methods

- LiPA (reverse hybridization line probe)
  - (5'UTR, Core)
- Nucleic Acid Sequencing (Sanger or NGS)
  - (5'UTR, Core, NS5)
- Primer specific PCR (Abbott TaqMan) FDA approved
  - (5'UTR, NS5)
- GenMark
  - (5'UTR, Core)
HCV Genotyping Test Issues

- Tests targeting only 5’ UTR do not reliably discriminate types 1a vs 1b or type 1 vs rare type 6 HCV
- Interrogation of core and NS5B associated with low percentage of no calls due to sequence variability of targets

HCV Genotyping for Drug Resistance

- Resistance Associated Variation (RAVs) arise due to selection (previous failed therapies)
- Spontaneous RAVs also present in untreated populations
- Mutations may confer fitness cost
- Barrier to resistance varies with drug class
- Evolving recommendations for resistance testing

HCV GT1a Infections with NS3 (protease) Q80K Polymorphism

- Efficacy of SMV/PEG/RBV substantially reduced*
- Sofosbuvir plus simprevir**
  - 1a patients with Q80K mutation have lower rates of SVR
- Recommendations for testing for NS5A and other mutations are now emerging

*Simprevir (Olysio®) Prescribing Information, Janssen Therapeutics, Titusville, NJ; November 2013.
**Lawitz E, Matusow G, DeJesus E et al EASL 2015;S264  AASLD/IDSA HCV Guidance 05-29-15
New Indications for RAV Testing

- NS5A mutations likely detected in setting of virologic breakthrough post DAA treatment
  - ledipasvir, ombitasvir, and daclatasvir
- NS5A inhibitor mutations likely stable and detectable as long as 2 years after treatment.
- NS3 region mutations may also occur (protease inhibitors)
  - Paritaprevir and simeprevir
- Treatment examples
  - ledipasvir/sofosbuvir
  - ombitasvir/paritaprevir/ritonavir/dasabuvir
  - Daclatasvir/sofosbuvir

- Indication for RAV testing: Treatment is urgent and previous treatment with NS5A/NS3 inhibitors has failed
- Test NS5A and NS3 regions
- Indications NS5B polymerase testing less clear
- Testing currently limited to a few specialty labs
- Field new and rapidly evolving

Evaluating the Cost Effectiveness of New Therapies

- In 2011, average wholesale acquisition costs of drugs alone were $32,000 to over $100,000
- Quality adjusted life years for those regimens considered reasonable
- New regimens are $100,000 to $175,000 in U.S.
- Incremental cost benefits have been demonstrated
- Evaluating cost effectiveness of new regimens also has to reflect the increased efficacy of the treatment (cost/cure)
- Will competition and or regulation bend the cost curve?
The HCV Revolution

- Viral discovery
- Advancing therapeutics
- Evolving laboratory technology
- Convergence on use of high quality molecular tests for detection and genotyping (VL considered)
- Broad population screening
- Education, screening, resource availability, team based management
- Economic models to bring affordable care for chronic HCV infection

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