CHRONIC HEPATITIS C: UPDATE

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The Hepatitis C Epidemic in the United States

- Incidence, acute hepatitis C
  - 1980’s: 180,000 cases/yr
  - 1990’s: 30,000-35,000 cases/yr
- 1.8% of Americans test positive for hepatitis C antibody
- 3.9 million Americans have chronic hepatitis C

Alter MJ. NIH Consensus Conference, 1997
Chronic Hepatitis C

• A leading cause of cirrhosis in the US.
• 8,000-10,000 deaths/yr
  – This number expected to triple in the next 10 to 20 years
• Associated with an increased risk of liver cancer
• Most common reason for liver transplantation in the US

Hoofnagle JH. NIH Consensus Conference, 1997
## Estimated Disease Burden and Costs for Hepatitis C - United States 1992

<table>
<thead>
<tr>
<th></th>
<th>Acute cases</th>
<th>33,200</th>
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<tr>
<td><strong>Acute Disease</strong></td>
<td>Medical/work loss costs</td>
<td>$100 million</td>
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<tr>
<td><strong>Chronic Disease</strong></td>
<td>Deaths</td>
<td>10,000</td>
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<tr>
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<td>Medical/work loss costs</td>
<td>$512 million</td>
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<td>Total Annual Costs</td>
<td>$612 million</td>
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</table>

Center for Disease Control
HCV Infection: Worldwide Prevalence
HCV Life Cycle

Adapted from Davis GL et al. Semin Liver Dis. 1999;19(suppl 1):105.
Hepatitis C Virus

capsid  envelope  protease/helicase  RNA-dependent RNA polymerase

c22  33c  c-100

core  E1  E2  NS 2  NS 3  NS 4  NS 5

hypervariable region
HCV Genome Heterogeneity

• Genotypes
  – ≥ 30% difference at nucleotide level
  – 25% - 30% difference at amino acid level
  – Long-standing viral diversity

• Quasispecies
  – Diverse population with less genetic difference
  – Dynamic, rapid changes in viral populations
  – Emergence of minor species after documented clearance of dominant species

HCV Infection: Genotype Distribution

Risk Factors for Acute Hepatitis C

- IV Drug Use – 43%
- Sexual (Multiple Partners) – 15%
- Transfusions – 4%
- Occupational – 4%
- Household – 3%
- Unknown – 1%
- Other – 30%
  - Intranasal cocaine use
  - Tattoos
  - History of STD’s
  - Prison inmates
  - Low socioeconomic status
  - US Veterans

Alter MJ. NIH Consensus Committee, 1997
Diagnosis of Chronic Hepatitis C

• Ask patients about risk factors
  – Remember that many infected patients deny risk factors
• Obtain liver enzymes as part of routine blood work
• Order serologic tests in all patients with viral risk factors or elevated ALT levels
New CDC Recommendation for HCV Screening
The “Birth Cohort”

CDC is recommending that everyone born during 1945 through 1965, also known as baby boomers, get a blood test for Hepatitis C. This recommendation calls for one-time testing of baby boomers.
Hepatitis C Antibody (ELISA)

- EIA-2 test for detection of hepatitis C Ab
  - Assay detects 2 epitopes of Ab
- Sensitivity 92%-95%
- Detection of anti-HCV averages 12 weeks following infection
- Positive test is diagnostic in patients with elevated ALT and viral risk factors

Alter MJ. Semin Liver Dis, 1995
Hepatitis C Antibody (ELISA)

- **False positives**
  - Autoimmune diseases
  - Hypergammaglobulinemia
  - Suspect if positive in patient with normal ALT and no viral risk factors

- **False negative**
  - Immunosuppressed patients (eg. transplant patients)
  - Chronic dialysis patients

Hsu HH. Gastroenterology 1991
Hepatitis C Virus RNA Tests

• Polymerase Chain Reaction (PCR)
  – Qualitative test
  – Most sensitive and specific test
  – Detects down to 200 genome copies/ml

• Branched DNA amplification (bDNA)
  – Quantitative test (comes as kit)
  – Detects down to 2000 genome copies/ml
  – Variability in results as not standardized

De Medina M. Semin Liver Dis, 1995
Gish RB. Viral Hepatitis Review, 1997
Recommendations to Avoid Transmission of Hepatitis C

- Adherence to universal healthcare precautions
- No donation of blood, organs, tissues, or semen of individuals who are hepatitis C positive
- Use of condoms by individuals who have multiple sexual partners
- NO changes recommended in sexual practices in monogamous long-term relationships
- Testing for HCV recommended for sexual partners of infected patients

NIH Consensus Committee, 1997
Recommendations to Avoid Transmission of Hepatitis C (cont.)

- Avoiding household transmission:
  - Avoid sharing razors, toothbrushes
  - Cover open wounds
  - NO need to avoid close contact with family members or sharing of meals or utensils

- Pregnancy not contraindicated
  - Risk of transmission to baby <6%
  - Breast-feeding considered safe

NIH Consensus Committee, 1997
Estimated Incidence of Acute Hepatitis C
United States, 1982-1993

Surrogate testing of blood donors

Anti-HCV test (1st generation) licensed

Anti-HCV test (2nd generation) licensed

Decline among injecting drug users

Decline among transfusion recipients

CDC Sentinel Counties Study of Acute Viral Hepatitis
Acute Hepatitis C

Clinical Presentation and Natural History

• Incubation period is 6-7 weeks
• Symptoms develop in fewer than 25% of patients
  • Nonspecific
  • Jaundice uncommon (less than 20%)
  • Diagnosis rarely established
• >85% will develop chronic hepatitis C

Hoofnagle JH. NIH Consensus Conference, 1997
Hepatitis C – Serologic Course

Titer

Symptoms

anti-HCV

ALT

Normal

Time After Exposure

0 1 2 3 4 5 6 1 2 3 4

Months

Years

Time After Exposure
20 Year Progression of Chronic Hepatitis C

Acute Hepatitis C

>85%

Chronic Hepatitis C

20%

Cirrhosis

<20%

Hepatic failure

HCC

Davis GL. Gastro Clin N. Am., 1994
Factors Which Accelerate Hepatitis C Progression

• Concurrent alcoholism!
• Non-alcoholic steatohepatitis (NASH)
  – Diabetics
  – Obesity
  – Hyperlipidemia
• HIV co-infection
• Immunosuppressed patients
Clinical Presentation of Chronic Hepatitis C

• Typical patient is asymptomatic
• ALT (SGPT) may be normal or have mild-to-moderate elevations
  – As many as 45% have normal ALT at initial evaluation
• Any degree of ALT abnormality must be evaluated further!
Symptoms of Chronic Hepatitis C

Hoefnagle JH. NIH Consensus Conference, 1997
Diagnostic Approach to Chronic Hepatitis C

Birth Cohort
Elevated ALT Levels + Risk Factors

Anti-HCV (ELISA) test

(-) (+)

<8% chance of chronic hepatitis C  Diagnosis 95% certain

Consider treatment
Diagnostic Approach to Chronic Hepatitis C

Normal ALT Levels / No Risk Factors
Anti-HCV (ELISA) positive

HCV RNA

(-) (+)

False-positive ELISA
Spontaneous Resolution

Chronic infection
Consider therapy
Tests to Evaluate Degree of Liver Disease

- ALT levels
- Liver function tests (PT, albumin)
- Ultrasound of liver
- Liver Biopsy or non-invasive tests
- Quantitative Viral Load
Assessing Severity of Liver Disease

Liver Biopsy or Non-Invasive Testing (Fibroscan or MRI/UTZ Elastography)

- The definitive method of determining disease severity and activity
- Helpful in establishing prognosis and guiding treatment decisions
Rate of Progression to Cirrhosis

Stage of Fibrosis

- Stage A
- Stage B
- Stage C

% Progression to Cirrhosis

Years

Yano M. Hepatology, 1996
Rate of Progression to Cirrhosis

Grade of Inflammation on Initial Liver Biopsy

Yano M. Hepatology, 1996
Hepatitis C Treatment
Chronic Hepatitis C: Patterns of Response

- Baseline
- Treatment
- Follow-up

HCV RNA

HCV RNA
Negative

Nonresponder
Relapser
Sustained Responder

Time
## Agents in Development for Chronic Hepatitis C

<table>
<thead>
<tr>
<th>Class</th>
<th>Abbreviation</th>
<th>Agent Name</th>
<th>Drug</th>
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<tr>
<td></td>
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<td>ABT-450</td>
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<td>AbbVie</td>
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<tr>
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<td>LMV</td>
<td>Lomibuvir</td>
<td>VX-222*</td>
<td>Vertex</td>
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<td>NS5A Inhibitor</td>
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FDA-Approved Hepatitis C DAA Treatment Regimens

<table>
<thead>
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<th>Regimen</th>
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<tr>
<td>Daclatasvir + Sofosbuvir +/- ribavirin</td>
</tr>
<tr>
<td>Elbasvir + Grazoprevir +/- ribavirin</td>
</tr>
<tr>
<td>Ledipasvir + Sofosbuvir</td>
</tr>
<tr>
<td>Paritaprevir + Ritonavir + Ombitasvir + Dasabuvir +/- ribavirin</td>
</tr>
<tr>
<td>Paritaprevir + Ritonavir + Ombitasvir + ribavirin</td>
</tr>
<tr>
<td>Simeprevir + Sofosbuvir +/- ribavirin</td>
</tr>
<tr>
<td>Sofosbuvir + ribavirin</td>
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# Genotype 1a Treatment Regimens

(AASLD – IDSA Guidelines)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Treatment Naïve</th>
<th>Treatment Experienced</th>
<th>No Cirrhosis / Cirrhosis</th>
<th>NS5A Resistance</th>
<th>SVR12</th>
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</thead>
<tbody>
<tr>
<td>SOF/DAC x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X / -</td>
<td></td>
<td>97%</td>
</tr>
<tr>
<td>SOF/DAC +/- RBV x 24 wks</td>
<td>X</td>
<td>X</td>
<td>- / X</td>
<td></td>
<td>82%</td>
</tr>
<tr>
<td>EBV/GZR x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X / X</td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>EBV/GZR + RBV x 16 wks</td>
<td>X</td>
<td>X</td>
<td>X / X</td>
<td>X</td>
<td>97%</td>
</tr>
<tr>
<td>SOF/LED x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X / -</td>
<td></td>
<td>98%</td>
</tr>
<tr>
<td>SOF/LED x 24 wks</td>
<td>X</td>
<td>X</td>
<td>- / X</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>3D + RBV x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X / -</td>
<td></td>
<td>96%</td>
</tr>
<tr>
<td>3D + RBV x 24 wks</td>
<td>X</td>
<td>X</td>
<td>- / X</td>
<td></td>
<td>95%</td>
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<tr>
<td>SOF/SIM x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X / -</td>
<td></td>
<td>96%</td>
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<tr>
<td>SOF/SIM +/- RBV x 24 wks</td>
<td>X</td>
<td>X</td>
<td>- / X</td>
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<td>95%</td>
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# Genotype 1b Treatment Regimens (AASLD – IDSA Guidelines)

<table>
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<th>Regimen</th>
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<th>SVR12</th>
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<td>Treatment Experienced</td>
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<td>SOF/DAC x 12 wks</td>
<td>X</td>
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</tr>
<tr>
<td>SOF/DAC +/- RBV x 24 wks</td>
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<tr>
<td>EBV/GZR x 12 wks</td>
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<td>SOF/LED x 12 wks</td>
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<tr>
<td>SOF/LED x 12 wks</td>
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<tr>
<td>SOF/LED x 24 wks</td>
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</tr>
<tr>
<td>3D x 12 wks</td>
<td>X</td>
<td>X</td>
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<tr>
<td>SOF/SIM x 12 wks</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SOF/SIM +/- RBV x 24 wks</td>
<td>X</td>
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# Genotype 2 Treatment Regimens

(AASLD – IDSA Guidelines)

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<th>Cirrhosis</th>
<th>SVR12</th>
</tr>
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<tbody>
<tr>
<td>SOF + RBV x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>93%</td>
</tr>
<tr>
<td>SOF + RBV x 24 wks</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>100%</td>
</tr>
<tr>
<td>SOF/DAC x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>90%+</td>
</tr>
<tr>
<td>SOF/DAC x 24 wks</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>90%+</td>
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## Genotype 3 Treatment Regimens (AASLD – IDSA Guidelines)

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<th>No Cirrhosis</th>
<th>Cirrhosis</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + RBV x 24 wks</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>85%</td>
</tr>
<tr>
<td>SOF/DAC x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>SOF/DAC +/- RBV x 24 wks</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>89%+</td>
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</table>
### Genotype 4 Treatment Regimens (AASLD – IDSA Guidelines)

<table>
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<th>Cirrhosis</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV/GZR x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>97%</td>
</tr>
<tr>
<td>EBV/GZR + RBV x 16 wks</td>
<td>X (NR)</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>SOF/LED x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>93%</td>
</tr>
<tr>
<td>SOF/LED + RBV x 12 wks</td>
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<td>X</td>
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<td>SOF/LED x 24 wks</td>
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<td>X</td>
<td>89%</td>
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<tr>
<td>2D + RBV x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>100%</td>
</tr>
<tr>
<td>SOF + RBV x 24 wks</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>89%</td>
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# Genotype 5/6 Treatment Regimens
(AASLD – IDSA Guidelines)

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</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Naïve</td>
<td>Treatment Experienced</td>
<td>No Cirrhosis</td>
<td>Cirrhosis</td>
<td>SVR12</td>
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<tr>
<td>SOF/LED x 12 wks</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>93%-96%</td>
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</table>
Sofosbuvir/Velpatasvir for 12 Weeks

SVR12 For ABT-493 300 mg/ABT-530 120 mg
Dosing Arms (No RBV)

Once-daily oral dosing in Phase III without RBV: ABT-493 300 mg/ABT-530 120 mg

Total SVR12* 99% (269/272)
Safety established in >500 patients

% of patients, SVR 12

<table>
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<th>Duration</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
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<tbody>
<tr>
<td>GT1</td>
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<tr>
<td>GT2</td>
<td>100*</td>
<td>53/53</td>
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<td>GT3</td>
<td>100*</td>
<td>28/28</td>
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<tr>
<td>GT4-6</td>
<td>100</td>
<td>28/28</td>
</tr>
</tbody>
</table>

* mITT: excludes LTFU & discontinuation due to factors other than study drug
F4, patients with cirrhosis

1. Poordad F., et al. EASL 2016 SAT-157
2. Kwo P., et al. EASL 2016 LBO1
5. Wyles D, et al. AASLD 2015
6. Kwo P., et al. EASL 2016 LBO1
8. Gane E., et al. EASL 2016 SAT-137
Special HCV Patient Groups

- Patients with normal ALT
- Patients with cirrhosis/hepatocellular carcinoma
- Nonresponders
- Relapsers
- Transplant patients

- Immunosuppressed patients
- HIV / HCV coinfected patients
- Liver transplant patients
- Patients with renal failure
Chronic Hepatitis C

Major Points

• Chronic hepatitis C progresses in a large number of patients
• Hepatitis C should be suspected on the basis of risk factors or elevated ALT levels
• Severity of disease is best assessed by histologic exam of liver tissue
• Curative treatment is available