Hepatitis C Overview
Viral Hepatitis Summit
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HCV Infection Worldwide

- 170 million persons with HCV
- 3-4 million newly infected each year

Prevalence of infection

- > 10%
- 2.5% to 10%
- 1% to 2.5%
- 0.1% to 1%
- NA

HCV Prevalence in High-Risk US Populations

- Incarcerated
  - ~310,000 (15%)
- IDUs
  - ~300,000 (80%-90%)
- Alcoholics
  - ~250,000 (11%-36%)
- Homeless
  - ~175,000 (22%)
- HIV Infected
  - ~300,000 (30%)
- Veterans
  - ~280,000 (8%)

Over 5.2 Million People Living With Chronic HCV in the US

- **NHANES Estimate**: 3.2
- **HCV Cases Not Included in NHANES**
  - Conservative estimate: 1.9
  - Upper limit of estimate: 3.8
- **Estimated Total HCV Cases**: 7.1

*Homeless (n=142,761-337,610); incarcerated (n=372,754-664,826); veterans (n=1,237,461-2,452,006); active military (n=6805); healthcare workers (n=64,809-259,234); nursing home residents (n=63,609); chronic hemodialysis (n=20,578); hemophiliacs (n=12,971-17,000).

Global Burden of Disease Study 2010: Causes of Death From Chronic Liver Disease

Increase in liver-cancer deaths (past 20 years):
Globally (from 1.25 to 1.75 million/year); USA (45,000 to 70,000/year).

Clinical Considerations on the Progression of HCV Infection

- Of every 100 persons infected with HCV, approximately
  - 75% to 85% will develop chronic infection
  - 60% to 70% will develop chronic liver disease
  - 5% to 20% will develop cirrhosis in 20 to 30 years
  - 1% to 5% will die from the consequences of chronic infection (liver cancer or cirrhosis)

Extrahepatic Manifestations of Chronic HCV Infection

- Arthralgia
- Arthritis
- Behcet’s disease
- Canities
- Cerebral vasculitis
- Cryoglobulinemia
- Diabetes
- Fatigue
- Fibromyalgia
- Hypertrophic cardiomyopathy
- Immune thrombocytopenic purpura
- Insulin resistance
- Lichen myxoedematosus and planus
- Lung abnormalities
- Membranoproliferative glomerulonephritis
- Membrane nephropathy
- Mooren corneal ulceration
- Multiple myeloma
- Neutropenia
- Non-Hodgkin’s lymphoma
- Paresthesia
- Porphyria cutanea tarda
- Pruritus
- Raynaud’s syndrome
- Sialadenitis
- Sjogren’s syndrome
- Spider nevi
- Systemic lupus erythematosus
- Thrombocytopenia
- Thyroid disease
- Vasculitis
- Vitiligo
- Waldenstrom macroglobulinemia
Chronic HCV in the US: Underdiagnosed and Untreated

Estimated treatment rate is based on Q2 and Q4 2011 chart audits.

Hepatitis C Monitor. Ipsos Healthcare.
HCV and HIV Mortality in the US (1999-2007)

- US multiple-cause mortality data (NCHS, 50 states plus DC)
  - Death certificate data
  - Approximately 21.8 million decedents
- Change in age-adjusted mortality rates (per 100,000 person-years)
  - HCV: increased 0.18 ($P=0.002$)
  - HIV: decreased 0.21 ($P=0.001$)
- New policy initiatives are needed to detect and link HCV patients to care and treatment

Annual Age-Adjusted Mortality Rates*

NCHS: National Center for Health Statistics.
*A record listing >1 type of infection was counted for each type of infection.

HCV Screening and Testing Recommendations (CDC and AASLD/IDSA)

- HCV testing is recommended at least once for persons born between 1945 and 1965

- Other persons should be screened for risk factors for HCV infection

- 1-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection

- Annual HCV testing is recommended
  - Persons who inject drugs
  - HIV-positive MSMs who have unprotected sex

- Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV
HCV Screening: Behaviors, Exposures, and Conditions Associated With Increased Risk of HCV Infection

• Adults born between 1945 and 1965

• Risk behaviors
  – Past or current injection drug use
  – Intranasal illicit drug use

• Risk exposures
  – Chronic hemodialysis
  – Getting tattoo in an unregulated setting
  – Persons with recognized exposures (needlesticks, mucosal exposures)
  – Birth to an infected mother
  – Recipients of transfusions or organ transplants
  – Recipients of clotting factors (prior 1987)
  – Ever incarcerated

• Other medical conditions
  – HIV infection
  – Unexplained chronic liver disease and chronic hepatitis including persistently abnormal ALT


General Risk Factors

- General Population: 1.6% (1.3-1.9)
- IDU Blood Transfusion (<1992): 57.5% (44.1-69.9)
- Blood Transfusion (1992): 5.8% (3.7-9.0)
- HIV: 13.8% (5.3-31.3)
- Dialysis: 7.8% (3.7-9.0)

Number of Sex Partners

- 0.5% (0.2-1.4) for 1
- 1.1% (0.5-2.1) for 2
- 2.6% (1.5-4.6) for 3
- 7.5% (5.3-10.6) for 4
- 12.0% (8.5-16.7) for 5

## Recommended Laboratory Tests for Chronic HCV Infection

<table>
<thead>
<tr>
<th>Test Application</th>
<th>Test Application</th>
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<tbody>
<tr>
<td>Hepatitis C antibody by enzyme immunoassay (EIA)</td>
<td>Screening for past or present HCV infection</td>
</tr>
<tr>
<td></td>
<td>Sensitive and inexpensive</td>
</tr>
<tr>
<td>PCR for HCV RNA</td>
<td>Confirmation of positive EIA</td>
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<td></td>
<td>Medical evaluation and management</td>
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</tbody>
</table>
Markers for Chronic HCV Infection

ELISA Screening Tests for HCV

- Serologic assays to detect circulating HCV antibodies
- Sensitivity (97% to 100%)
- Positive predictive value
  - 95% with risk factors and elevated ALT
  - 50% without risk factors and normal ALT
- False positives
  - More likely in patients with low risk of HCV infection
- False negatives
  - More likely in severely immunocompromised patients, transplant recipients, patients with chronic renal failure on dialysis, HIV-positive patients
When to Test for HCV RNA (AASLD Recommendation)

- Positive anti-HCV antibody test
- Considering antiviral treatment
  - Use sensitive quantitative assay
- Unexplained liver disease and negative anti-HCV antibody test and who are
  - Immunocompromised
  - Suspected of having acute HCV infection

### HCV Assays: What the Results Mean

<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV RNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Acute or chronic HCV depending on the clinical context</td>
</tr>
<tr>
<td>+</td>
<td>–</td>
<td>False positive HCV antibody</td>
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<tr>
<td></td>
<td></td>
<td>Resolved infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low-level intermittent viremia</td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>Early acute HCV infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic HCV in setting of immunosuppressed state</td>
</tr>
<tr>
<td></td>
<td></td>
<td>False positive HCV RNA test</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>Absence of HCV infection</td>
</tr>
</tbody>
</table>

Counseling HCV-Infected Patients: Avoiding Transmitting HCV to Others

• Items to avoid
  – Sharing toothbrushes and dental or shaving equipment
  – Using illicit drugs
    • Those who continue to inject drugs, avoid reusing or sharing syringes, needles, water, cotton or other paraphernalia. Clean the injection site with a new alcohol swab and dispose of syringes and needles after one use in a safe, puncture-proof container

• Bandage bleeding wounds to prevent contact with others

• Do not donate blood, body organs, other tissue or semen

• Safe, sexual practices
  – Encourage barrier protection for HIV-positive MSMs and those with multiple sexual partners or STIs
    • For others with HCV infection, the risk of sexual transmission of HCV is low

Counseling HCV-Infected Patients: Minimizing Disease Progression

- Avoid alcohol
  - HCV-related fibrosis progression is increased with alcohol consumption >50 g/day
  - Lower levels of alcohol consumption is associated with increases in HCV RNA levels
- Administer HAV and HBV vaccines as needed
- Consider treatment for chronic HCV infection

Vitamin D and Coffee: Role in Chronic HCV Infection

• Vitamin D levels (HCV genotype 1 [n=197] versus age- and sex-matched healthy controls [n=49])
  – 25(OH) D levels significantly lower in HCV versus controls (25 versus 43 µg/L; \( P < 0.001 \))
  – Low levels significantly associated with female sex, increased liver inflammation, increased liver fibrosis, and decreased SVR (n=167)

• Coffee consumption \( \geq 3 \) cups/day (HALT-C trial, serial liver biopsies every 2 years)
  – Lower rates of disease progression (relative risk 0.47 [\( P = 0.0003 \)])
  – Lower insulin and HOMA-2 score
  – Independent predictor of improved virologic response to PR (adjusted* odds ratio 1.80 [\( P = 0.034 \)])

*Adjusted for age, race/ethnicity, sex, alcohol, cirrhosis, AST/ALT ratio, IL28B polymorphism rs12979860, and dose reduction in peginterferon. PR: pegIFN + RBV.

Tobacco and HCC Risk

• The relationship between cigarette smoking and HCC has been examined in >60 studies (both areas of high and low incidence of HCC)
  – Both positive associations and no associations have been reported

• Studies with positive associations
  – Effects limited to subgroups defined by HCV or HBV status
  – Meta-analysis of 16 publications
    • HBV and cigarette smoking: more than additive interaction
    • HCV and cigarette smoking: more than multiplicative interaction

HCV Linkage-to-Care: Missed Opportunities in a Large Primary Care Setting (2005-2010)

Patients with a positive anti-HCV antibody test and visit to primary care from 2005-2010 (n=566). Of these patients, 458 underwent HCV RNA testing.

Stepwise Barriers to Hepatitis C Treatment

HCV Infection → Diagnosis

- **Barriers**
  - Asymptomatic disease
  - Poor awareness/education
  - Lack of medical coverage
  - MD failure to screen/test

Diagnosis → Referral to Specialist

- **Barriers**
  - Non-adherence
  - MD failure to identify need for referral
  - Logistical concerns
  - Limited specialists availability

Referral to Specialist → Treatment Initiation

- **Barriers**
  - Patient fears/misunderstandings
  - Stigmatization
  - Substance abuse
  - Psychiatric comorbidity
  - Financial concern
  - Transportation/logistical concern
  - Communication difficulties

Achieving a Sustained Virologic Response is Associated With Improved Outcomes

- Sustained viral response
  - Durable
    - 99% stay HCV negative for >10 years
  - Leads to improved histology
  - Leads to clinical benefits
  - Decreased decompensation
  - Prevents de novo esophageal varices
  - Decreased hepatocellular carcinoma
  - Decreased mortality

SVR is Significantly Associated With Reduction in All-Cause Mortality

Retrospective analysis of veterans who received pegIFN + RBV at any VA medical facility (2001-2008).

Advanced Liver Disease: Basic Principles

- Hepatic fibrosis
  - Not reliably diagnosed by ultrasound or other imaging modalities

- Liver fibrosis rates
  - Not predictable or linear

- Progression from compensated cirrhosis to decompensated liver disease
  - Occurs in 5% of patients per year

- Hepatocellular carcinoma
  - Develops in 1% to 2% of patients with hepatitis-related cirrhosis each year

- Liver Biopsy no longer routinely recommended for Hepatitis C therapy decisions

Progression of Fibrosis in Viral Hepatitis on Biopsy (Metavir)

No Fibrosis
- Fibrous expansion of some portal areas

Stage 1
- Cirrhosis

Stage 2
- Fibrous expansion of most portal areas with occasional portal-to-portal bridging

Stage 3
- Fibrous expansion of portal areas with marked bridging (portal-to-portal and portal-to-central)

Stage 4
- Cirrhotic Liver

Chronic HCV Infection: Natural History

Risk Factors for Progressive Fibrosis and Cirrhosis

- Persistently elevated ALT levels
- Longer duration of infection
- Alcohol excess (>50 g/day)
- Age >40 years at time of infection
- HIV or HBV coinfection
- High BMI
- Male gender

Health Maintenance of the Cirrhotic Patient

- Vaccinations
- Bone disease screening, surveillance, and management
- HCC screening and surveillance
- Varices screening and surveillance
- Nutritional support
  - Vitamin assessment for vitamin A and D deficiency
  - Mineral assessment: zinc and magnesium (Mg++)
- Review medication list
Estimated 3-Month Survival as a Function of MELD

MELD = 3.8[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.6[Ln serum creatinine (mg/dL)] + 6.4

When to Refer to Hepatology

- Any hepatic decompensation
  - Ascites
  - Jaundice
  - Encephalopathy
  - Variceal bleeding
- MELD >10
- Hepatocellular carcinoma
Chronic HCV Therapy: Advances in Raising Cure Rates

- **1991**: IFN, 16%
- **1998**: IFN/RBV, 35%
- **2001**: PegIFN/RBV, 44%
- **2011**: Telaprevir or Boceprevir + PegIFN/RBV, ~70%
- **>2013**: 2nd Generation DAAs PegIFN-Free Regimens, >90%


Thank You

Richard.Manch@dignityhealth.org
What to know even more about HCV?

4th Annual Current Trends in Liver Disease
Hepatitis C From A to Z
CME Conference

Friday, October 9
11:30 a.m. – 5 p.m.

Sonntag Pavilion
St. Joseph’s Hospital and Medical Center

Course Director:
Richard A. Manch, MD, FACP, FACG
Chief of Hepatology
St. Joseph’s Hospital and Medical Center

A special CME conference focused on the latest developments in Hepatitis C management.

Target Audience:
Specialists (hepatology, gastroenterology, infectious disease), general practitioners, physician assistants, nurse practitioners, registered nurses, residents and others who manage patients with hepatitis C, including those with HCV/HIV coinfection.

Register today by calling the Resource Link at 1.877.602.4111

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