Objectives

- Review the epidemiology and pathophysiology of hepatitis C virus (HCV)
- Define who is at risk for HCV and describe the diagnosis of HCV
- Identify goals of HCV therapy
- Compare methods of grading and staging liver disease
Hepatitis C Virus (HCV)

- Most common blood-borne pathogen
  - An estimated 2.7-3.9 million people in the United States have chronic HCV
  - >50% are unaware of their diagnosis

- Leading indication for liver transplantation
  - 6729 liver transplants performed in 2014
  - 28.6% of adult liver transplant recipients

www.cdc.gov/hepatitis/hcv/statisticshcv.htm/

HCV Life Cycle

Hepatitis C Progression

For every 100 people infected with HCV

75 - 85 will develop chronic infection

60 - 70 will develop chronic liver disease

5 - 20 will develop cirrhosis

1 - 5 will die of cirrhosis or hepatocellular carcinoma

Factors Associated with Accelerated Fibrosis Progression

<table>
<thead>
<tr>
<th>Host</th>
<th>Viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-modifiable</td>
<td></td>
</tr>
<tr>
<td>• Fibrosis stage</td>
<td></td>
</tr>
<tr>
<td>• Inflammation grade</td>
<td></td>
</tr>
<tr>
<td>• Older age at time of infection</td>
<td></td>
</tr>
<tr>
<td>• Male</td>
<td></td>
</tr>
<tr>
<td>• Organ transplant</td>
<td></td>
</tr>
<tr>
<td>Modifiable</td>
<td></td>
</tr>
<tr>
<td>• Alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>• Tobacco smoking</td>
<td></td>
</tr>
<tr>
<td>• Non-alcoholic fatty liver disease</td>
<td></td>
</tr>
<tr>
<td>• Obesity</td>
<td></td>
</tr>
<tr>
<td>• Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>HCV Genotype 3</td>
<td></td>
</tr>
<tr>
<td>Co-infection with hepatitis B virus</td>
<td></td>
</tr>
<tr>
<td>Co-infection with HIV</td>
<td></td>
</tr>
</tbody>
</table>


The abCs of Hepatitis C

• Modes of Transmission
  • Large or repeated percutaneous exposure to blood of an infected person primarily through:
    – Sharing of contaminated needles, syringes, or other injection drug equipment
    – Injection drug use is the most common means of HCV transmission in the US
  • Less commonly through:
    – Sexual contact with an infected person (inefficient)
    – Birth to an HCV-infected mother
    – Needlestick or other sharp injuries
    – Receipt of donated blood, blood products, and organs prior to 1992

The abCs of Hepatitis C

• Persons at Risk
  • Current or former injection drug users
  • Recipients of clotting factor concentrates before 1987
  • Recipients of blood transfusions or donated organs before July 1992
  • Long-term hemodialysis patients
  • Persons with known exposures to HCV (e.g., healthcare workers after needlesticks)
  • HIV-infected persons
  • Infants born to infected mothers
  • Incarceration
  • Tattoos/body piercings in unregulated settings
  • US birth cohort 1945-64 (‘baby boomers’)
HCV and the IV Drug Use Epidemic

- Approximately 1/3 of young (18-30 yo) people who inject drugs are HCV-infected
- Older/former IV drug users have a higher prevalence, approximately 70-90%, of HCV infection
- Viral transmission uncontrolled with incidence rates ranging from 16-42% per year
- HCV can also be rarely transmitted via intranasal drug use

Uneven Burden of HCV

USA Birth cohort 1945-65
- Prevalence (3.29%) is 5.3x higher in this group versus other adults
- 81% of adult infections were people born from ‘45-’65
- ~60% do not know status
- 45% report no risk

Spread of HCV in North America

- Most of the spread of HCV (genotype 1a) occurred before 1965
- Key contributors to the epidemic in North America are likely nosocomial or iatrogenic
  - Less likely behavioral risk factors
- Decrease the stigma and increase screening!

HCV – The Potential for Cure

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>HIV</th>
<th>Hepatitis C</th>
<th>Hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>1 million</td>
<td>5 million</td>
<td>2 million</td>
</tr>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Mutation Rates</td>
<td>Very high</td>
<td>Very high</td>
<td>High</td>
</tr>
<tr>
<td>Virions produced daily</td>
<td>$10^{10}$</td>
<td>$10^{12}$</td>
<td>$10^{12}-10^{13}$</td>
</tr>
<tr>
<td>Drug Targets</td>
<td>Multiple</td>
<td>Multiple</td>
<td>One</td>
</tr>
<tr>
<td>Ability to Cure</td>
<td>No (Integrated viral DNA)</td>
<td>YES (No DNA integration)</td>
<td>No (cccDNA)</td>
</tr>
<tr>
<td>Current therapeutical goal</td>
<td>Lifelong suppression</td>
<td>Cure: Clearance from plasma and liver</td>
<td>Lifelong suppression</td>
</tr>
</tbody>
</table>

Hepatitis C Genotypes

Most Cases of HCV Infection in the US are with Genotype-1

Who should be tested for HCV?

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>American Gastroenterological Association</th>
<th>Centers for Disease Control</th>
<th>American Association for the Study of Liver Diseases</th>
<th>Infectious Diseases Society of America</th>
<th>Centers for Medicare and Medicaid Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current or historic IVDU</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion or organ before 7/92</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born 1945-1965</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained chronic liver disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children born to HCV positive mothers</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous exposures</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HCV Screening

- HCV Antibody Test (anti-HCV)
  - Positive anti-HCV indicates exposure to HCV
  - Should be confirmed by HCV-RNA testing
  - FDA approved tests include laboratory based assays and point-of-care assays

- HCV Nucleic Acid Test (HCV-RNA Testing)
  - Detects viremia – used to confirm chronic infection
  - Indicates active HCV infection
  - Should also be done in persons with anti-HCV test who are immunocompromised or exposed to HCV within the last 6 months

HCV Screening

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Interpretation</th>
<th>Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody non-reactive</td>
<td>No HCV antibody detected</td>
<td>• No further action required • If recent HCV exposure, test for HCV RNA</td>
</tr>
<tr>
<td>HCV antibody reactive</td>
<td>Presumptive HCV infection</td>
<td>• Current or past HCV infection or false positivity • Test for HCV RNA</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA detected</td>
<td>Current HCV infection</td>
<td>• Link patient to care for consideration for treatment</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA not detected</td>
<td>No current HCV infection</td>
<td>• No further action required • Use different HCV antibody assay if distinction between true positivity and false positivity desired</td>
</tr>
</tbody>
</table>


Acute vs Chronic Hepatitis C Virus

• Approximately 20-30% of those newly infected with HCV experience symptoms
  – Fever, fatigue, dark urine, abdominal pain, nausea, vomiting, loss of appetite, jaundice
  – Average time of onset is 4-12 weeks
• For the 75-85% who develop chronic HCV infection, most patients are asymptomatic
  – Chronic liver disease 2/2 HCV is insidious and can progress slowly without symptoms

www.cdc.gov/hepatitis/hcv/hcvfaq.htm
Extrahepatic Manifestations of HCV

• Mixed cryoglobulinemia
  – Triad of symptoms: fatigue, arthralgias, palpable purpura
  – Skin is the most frequently involved target organ
  – Rare fulminant, life-threatening complications (glomerulonephritis, widespread vasculitis)
  – Manifestations respond to clearance of HCV from antiviral therapy


Extrahepatic Manifestations of HCV

• B-cell lymphoproliferative diseases
• Cardiovascular disease
  – Higher risk of carotid atherosclerotic plaques
• Renal insufficiency
  – Most often associated with mixed cryoglobulinemia
  – Some evidence for association with other glomerular diseases
• Type 2 diabetes
  – Interaction between insulin resistance, steatosis and inflammatory processes

Clinical Progression of liver disease

• Cirrhosis – associated with a host of complications including
  – Ascites
  – Encephalopathy
  – Spontaneous Bacterial Peritonitis
  – Bleeding complications
  – Hepatorenal syndrome

• Hepatocellular Carcinoma
  – Primary liver cancer more common in patients with cirrhosis

Harrison's Principles of Internal Medicine, 19th Ed.

Successful Treatment of HCV Is Associated With Improved Outcomes

Sustained Viral Response

Definition: HCV RNA negative at least 12 weeks after cessation of treatment
  – Durable
    . 99% stay HCV negative for > 10 years
  – Decreased HCV transmission
  – Leads to clinical benefits
    • Decreased decompensation
    • Prevents de novo esophageal varices
    • Decreased hepatocellular carcinoma
    • Decreased liver related transplant and mortality
    • Decreased mortality

Benefits of Achieving SVR

- Improved liver histology
  - ↓ Cirrhosis
  - ↓ Decompensation
  - ↓ HCC
  - ↓ Transplantation

- ↓ All-cause mortality
- Improved QoL
- Malignancy
- Diabetes
- Cardiovascular Disease
- Renal
- Neurocognitive

Overall Goal of Treatment

- Reduce all-cause mortality and liver-related complications including end-stage liver disease and hepatocellular carcinoma by achieving virological cure (e.g., sustained virologic response)

Evolution of Treatment for HCV

- **1989**: Interferon used to cure hepatitis C infection
- **1990-1**: Isolation and cloning of hepatitis C virus
- **1998**: Interferon + ribavirin used to cure hepatitis C infection
- **2001**: Pegylated interferon with ribavirin used to cure hepatitis C
  - SVR: 40-50% for GT1, 70-80% for GT2/3
- **2011**: Addition of protease inhibitors used to peg-IFN and ribavirin
  - SVR for GT1 increases to ~75%
- **2012**: Proof of principle that therapy with directly acting antivirals only can cure hepatitis C


HCV Care Cascade

- **3,560,000**: Chronic HCV-infected
- **100%**: Diagnosed and Awaited
- **50%**: Access to Outpatient Care
- **43%**: HCV RNA Confirmed
- **17%**: Underwent Liver Biopsy
- **16%**: Prescribed HCV Treatment
- **9%**: Achieved SVR

WORK-UP AND STAGING

Assessing Severity of Disease

• All patients with HCV infection should be evaluated for advanced fibrosis with one or a combination of:
  – Liver biopsy
  – Imaging
  – Non-invasive biomarkers
• Degree of hepatic fibrosis is one of the strongest prognostic factors to predict disease progression and outcomes
• Can impact treatment selection and duration

METAVIR Scoring System

Calculation of the A score

<table>
<thead>
<tr>
<th>A0</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>no histologic necroinflammatory activity</td>
<td>minimal activity</td>
<td>moderate activity</td>
<td>severe activity</td>
</tr>
</tbody>
</table>

Calculation of the F score

<table>
<thead>
<tr>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>absence of fibrosis</td>
<td>portal fibrosis without formation of septa</td>
<td>portal fibrosis and a few septa</td>
<td>portal fibrosis with several septa/bridging fibrosis</td>
<td>cirrhosis</td>
</tr>
</tbody>
</table>

Bedossa P. Hepatology 1996;24:289-93.

Metavir Score - Staging
Liver Biopsy

- Diagnostic standard
- Provides the **grade** and **stage** of liver disease and may reveal unsuspected cirrhosis, necessitating surveillance for HCC and/or search for esophageal varices.
- Limited by sampling error, observer variability
  - Up to 1/3 of bilobar biopsies have differences of at least 1 stage between lobes
- Invasive, costly, risk of complications


Non-Invasive Methods

- “Biological” approach
  - Quantification of biomarkers in serum samples
  - Not strictly liver specific parameters that have been associated with fibrosis stage

- “Physical” approach
  - Based on measurement of liver stiffness

Select Serum Biomarkers

- *Fibrotest® /Fibrosure®* - α-2-macroglobulin, γGT, apolipoprotein A1, haptoglobin, total bilirubin, age, gender
- AST to Platelet Ratio (APRI) = AST/[ULN]/platelet (10^5/L) x 100
- Enhanced Liver Fibrosis Score (ELF) * - age, hyaluronate, MMP-3, TIMP-1
- Fibrosis Probability Index (FPI) = 10.929 + (1.827 x Ln[AST]) + (0.081 x age) + (0.768 x past EtOH use graded 0-2) + (0.385 x HOMA-IR) – (0.447 x cholesterol)
- Fib4 - AST, ALT, platelet count, age: (Age x AST) / (Pit x V(ALT))

Pros/Cons of Serum Biomarkers

**Pros**
- Widespread availability (for the non-patented ones)
- Inter-laboratory reproducibility
- Low cost
- Well validated
- Can be performed in outpatient clinics

**Cons**
- Not liver specific
- Cannot differentiate between intermediate stages of fibrosis
- Issues with certain components
  - Elevated bilirubin 2/2 concomitant medications (e.g., atazanavir)
  - Increased levels of hyaluronate in the post-prandial state

Liver Stiffness Measurement

• FibroScan®
  • Transient elastography that defines liver fibrosis using 1-dimensional ultrasound and low-frequency elastic waves to obtain liver stiffness measurement (LSM), expressed as kilopascal (kPa)
  • A kPa of 7.1 is equivalent to METAVIR stage F2
  • Should ideally be done fasting

Pros/Cons of Transient Elastography

• Pros
  – Short procedure time (<5 min)
  – Immediate results
  – Can be performed outpatient

• Cons
  – Potential for unreliable results, particularly in obese patients or limited operator experience
  – Other confounders: ascites, ALT flares, extra-hepatic cholestasis, congestive heart failure, excessive EtOH intake
  – Access to the machine ($$)
Algorithm for Liver Disease Staging

Two non-invasive tests: TE + Serum Biomarker

FIB-4 and/or APRI. If contradicting results b/t FibroSURE® and FIB-4 (APRI), consider proceeding with liver biopsy

=/> F3, refer for cirrhotic workup


Child-Turcotte-Pugh Score

- Used to classify the severity of cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>PT (sec prolonged)</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Or INR</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

A = 5-6 points
B = 7-9 points
C = 10-15 points

Child CG. The liver and portal hypertension 1964;50-64.
Other assessments prior to starting therapy

- Potential drug-drug interactions with concomitant medications
- Adherence counseling!!
- Pregnancy status for regimens including ribavirin
- Labs
  - CBC, INR, hepatic function panel (albumin, total and direct bilirubin, ALT, AST, alk phos)
  - Renal function assessment
  - HCV genotype and subtype
  - Quantitative HCV RNA
  - HBV Co-infection: HBsAg, anti-HBs, anti-HBc

Pre-Treatment Resistance Testing

- Presence of baseline mutations may affect duration of therapy and need for ribavirin
- Pre-treatment resistance testing may be required prior to using particular therapies/certain patients with HCV genotype 1a or genotype 3
- Rapidly evolving area in the field
PREVENTION

Prevention – Patient Counseling Points

• Low but present risk for transmission with sex partners
• Do not share personal items that might have blood on them (e.g., toothbrushes, razors)
• Cover cuts and sores on the skin
• Avoid alcohol and daily marijuana use as it can accelerate cirrhosis and ESLD
• Seek advice of pharmacist before starting any new medications, including OTCs
• Antibody positivity does not protect against re-infection
Future of an HCV Vaccine?

• No vaccine currently available
• Vaccines targeting both humoral and cellular immune responses have been studied
• Virus vector and DNA vaccines are currently under going clinical trials
• Challenge to cover all genotypes and subtypes

Risk to Health Care Personnel

• Risk of HCV infection is approximately 1.8% (range 0%-10%) after needlestick or sharps exposure to HCV-positive blood
• Test healthcare working for anti-HCV within 48 hours of exposure
  – If negative, follow up with HCV RNA at least 3 weeks after exposure
• Use of direct-acting anti-virals for HCV post-exposure prophylaxis not recommended
Mother-to-Child Transmission

• No indication to test pregnant women for anti-HCV unless they have risk factors for HCV infection
• Risk of mother-to-child transmission occurs at time of birth, no prophylaxis available
• Approximately 6 of 100 infants born to HCV-infected mothers become infected with the virus
• Children born to HCV-infected mothers should be tested for anti-HCV no sooner than 18 months of age

Centers for Disease Control, www.cdc.gov/hepatitis/hcv/hcvfaq.htm

Role of the Pharmacist

• Educate about prevention measures and reducing transmission
• Improve medication adherence
• Assist in the selection of an optimal regimen based on patient and drug-specific characteristics including adverse effects and drug interactions
• Navigate the challenging logistics of medication access
• To be expanded on in future modules

Helpful Resources

<table>
<thead>
<tr>
<th>Resource</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD/IDSA Guidelines</td>
<td><a href="http://www.hcvguidelines.org">www.hcvguidelines.org</a></td>
</tr>
<tr>
<td>CDC</td>
<td><a href="http://www.cdc.gov/hepatitis/hcv">www.cdc.gov/hepatitis/hcv</a></td>
</tr>
<tr>
<td>University of Washington Hepatitis C Online</td>
<td><a href="http://www.hepatitisc.uw.edu">www.hepatitisc.uw.edu</a></td>
</tr>
<tr>
<td>University of Liverpool HEP Drug Interactions</td>
<td><a href="http://www.hep-druginteractions.org">www.hep-druginteractions.org</a></td>
</tr>
</tbody>
</table>

Roadmap for the remaining modules

- Module 2: Direct Acting Antivirals for the Treatment of Hepatitis C Infection
- Module 3: HCV Drug Therapy Management
- Module 4: HCV in Special Populations