Financial Disclosure Information

- None
HCV: The Facts

• Estimated 170,000,000 infected people worldwide. 3,000,000 in the US

• Risk of chronicity: 80-85%

• Risk of cirrhosis: 20% within 20 years
  30% within 30 years

• Cirrhosis-related mortality: 2% – 5% / year

• Incidence of liver cancer: 3% – 10% / year among patients with cirrhosis

• HCV is curable
The Basics

• Risk factors for progression to cirrhosis
  – Alcohol use
  – Older males
  – Diabetes and metabolic syndrome
  – Marijuana/THC use

• Liver cancer risk is highest in cirrhotic patients

• HCV transmission
  – Blood to blood
  – Sexual, needle stick, vertical is <3%
  – Blood transfusion risk of HCV transmission is 1:2,000,000
Spectrum of HCV infection

Acute HCV Infection
- Recovery: 15%

Chronic HCV Infection
- “Normal” ALT: ~30%
- Chronic Hepatitis C
  - Mild
  - Moderate
  - Severe
  - Cirrhosis: 20%
  - End-Stage Liver Disease
  - Hepatocellular Carcinoma

Liver Transplantation
Death
Extrahepatic Manifestations of Chronic Hepatitis C Infection

- Metabolic
- Cardiovascular
- Dermatologic
- Neuropsychiatric
- Rheumatologic
- Renal
- Hematologic
Extrahepatic Manifestations of Chronic Hepatitis C Infection

- Cardiovascular:
- Increased rates of CAD, PVD, cerebrovascular disease
- HCV identified in vascular plaques may lead to inflammatory response
- Elevated CRP
- Despite lower total cholesterol, LDL, Triglyceride
Extrahepatic Manifestations of Chronic Hepatitis C Infection

- Neuro/Psychiatric:
  - Sensory, motor and autonomic neuropathies
  - Cognitive impairment (HCV “brain fog”)
  - Fatigue
- Increased rates of depression, anxiety, BAD, schizophrenia. Independent of pre-infection psychological disorders
- Evidence of HCV in brain tissue with elevated cerebral choline reflecting inflammation
- Eradication of HCV improves cognitive function
Extrahepatic Manifestations of Chronic Hepatitis C Infection

- **Endocrinologic:**
- **Autoimmune thyroiditis**
- **Increased risk of insulin resistance, Type 2 DM, fatty liver**
- **Variable effect based on HCV genotype. Genotype 3 has greatest effect.**
- **Eradication of HCV results in decreased insulin resistance**
Extrahepatic Manifestations of Chronic Hepatitis C Infection

- Dermatologic:
  - Porphyria cutanea tarda (most common). Painful vesicular lesions on sun exposed skin that rupture and scar
  - Lichen planus
  - Palpable purpura (due to MC)
  - Raynaud’s phenomenon
Extrahepatic Manifestations of Chronic Hepatitis C Infection

- Rheumatologic:
- Inflammatory oligoarthritis (similar to RA)
- Leukocytoclastic vasculitis
- Mediated by immune complexes. Typically mixed cryoglobulinemia (MC) occurs in association with HCV
- Up to 45% of chronic HCV patients will demonstrate mixed cryoglobulinemia
- MC typically resolves with eradication of HCV
Extrahepatic Manifestations of Chronic Hepatitis C Infection

- Renal:
  - Most common severe manifestation of MC
  - Usually due to membranoproliferative glomerulonephritis (MPGN)

- Hematologic:
  - Increased risk of non-Hodgkins lymphoma
Screening for HCV

- Prior drug use (IV and intra-nasal)
- HIV positive
- Received blood products before 1992
- Chronically abnormal liver tests
- Children of HCV positive mothers
- Hemodialysis patients, non-professional tattoos, healthcare workers with exposures
- Sexual partners of HCV infected individuals
- **All baby boomers born 1945-1965** (CDC 2012)
Hepatitis C Testing

• Anti-HCV initial testing
• HCV nucleic acid testing (NAT) to confirm current/active infection and guide therapy
• HCV RNA testing should also be performed if anti-HCV negative if patient is immunocompromised or exposed in past 6 months to assess for acute HCV infection
• HCV genotype testing
General Measures

- Alcohol abstinence
- Testing for co-infection with HBV and HIV
- Evaluation for advanced fibrosis using imaging, non-invasive markers, liver biopsy
- Vaccination against hepatitis A and B
- Counseling obese and overweight patients regarding weight loss
- Counseling on how to avoid HCV transmission to others
Who to Treat

- Priority for select groups:
- Advanced fibrosis and compensated cirrhosis
- Organ transplant recipients
- HIV and HBV coinfected patients
- Patients with severe extrahepatic manifestations
- No contraindications
  - decompensated liver disease
- Today: All chronic HCV infected persons, except those with limited life expectancy
The Evolution of HCV Therapy: 
*The Goal is Virologic Cure*

<table>
<thead>
<tr>
<th>Year</th>
<th>IFN 6m</th>
<th>IFN 12m</th>
<th>IFN/RBV 6m</th>
<th>IFN/RBV 12m</th>
<th>PEG-IFN 12m</th>
<th>PEG-IFN /RBV 12m</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>6</td>
<td>16</td>
<td>34</td>
<td>40</td>
<td>39</td>
<td>50</td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment of HCV genotype 1 2002-2012

- Pegylated interferon and ribavirin
- Overall SVR rate of approximately 45%
  - Varies based on co-morbidities and prior treatment response
- Treatment decision based on extent of liver disease (biopsy)
Treatment of HCV Genotype 1 in 2013

- Pegylated interferon
- Ribavirin
- Protease inhibitor*
  - telaprevir (Incivek)
  - boceprevir (Victrelis)
- Overall response rates of approximately 70%
- Duration 24 to 48 weeks
- Response guided therapy
Treatment of HCV Genotype 1 in 2014

- Pegylated interferon
- Ribavirin
- Sofosbuvir*
- Simepravir*
- Overall response rates approximately 90%
- Duration 12 to 24 weeks
Treatment of HCV in 2016
**Sofosbuvir**

- **Sovaldi™ (Gilead Sciences) approved 2013**
- **NS5B polymerase inhibitor**
- **Dosing:** 400mg qd orally in combination with other agent (ribavirin, simeprevir, ledipasvir)
- **Indicated for genotypes 1a, 1b, 2a, 2b, 3, 4**
- **SVR rates of 95-100% after 12-24 weeks of therapy**
- **Cost:** $1,000/pill. $84,000 for 12 week course. $168,000 for 24 week course
- **Side effects:** fatigue, headache
Ledipasvir/Sofosbuvir

- Harvoni™ (Gilead Sciences) approved 2014
- NS5A polymerase inhibitor/NS5B polymerase inhibitor. First IFN/ribavirin free HCV therapy
- Dosing: ledipasvir 90mg/sofosbuvir 400mg fixed dosed tablet once daily
- Indicated for genotype 1 naïve, treatment failures, cirrhotics
- SVR rates 96-99% after 8-24 weeks
- Cost: $1,125/pill. $63,000 for 8 week course. $94,500 for 12 week course. $189,000 for 24 week course
- Side effects: fatigue, headache
Simeprevir

- Olysio™ (Janssen) approved 2013
- NS3/4a protease inhibitor
- Dosing: 150mg qd orally in combination with other agent (sofosbuvir, IFN, ribavirin)
- Indicated for treatment of genotype 1a, 1b
- Cost $790/capsule. $66,000 for 12 week course. $85,000 for 24 week course
- Side effects: rash/photosensitivity, pruritus, nausea
- Resistance
Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir

- **Viekira Pak™ (Abbvie) approved 2014**
- **NS5A inhibitor/protease inhibitor/CYP3A inhibitor/NS5B polymerase inhibitor**
- **Dosing:** 12.5mg/75mg/50mg/250mg bid +/- weight based ribavirin
- **Indicated for treatment of genotype 1a, 1b with or without cirrhosis**
- **Cost:** $83,000 for 12 week course
- **Side effects:** fatigue, nausea, HA, liver failure
- **Resistance**
Sofosbuvir/Velpatasvir

- Epclusa™ (Gilead Science) approved 2016
- NS5B polymerase inhibitor/NS5A polymerase inhibitor
- Dosing: sofosbuvir 400mg/velpatasvir 100mg fixed dose tablet once daily without food
- Indicated for genotypes 1,2,3,4,5,6
- Cost: $890/pill. $75,00 for 12 week course
- Side effects: fatigue, headache, bradycardia
Elbasvir/Grazoprevir

- Zepatier™ (Merck) approved 2016
- NS5A polymerase inhibitor/NS3/4A protease inhibitor
- Dosing: elbasvir 50mg/grazoprevir 100mg fixed dose tablet daily with or without food
- Indicated for genotype 1 or 4
- Cost: $55,000 for 12 week course
- Side effects: fatigue, headache, nausea
- Resistance
Monitoring During Antiviral Therapy

- CBC, Cr, liver function panel every 4 weeks
- Quantitative HCV viral load testing after 4 weeks of therapy and at 12 weeks following completion of therapy
- Discontinuation of therapy recommended if >10 fold increase in ALT or signs of decompensated liver function
- Futility rule: if detectable viral load present at week 4 and rises at week 6 discontinuation recommended
Initial Treatment of Hepatitis C Genotype 1a

- Daily fixed-dose combination of ledipasvir 90mg and sofosbuvir 400mg (Harvoni) for 12 weeks
- Daily fixed-dose combination of paritaprevir 150mg/ritonavir 100mg/ombitasvir 25mg plus dasabuvir 250mg (Viekira Pak) and weight based ribavirin for 12 weeks (non-cirrhotic) or 24 weeks (cirrhotic)
- Daily fixed-dose combination of sofosbuvir 400mg and velpatasvir 100mg (Epclusa) for 12 weeks (non or compensated cirrhotic). Add weight based ribavirin for 12 weeks (decompensated cirrhotic)
Initial Treatment of Hepatitis C Genotype 1b

- Daily fixed-dose combination of ledipasvir 90mg and sofosbuvir 400mg (Harvoni) for 12 weeks
- Daily fixed-dose combination of paritaprevir 150mg/ritonavir 100mg/ombitasvir 25mg plus dasabuvir 250mg (Viekira Pak) for 12 weeks (non-cirrhotic). Addition of weight based ribavirin if cirrhotic
- Daily fixed-dose combination of sofosbuvir 400mg and velpatasvir 100mg (Epclusa) for 12 weeks (non or compensated cirrhotic). Add weight based ribavirin for 12 weeks (decompensated cirrhotic)
Initial Treatment of Hepatitis C Genotype 2

- Daily sofosbuvir 400mg (Sovaldi) and weight based ribavirin for 12 weeks (non-cirrhotic) or 16 weeks (cirrhotic)

- Daily fixed-dose combination of sofosbuvir 400mg and velpatasvir 100mg (Epclusa) for 12 weeks (non or compensated cirrhotic). Add weight based ribavirin for 12 weeks (decompensated cirrhotic)
Initial Treatment of Hepatitis C Genotype 3

- Previously most difficult genotype to treat with current DAAs
- Daily sofosbuvir 400mg (Sovaldi) and weight based ribavirin for 24 weeks
- Daily fixed-dose combination of sofosbuvir 400mg and velpatasvir 100mg (Epclusa) for 12 weeks (non or compensated cirrhotic). Add weight based ribavirin for 12 weeks (decompensated cirrhotic)
Initial Treatment of Hepatitis C Genotype 4

- Daily fixed dose ledipasvir 90mg/sofosbuvir 400mg (Harvoni) for 12 weeks
- Daily fixed-dose combination of sofosbuvir 400mg and velpatasvir 100mg (Epclusa) for 12 weeks (non or compensated cirrhotic). Add weight based ribavirin for 12 weeks (decompensated cirrhotic)
- Daily fixed dose combination of paritaprevir 150mg/ritonavir 100mg/ombitasvir 25mg and weight based ribavirin for 12 weeks
- Daily sofosbuvir 400mg (Sovaldi) plus simeprevir 150mg (Olysio) for 12 weeks
Hepatitis C Treatment Considerations

- Efficacy
- Compliance
- Length of treatment
- Side effect profile
- Cost
- Insurance/pharmacy coverage
Hepatitis C Treatment Cost

• Medicaid restricting treatment to only those with advanced fibrosis in 30 states
• Old IFN based treatment costs $26,000-$64,000 per QALY
• New DAA based treatment costs $10,000-$200,000
• Treatment in 2015 on an average costs 54% of the wholesale acquisition cost
• Compared to HIV lifetime treatment cost of $315,000. HCV cure cost is $58,000
Non Alcoholic Fatty Liver Disease
Non Alcoholic Fatty Liver Disease (NAFLD)

- **Definition:** clinical disease state characterized by hepatic steatosis, either by imaging or histology, in an individual without significant alcohol use.
- **Encompasses** non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH).
- **NAFL:** presence of hepatic steatosis with no evidence of hepatocellular injury.
- **NASH:** presence of hepatic steatosis and inflammation with hepatocyte injury.
Prevalence of NAFLD

- Most common cause of chronic liver disease in the United States
- 80-100 million individuals affected (25% with NASH)
- Third most common indication for liver transplant in the United States
Natural History of NAFLD

- Most patients with NAFL/NASH will outlive their liver disease
- Higher overall mortality with most common cause of death from cardiovascular disease
- NAFLD is the hepatic manifestation of metabolic syndrome (obesity, IGT, high Trig, elevated BP, low LDL)
- 20-25% of patients with NASH will develop cirrhosis
- Increased risk of HCC in advanced fibrosis and cirrhosis
Risk Factors for NAFLD

- Established association:
  - Metabolic syndrome
  - Obesity
  - Type 2 diabetes mellitus
  - Dyslipidemia

- Emerging association:
  - PCOS, OSA, hypothyroidism, hypogonadism
Initial Evaluation of Fatty Liver

- No screening of the general population currently recommended
- Frequent incidental finding on imaging
- Check liver enzymes on all patients
- Assess EtOH consumption
- Exclude other etiologies for fatty liver and coexisting common liver disease including EtOH, drugs, chronic viral hepatitis, AIH, Wilson’s disease, hemochromatosis
- Elevated ferritin and ANA common in NAFLD
Assessment of Steatohepatitis and Fibrosis in NAFLD

• Important to differentiate between NAFL (benign) and NASH (risk of progression)

• Liver biopsy remains gold standard. Generally reserved for those with highest risk of NASH such as those with metabolic syndrome

• Liver enzymes not reliable measure of NASH

• Non-invasive methods include serum markers (CK 18), elastography (not in US), NAFLD fibrosis score (age, BMI, AST, ALT, Plt, Alb, Glu)

• Biopsy those at high risk and to R/O 2º liver dz
Management of NAFLD

• Fundamental step is treating risk factors associated with metabolic syndrome through lifestyle modifications
• Exercise, even independent of weight loss, may improve histology
• Gradual weight loss $\leq 1\text{kg/week}$ with caloric restriction and exercise
• 3-5% weight loss improves steatosis
• 10% weight loss likely needed to improve inflammation
• Improvement in histology post bariatric surgery
Management of NAFLD Pharmacotherapy

- Metformin: no significant effect on liver histology
- Urso: no significant effect on liver histology
- Omega 3 Fatty Acids: no effect
- Thiazolidinediones: improvement of steatosis and inflammation. Option for biopsy proven NASH. Long term safety issues remain
- Obeticholic acid (Ocaliva): may reverse fibrosis in NASH
Management of NAFLD Pharmacotherapy

- **Vitamin E:**
  - Anti-oxidant effect
  - Improves liver enzymes, steatosis and inflammation. No change in fibrosis score
  - Recommended dosage 800 IU daily
  - First line therapy in biopsy proven non-diabetics with NASH
  - Not rec in NASH/diabetics, NAFLD without bx, NASH cirrhosis
  - May increase all cause mortality, prostate CA
Selected References

- The Diagnosis and Management of Non-alcoholic Fatty Liver Disease, American Journal of Gastroenterology, April 2014
- Cryoglobulinemia an Hepatitis C Virus, Clinical Hepatology, March 2012