Treatment of Hepatitis C in the Primary Care Setting

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Disclosures:

None
Objectives

1. Understand treatment options and be able to identify patients that can be managed within primary care
2. Be aware of recommended monitoring to identify progression of disease for patients with chronic hepatitis C
3. Comprehend major drug interactions between current hepatitis C treatments and other drug treatments to prevent adverse outcomes
4. Identify when a patient is cured of his/her hepatitis C
What is Hepatitis C (HCV)?

- RNA virus
- 6 genotypes
- Infectious blood
  - Percutaneous
  - Vertical
  - Sexual
  - Personal items
US Distribution of HCV Genotypes

HCV genotypes 1, 2 and 3 are the most prevalent genotypes in the U.S., representing over 98% of all infections.

- GT 1: 73%
- GT 2: 13%
- GT 3: 12%
- GT 4,5,6: 1.5%

Virus Basics

- Previously known as “Non-A, Non-B Hepatitis”
- 1989: identified
- 1992: Sensitive screening of the blood supply
- 2007: surpasses HIV in deaths
- 2012: CDC recommends testing baby boomers
- 2014: all oral regimens with ↑ cure rates

HCV Epidemic

- US: 3.5 million HCV ab+ (2010)
  - Prevalent cases: 1.3% (since 2006)
  - NHANES: excludes institutionalized, prison, homeless, HD
  - Boomers: 70% of those infected (3.5% prev.)

- US: 17,000 new (incident) cases 2010
  - Young IVDU

Chronic HCV

• Most exposed do not clear the virus (~80%)

• Typically asymptomatic

• ~20% go on to develop cirrhosis

• Cirrhosis: HCC develops at annual rate 1-4%

CDC.gov, El-Serag.Gastroenterology 2012
Chronic Inflammation from HCV *Can* Lead to Fibrosis & Cirrhosis
Identifying Infection

• 2013 USPSTF “B” rating: 1945-1965 cohort
• Previously risk factor based alone
• High risk considerations:
  – IDU                   Homelessness       Unsafe injections
  – MSM                   Prison            Religious
  – HIV                   Hemodialysis     Tattoos
  – # partners            Transfusion <1992 Piercings
HCV Screening Algorithm
HCV Triage

• Insurance
  • Each has different requirements; changes often

• Noninvasive assessment:
  • Labs
  • Estimates of fibrosis
  • CTP score

• Imaging
  – Anatomy: liver, spleen
  – Mass lesion
Comorbid Conditions

- HIV
- Hep B
- Alcohol
- Fatty liver disease
- Immunity: Hep A, B
Case Example

- 64 yo M: gt 1a
  - Recently received cohort screening (b. 1952)
  - Insurance is Medicaid
  - Alcohol x 40 yrs, stopped with dx of HCV
  - No swelling, jaundice, gi bleeding or confusion
  - Normal PE
  - HTN, BPH
  - Tattoos in his youth
Would You Want to Treat?

• Engaged in care
• Compliance
• Comorbid conditions
• Signs of advanced liver disease/mass lesion
• Substance abuse
• Live expectancy >1 year
• What barriers will the insurance pose?
Clinical Assessment

• Liver function/dysfunction
  – Hepatic panel  PT/INR
  – CBC
  – Child Pugh Class

• Non-invasive assessments of fibrosis
  – Calculations based on routine labs:
    • APRI, FIB-4:
  – Lab tests: Fibrosure
  – Imaging
Non-invasive Assessment: Calculations

- **FIB-4 < 1.45**  NPV of 90%
- **FIB-4 > 3.25**  PPV 65%, 97% specific
- **APRI > 1**  sensitivity 76%  specificity of 72%: cirrhosis
- **APRI > 0.7**  sensitivity 77%  specificity of 72%: adv fibrosis

http://www.hepatitisc.uw.edu/page/clinical-calculators
Imaging Assessment

- **Ultrasound:**
  - morphology of liver and spleen; ascites
  - Low cost, **first choice for screening** in cirrhosis

- **CT/MRI:**
  - morphology, collateral vasculature (varices), ascites, HCC

- **Elastography:**
  - measures liver stiffness
  - images tissue response to a mechanical stimulus
HCV and liver damage over time

- **Stage 1**: Some inflammation but minimal effect on function
- **Stage 2**: Some limited accumulation of scar tissue (fibrosis) but with liver function
- **Stage 3**: Extensive fibrosis (cirrhosis) and scarring but with relatively normal functioning
- **Stage 4**: Substantial cirrhosis damaging liver and impairing vital functions

- Treatment can slow, halt or reverse liver damage in stages 1 to 3
- Extent and rate of progression of liver damage within individuals is variable although several factors influence fibrosis progression.

http://www.correlation-net.org/hep_c_trainers_manual/Module03/slides/slide3_10.PNG
Benefits of Identifying Advanced Liver Disease

• Assessment & mgt of side effects
• Medication, education
• Ongoing surveillance necessary
  – Cirrhosis increases risk of liver cancer
  – Cure does not eliminate risk of liver cancer
• Evaluation for rx
  – Cure reduces risk of decomp, death & cancer
• Transplant evaluation
Laboratory assessment

- **Hepatic function panel:**
  - AST 79
  - ALT 86
  - Albumin 3.9
  - Tb 0.7

- **CBC:** platelets 199

- **INR:** 1.02
Case Example (continued)

Non-invasive assessment

• FIB-4 score: 2.87 (indeterminate)

• Ultrasound result:
  • borderline hepatic enlargement
  • mild coarsening of the echotexture
  • borderline splenomegaly (spleen at 12.6cm)
What Should You Do Next?

- Reassess insurance
- Elastography
- Liver biopsy
- Monitor
Case Example Resolution

• Received a liver biopsy
  – Cirrhosis

• Qualified for rx from Medicaid

• Patient is 64 doing well
  – Medicare pays for treatment
  – Consider life expectancy
Treatment Options

• Insurance dependent
• Preferred choice, formulary options
• PAR criteria
  - laborious, requires previous amount of w/u
  - may have restrictions for primary care providers
• Patient assistance programs
• HCV genotype
Selecting Treatment

• http://www.hcvguidelines.org
  – “Access the Full Report”
  – “HCV guidance”
  – “Initial treatment of HCV”
    • Broken out by genotype
    • No cirrhosis, cirrhosis
Key Points *Prior* to Treatment

- Genotype
- Fibrosis Stage
- HCV Treatment History
- Medical Co-morbidities

Slide courtesy Dr. Alvaro Martinez-Camacho
Direct Acting Antiviral (DAA) Targets

Maradpour Nature Reviews 2007
What’s In a Name?

- **NS3/4 Protease Inhibitors:**
  - telaprevir
  - paritaprevir
  - Simeprevir
  - grazoprevir

  \[ \text{PRE} \rightarrow \text{Protease Inhibitor} \]

- **NS5A Inhibitors:**
  - Ledipasvir
  - elbasvir
  - Ombitasvir
  - velpat asvir

  \[ \text{AS} \rightarrow \text{NS5A Inhibitor} \]

- **NS5B Inhibitors:**
  - sofosbuvir
  - dasabuvir

  \[ \text{BU} \rightarrow \text{NS5B Inhibitor} \]

Slide courtesy of Jacob Langness, PharmD
## Options for Treatment

### Rx Naïve, No Cirrhosis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Elbasvir/grazoprevir +/-ribavir</th>
<th>Ledipasvir/sofosbuvir</th>
<th>Paritaprevir/ritonavir Ombitasvir/dasabuvir +/- ribavir</th>
<th>Simeprevir+ sofosbuvir</th>
<th>Sofosbuvir+ velpatasvir</th>
<th>Daclatasvir + sofosbuvir</th>
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<tbody>
<tr>
<td>1a</td>
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</tbody>
</table>

Sofosbuvir: **Gilead** “Sovaldi” 2013  
Simeprevir: **Janssen** “Olysio” 2013  
Sofosbuvir+ Ledipasvir: **Gilead** “Harvoni” 2014  
Paritaprevir/ritonavir/ombitasvir/dasabuvir: **AbbVie** “Viekira Pak” 2014  
Daclatasvir: **Bristol-Myers Squibb** “Daklinza” 2015  
Elbasvir/grazoprevir: **Merck** “Zepatier” 2016  
Sofosbuvir+velpatasvir: **Gilead** “Epclusa” 2016
## Drug interactions

<table>
<thead>
<tr>
<th>Drug category/drug</th>
<th>Direct Acting Antiviral</th>
<th>Mechanism</th>
<th>Adverse Event/SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Sofosbuvir *all potentially</td>
<td>unclear</td>
<td>Bradycardia; cardiac</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>All</td>
<td>Inducers of CYP</td>
<td>Decrease DAA</td>
</tr>
<tr>
<td>Carbamazepine, phenytoin phenobarbital</td>
<td>All</td>
<td>Inducers of CYP</td>
<td>Decrease DAA</td>
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<td>Ethinyl-estradiol OCs</td>
<td>ProD</td>
<td>Drug-drug interaction study</td>
<td>Elevation liver enzymes</td>
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<td>Antiretrovirals</td>
<td>Protease inhibitors</td>
<td>Cyp interactions OATP1B1 inhib</td>
<td>Increased Tenofovir</td>
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<tr>
<td>Antidepressants</td>
<td>ProD</td>
<td>CYP3A4 inhibition by ritonavir</td>
<td>Increased Antidep</td>
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<tr>
<td>Atypical Antipsychotics</td>
<td>ProD Grazoprevir/elbasvir</td>
<td>Multiple interactions</td>
<td>Increased AA</td>
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<tr>
<td>Opioids</td>
<td>ProD Grazoprevir/elbasvir</td>
<td>CYP3A inhibition by DAA</td>
<td>Increased Opioid</td>
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<tr>
<td>Calcium Channel Blockers</td>
<td>ProD Grazoprevir/elbasvir</td>
<td>CYP3A4 inhibition by DAA</td>
<td>Increased CCB</td>
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<tr>
<td>Statins</td>
<td>All</td>
<td>Hepatocyte transporter inhibited by DAA</td>
<td>Increased statin</td>
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<tr>
<td>Gastric acid modifier</td>
<td>Ledipasvir Velpatasvir</td>
<td>Absorption pH dependent</td>
<td>Decreased DAA absorption</td>
</tr>
</tbody>
</table>

Adapted fr Christine MacBrayne, PharmD
## DAAs and Common Pain Medications

<table>
<thead>
<tr>
<th></th>
<th>SOF/LDV</th>
<th>SOF/VEL</th>
<th>PrOD</th>
<th>GZR/EBR</th>
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<tr>
<td>Hydromorphone</td>
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<td>✓&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Monitor*</td>
<td>✓&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<td>Fentanyl</td>
<td>✓</td>
<td>✓</td>
<td>Monitor*</td>
<td>✓</td>
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<tr>
<td>Hydrocodone</td>
<td>✓</td>
<td>✓</td>
<td>Monitor*</td>
<td>✓</td>
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<tr>
<td>Morphine</td>
<td>✓</td>
<td>✓</td>
<td>Monitor*</td>
<td>✓</td>
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<tr>
<td>Oxycodone</td>
<td>✓&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Monitor*</td>
<td>✓&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Methadone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tbody>
</table>

✓ = OK
*A reduction in dose may be needed with titration to effect
<sup>a</sup>Caution in hepatic impairment, may require a dose reduction

Slide courtesy of Christine MacBrayne, PharmD
Flow to Initiate Rx

• Identify low risk patient
• Hep A/B immunity?
• What is the genotype?
• Choose drug based on above
• Review drug interactions/Pharmacy review
• Submit rx-> triggers PAR
• Fill out PAR
• Teaching visit, rx agreement, set up labs,
• Track SVR
Suggested Monitoring

Week 0 (baseline)
• CBC, LFT, BMP, VL
• Review med list

Week 4
• CBC, LFT, BMP, VL
• Call patient to assess side effects and compliance

Week 8
• LFT
• Call patient to assess side effects and compliance

Week 12
• CBC, LFT, BMP, VL
• Call patient to assess side effects
• Adjust any baseline medications to original dosing
• Discuss timing of SVR assessment
Cure of HCV

• Sustained Virologic Response (SVR)
  – Viral load negative **12 weeks after end of rx**

  – No need for repeated checks of VL
    • HCV antibody will always be +

– Can become re-infected
  • Counsel against high-risk behaviors
HCV Monitoring

• Treated/cured patients:
  – ALT abnormal/fatty disease
  – Cirrhosis: routine HCC surveillance imaging

• No treatment
  – At least once yearly BMP, Hepatic, CBC
  – Repeated VL not necessary
  – HCC surveillance for cirrhotics
Summary

• Reviewed those at risk for Hepatitis C (HCV)
• Assessment & staging fibrosis in chronic HCV
• Identification of candidates for treatment
• Directions for selecting treatment
• Suggestions for initiation & monitoring therapy
• Who to monitor post cure of HCV or no rx
The End

Thank You!
Resources

• www.hcvguidelines.org
• www.hep-druginteractions.org
• www.hepatitisc.uw.edu