Update on Hepatitis C Management

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Objectives

- At the completion of this presentation,
  - pharmacists should be able to (1-4)...
  - technicians should be able to (2-4):
  1. Identify appropriate monitoring tests for diagnosis of hepatitis C (HCV) and assessment of liver function.
  2. Select appropriate vaccinations for a hepatitis C patient.
  3. Recognize the most common and/or severe side effects of interferon, ribavirin and HCV protease inhibitors.
  4. Contrast the dosing differences between boceprevir and telaprevir.

Definitions - Hepatitis

- Incubation period
- Prodrome
- Icteric
- Resolution
- Anicteric
- Flare
- Fulminant
- Prolonged
Hepatitis Viruses

Acute and Chronic

Most common-hepatitis

Most common-acute

Acute

Non-pathogenic

Clinical Symptoms

• Acute hepatitis:
  – fever
  – jaundice, dark urine
  – fatigue, malaise, anorexia
  – nausea, abdominal discomfort

• Chronic:
  – fatigue
  – jaundice

Incidence of Acute Hepatitis C in United States, 1992-2007

Sources of Infection for Persons with Hepatitis C

- Injecting drug use 60%
- Sexual 15%
- Transfusion 10% (before screening)
- Other* 5%
- Unknown 10%

*Nosocomial; Health-care work; Perinatal


HCV Genotype in United States

- Genotype 1 (a, b): 72%
- Genotype 2 (a-d): 17%
- Genotype 3 (a-f): 10%
- Others (4 a-j, 5a, 6a): 1%
- 6 genotypes (@15 subtypes)

Magnitude of the Problem

- Nearly 200 million worldwide
- 3-5 million persons in U.S. infected
- Approximately 35,000 new cases yearly
- Plus hepatitis B= 75% all cases of liver disease
- Leading cause of:
  - chronic liver disease*
  - cirrhosis*
  - liver cancer*
  - *death due to liver disease
  - liver transplantation

Features of Hep C Infection

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
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<tbody>
<tr>
<td>Incubation Average</td>
<td>Average 6-7 weeks</td>
</tr>
<tr>
<td></td>
<td>Range 2-26 weeks</td>
</tr>
<tr>
<td>Acute Illness</td>
<td>Mild (&lt;20%)</td>
</tr>
<tr>
<td>Case Fatality Rate</td>
<td>Low</td>
</tr>
<tr>
<td>Chronic Infection</td>
<td>75%-85%</td>
</tr>
<tr>
<td>Chronic Hepatitis</td>
<td>70% (most asymptomatic)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>10%-20%</td>
</tr>
<tr>
<td>Mortality from CLD</td>
<td>1%-5%</td>
</tr>
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Extrahepatic Manifestations

- Nonspecific antibodies
- Essential mixed cryoglobulinemia
- Glomerulonephritis
- Porphyria cutanea tarda
- Leukocytoclastic vasculitis
- Mooren’s corneal ulcer
- Non-Hodgkin’s lymphoma
- Autoimmune thyroiditis
- Diabetes mellitus
- Sjögren’s syndrome

HCV and HIV Commonalities

- “Blood borne” pathogens
- Acquired/transmitted/prevented in similar ways
- Co-infection:
  - @ 30% of HIV+ patients are co-infected with HCV
  - 5% of HCV+ patients are co-infected with HIV+
- Viral load technology (used first for HIV)
- Co-infection with HIV:
  - Leading cause of non-AIDS death in HIV+ pts
  - More treatment challenges (efficacy, SE, drug intxns)

Challenges and Goals

- 55-85% acute HCV will remain infected
- Difficult to identify those at risk of progression
- HIV or Hepatitis B co-infection
- Liver biopsy is important
- Consider
  - Co-morbid conditions
  - Symptomatic cryoglobulinemia
  - Continuing substance abuse
- Goals:
  - Prevent complications and death
- No vaccine!!!! (no pre-exposure prophylaxis)

Lab Tests, Diagnosis, Work-up

Liver Function Tests

- AST
- ALT
- Bilirubin (total = direct + indirect)
- Albumin
- Total protein
- PT (INR)
Liver Enzymes

- Leak into bloodstream when cells are damaged
- Can vary over time
- Males can have higher levels than women
- ALT
  - 0-50 IU/L (most reference labs)
  - found in liver
  - men < 30 IU/L; women < 19 IU/L
- AST
  - 0-45 IU/L (most reference labs)
  - found in liver (and red cells, cardiac and skeletal muscles)
  - African-American males can have higher levels than Caucasian males

Liver Biopsy

- Invasive
- Guided by ultrasound
- Risky if:
  - INR ↑/↓
  - platelets ↓
- Histology
- Staging:
  - fibrosis
- Grading:
  - inflammation

Scoring

- Metavir
  - Most common
  - More reproducible
  - Less discriminate than Ishak and Knodell for fibrosis and necroinflammation
- Scheuer
  - Same as Metavir
- Ishak
- Knodell’s HAI

Hepatitis C Serologic Tests

- Antibodies (anti-HCV)
  - main screening assay (enzyme or chemiluminscence assay)
  - time to seroconversion: 4-10 weeks (>97% by 6 mos)
  - > 99% specificity (false +: low prevalence HCV)
  - false -: severe immunosuppression
- RIBA (immuno blot) confirm Ab presence
- Viral Load (HCV-RNA)
  - qualitative:
    - confirmation for a positive test (i.e. diagnosis, blood screening)
    - manual or semi-automated RT-PCR or TMA
  - quantitative:
    - treatment course
    - manual or semi-automated RT-PCR, bDNA, real-time PCR
  - IU/mL preferred unit for results

Interpretation of Assays

<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV RNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Acute or chronic depending on clinical context</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Resolution of HCV or acute HCV during period of low-level viremia</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Early acute HCV or chronic HCV in setting of immunosuppression or false + HCV RNA test</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Absence of infection</td>
</tr>
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Initial Evaluation - Hepatitis

- Chief complaint
- Signs and symptoms
- History and physical
- Family history (liver disease, HCC)
- Consider:
  - ultra-sound
  - biopsy (stage, grade)
Laboratory Testing

<table>
<thead>
<tr>
<th>Situation</th>
<th>Tests</th>
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<tbody>
<tr>
<td>Initial</td>
<td>CBC, TSH hepatic panel (CMP + LFTs), anti-HAV, HBsAg, anti-HBs, anti-HDV, HCV RNA (VL), Genotype, HIV+, AFP, ANA, Pregnancy Test</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>ALT (and other LFTs), HCV RNA, biopsy (histology), AFP, Tests for extra hepatic manifestations, Med side effects (i.e. anemia)</td>
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Serologic Pattern of Acute HCV Infection with Recovery

Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection
Prevention

- Alcohol consumption, watch hepatic meds
- Education (clean needles, safer sex, wound management, do not donate…)
- Pre-exposure vs. post-exposure
- Vaccination for everyone is the best prevention:
  - infants
  - adolescents
  - adults
  - dialysis and immunocompromised

Postexposure

- Antivirals not recommended for prophylaxis
- Follow-up after needle-sticks, sharps, or mucosal exposures to HCV-positive blood
  - test source for anti-HCV
  - test worker if source anti-HCV positive
    - anti-HCV and ALT at baseline and 4-6 months later
    - for earlier diagnosis, HCV RNA by PCR at 4-6 weeks
  - confirm all anti-HCV results
- Refer infected worker to specialist for medical evaluation and management

HCV Antiviral Therapy


**Treatment Concepts**

- Pegylated interferon and ribavirin is currently the standard of care ("background" or "prime")
- Genotype 1 (most common in U.S.) has lowest response rate to therapy (IFN + ribavirin)
- 2 new protease inhibitors approved (genotype 1) Spring 2011 used with above combination.
- Some patients: still in watch/wait mode.
- Goal: decrease VL, normalize ALT, prevent progression to ESLD, improve QOL
- Length of therapy: depends...

**Peginterferon-Alfa 2a (Pegasys®)**

- MOA: binds to cell membrane; induction of intracellular enzymes; viral replication inhibition, suppression of cell proliferation, immunomodulating activities
- Dose:
  - 180 mcg SQ Qwk x _________ wks
  - May have to dose-adjust for intolerance/CBC
  - Pre-filled syringes
- Side effects:
  - injection site reactions
  - flu like symptoms: fatigue, HA, fever, malaise, & chills
  - CNS: depression, anxiety, dizziness, sleep changes
  - itching, hypersensitivity reaction
  - hematological (i.e. thrombocytopenia)

**Ribavirin (Rebetol®)**

- MOA: ↓ cellular purine metabolism (inhibits viral protein synthesis); ↑ RNA virus mutation; ↑ antiviral cytokines
- Combination with interferon
- Oral daily dosing: depending on interferon, genotype, wt of patient
- SE:
  - hemolytic anemia (can be severe)
  - insomnia, nausea, diarrhea, anorexia, alopecia
- Pregnancy category: X
Ribavirin Dosing

• Peginterferon alfa-2a in hepatitis C genotype 1, 4
  – < 75 kg: 1000 mg/day PO in 2 divided doses
  – ≥ 75 kg: 1200 mg/day PO in 2 divided doses

• Peginterferon alfa-2a in hepatitis C genotype 2, 3
  – 800 mg/day in 2 divided doses x 24 wks

• Peginterferon alfa-2b (genotype 1- 48 weeks without protease inhibitors; genotype 2 & 3- 24 weeks)
  – 800 mg/day < 65 kg
  – 1,000 mg/day 65-84 kg
  – 1,200 mg/day 85-105 kg
  – 1,400 mg/day >105 kg but <125 kg

<table>
<thead>
<tr>
<th>Virological Response</th>
<th>Definition</th>
<th>Clinical Utility</th>
</tr>
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<tbody>
<tr>
<td>Rapid virological response (RVR)</td>
<td>HCV RNA – by week 4</td>
<td>May allow shortening course for genotypes 2/3</td>
</tr>
<tr>
<td>Early virological response (EVR)</td>
<td>≥ 2 log ↓ VL vs. baseline (partial) or – by week 12</td>
<td>Predicts lack of SVR</td>
</tr>
<tr>
<td>End-of-treatment response (ETR)</td>
<td>HCV RNA – at end of 24 or 48 weeks</td>
<td></td>
</tr>
<tr>
<td>Sustained virological response (SVR)</td>
<td>HCV RNA – 24 weeks after treatment cessation</td>
<td>Best predictor of long-term treatment response</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>Reappearance of HCV RNA while on therapy</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>Reappearance of HCV RNA after therapy d/c</td>
<td></td>
</tr>
<tr>
<td>Nonresponder</td>
<td>Failure to clear HCV RNA after 24 weeks</td>
<td></td>
</tr>
<tr>
<td>Null responder</td>
<td>Failure to ↓ HCV RNA by &lt; 2 logs after 24 weeks</td>
<td></td>
</tr>
<tr>
<td>Partial responder</td>
<td>2 log ↓ HCV RNA but still + at week 24</td>
<td></td>
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Protease Inhibitors

- Direct-acting antiviral agent
- Expensive; “game-changers”
- Approved for Genotype 1
- Adults with compensated liver disease (including cirrhosis)
- Previously untreated or failed previous interferon and ribavirin therapy
- Must be used in combination with PEG-interferon and ribavirin (triple therapy)
- Substrate and inhibitor of Cyp3A4/5

Boceprevir (Victrelis)

- Start PEG-INF + ribavirin for 4 weeks first
- Then add boceprevir
- Dose:
  - 800 mg PO TID (every 7-9 hrs) with food.
- SE: anemia, taste changes, fatigue, rash/itching, N/V/D, and insomnia
- $1,500/week (x 28-36 wks = $42,000-54,000)
Boceprevir Response-Guided Therapy

Telaprevir (Incivek)
- Begin with triple therapy for first 12 weeks
- Then drop telaprevir (duration of dual then depends on virological response)
- Dose: 750 mg PO TID with food
- SE: anemia, taste changes, fatigue, rash/itching, N/V/D, and anal or rectal problems
- Cost: $5,500/week (x 12 wks = $66,000)

Telaprevir Response-Guided Therapy
Treatment Contraindications

- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, or lung)
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin
- Untreated thyroid disease
- Pregnant or unwilling to comply with adequate contraception
- Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, COPD
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV

Therapeutic Options Summary

<table>
<thead>
<tr>
<th>Virus</th>
<th>Vaccine</th>
<th>IG</th>
<th>Antivirals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C</td>
<td>No</td>
<td>No</td>
<td>Yes Combination Therapy!</td>
</tr>
</tbody>
</table>

Treatment Issues

- Timing of starting, stopping meds
- Pregnancy- counseling both patient and partner
- Insurance/cost
- Injection- interferon
  - reactions
  - recovering addicts (needle phobia)
- Drug interactions- especially with protease inhibitors
- Management of side effects:
  - medication to treat: e.g. epo for anemia, anti-depressants
  - dose adjustment: ribavirin, PEG-INF, protease inhibitor-rash
- Co-infection with HIV
Pipeline

- Goals: PO, without RBV + IFN, once a day, no drug resistance
- Direct-acting antivirals (DAA)- here they come!
- Promising:
  - Daclatasvir (BMS)- NSSA inhibitor PLUS
  - Sofosbuvir (Gilead)- nucleotide analog
  - 40 patients who failed combo with boceprevir or telaprevir
  - 12 weeks
  - 100% clear virus
  - Pilot data presented at CROI 2013
  - However, Gilead is halting collaborative trials to study
    sofosbuvir with an in-house NSSA inhibitor- ledipasvir

Statin Therapy- Why NOT?

- Pilot studies: statin use leads to \(^{\uparrow}\) SVR and anti-HCV activity
- Population-based cohort Taiwan
- Relationship: statin use (cumulative DDD) and HCC in HCV+
- 95% CI after adjusting for confounders:
  - age, sex, urbanization, income, liver cirrhosis and diabetes
- 4 groups statin users (cDDD):<br>  - < 28 (non-users)<br>  - 28-89<br>  - 90-180<br>  - >180
- Results:
  - 340.5 (statins) versus 1110.2 (non-statins) patient cases/100,000 person-years; absolute RR: 770 (95% CI: 730-811); adjusted HR: 0.53 (0.49-0.58)<br>  - dose-response relationship: adjusted HR:
    - < 28 (non-users)<br>    - 28-89<br>    - 90-180<br>    - >180

Immunization Recommendations- ACIP

[Immunization Recommendations- ACIP image]


Useful Resources

• www.hepb.org
• www.aasld.org (guidelines)
• www.medscape.com
  – (Hep B and C resource center)
• University of Liverpool- Drug Interactions:
  – HIV
  – Hepatitis C
• www.cdc.gov
• www.who.int

Self Assessment Questions

1. Match the following labs to the appropriate
diagnosis or monitoring parameter:
   I. ALT
   II. Anti-HCV
   III. Genotype
   IV. HCV viral load
      a. Diagnosis only
      b. Diagnosis and monitoring therapy
      c. Monitoring disease
      d. Selecting therapy

2. All of the following are recommended for a
72 year old HCV+ patient co-infected with
HIV (CD4+ count 577) EXCEPT:
   a. Hepatitis A
   b. Hepatitis B
   c. Pneumococcal- PPSV23 and PCV13
   d. Zoster
Self-Assessment Questions

3. Considering triple therapy treatment for Hepatitis C, identify the common side effect which could be caused by any of the medications.
   a. Anemia
   b. Flu-like symptoms
   c. Psychosis
   d. Rectal itching

Self-Assessment Questions

4. What is one main difference between boceprevir and telaprevir?
   a. Dosing frequency
   b. Main side effects
   c. When to start and when to stop
   d. Cost (cheap vs. expensive)