Hepatitis C ECHO Clinic
Introduction-Part 2 :Treatment

Charles Krasner, M.D.
UNSOM
Veterans Affairs Medical Center
November 6, 2014
Course of illness with Hepatitis C

- Acute infection
- Chronic inflammation of the liver (80%)
- Fibrosis
- Cirrhosis of the liver (2-6% per annum)
- Cancer of the liver
You screened your patient, and now the **HCV antibody test** is positive. What do you do next?

- The antibody test only means they have been exposed to HCV. **About 20% of patients will spontaneously clear the infection**, but their antibody test will **remain positive**. They do **not** need treatment!

1. To confirm active disease obtain:

   **Virus (HCV), Quantitative, PCR (QuantaSURE®)**

   If HCV RNA is **detectable**- they have active disease
   If HCV RNA is **not-detectable**- the disease has resolved—either spontaneously or due to prior successful treatment
2. HCV virus RNA is detectable, what next?
Order a panel of blood tests and an ultrasound:

Blood work

1. **HCV Genotype** – over time, HCV has evolved into different strains, referred to as genotypes 1 thru 6. Some HCV drugs may only block viral replication in a specific genotype, while other drugs may work against all genotypes. Genotype 1, the most common genotype in the United States is broken down further into genotype 1a and 1b. It is critical to determine the genotype before prescribing therapy.

In the United States:

- Genotype 1a – 55%
- Genotype 1b – 15%
- Genotype 2 – 15%
- Genotype 3 – 14%
- Genotype 4 – 1%
Other blood tests:

- **Chemistry panel** and **ProTime** – evaluates liver function – albumin, t. bili and ProTime; and inflammation- AST and ALT
- **CBC** - thrombocytopenia is a good predictor of cirrhosis
- **Iron panel and ferritin** - increased levels could mean hemochromatosis or cirrhosis
- **AFP** - elevated levels seen in cirrhosis and liver cancer
- **Hepatitis A antibody, total** and **Hepatitis B Surface ag and Surface ab** - if not immune, good to vaccinate these patients against HAV and/or HBV
- **HIV screen**
Other tests:

- **Liver /spleen Ultrasound**– don’t order an abdominal ultrasound, L/S ultrasound is cheaper and it is all you need: write “evaluate Hepatitis C” – this way the radiologist knows to look for signs of cirrhosis, portal hypertension and hepatoma.

- **Hepatitis C FibroSURE©** – (A LabCorp test) A blood test that takes a number of lab values and correlates them with **stage** of liver disease.
Stage of Disease-how much damage has occurred to the liver
Does your patient have cirrhosis?

- Need to know if the patient has cirrhosis, since this is when the risk of liver cancer or decompensation increases, and the course of therapy may be extended
- Liver biopsies have greatly fallen out of favor because the new treatments are so effective and well tolerated, so staging mostly determined by lab tests and physical exam
- Degree of liver damage is described by Stage, and reflects the amount of scarring to the liver
Stage of liver disease – on a Metavir scale of 0 to 4. Indicates degree of scarring (fibrosis) in the liver

- **Stage 0** - no damage
- **Stage 1** – mild scarring
- **Stage 2** - moderate scarring
- **Stage 3** - advanced disease
- **Stage 4** - severe scarring with distortion of the liver structure - this is cirrhosis
Results suggesting cirrhosis

- **Physical exam**: palmer erythema, spider angiomata, irregular liver edge
- **Labs**: ultrasound shows nodular liver or big spleen, low platelet count <150,000, low albumin, increased Pro-time, increased bilirubin
- **FibroSURE®**: good for identifying early and advanced disease, not so much for middle stages
- **APRI (AST to Platelet Index) score**: uses AST and platelet count to estimate likelihood of cirrhosis
Currently, Very Few HCV Patients Are Treated

- 2.7-3.9 million infected
- 50% HCV detected
- 32% to 38% referred for care
- 7% to 11% treated

HCV life cycle targeted by the new drugs

**Sofosbuvir** is a NS5B polymerase inhibitor blocking viral replication

**Ledipasvir** is a NS5A enzyme inhibitor blocking viral assembly

**Ribavirin** is a nucleoside analog that reduces relapse rate

If you block viral replication effectively enough - the virus has no where to hide and the infection resolves. Two potent anti-virals working together at different sites in the life cycle are enough to cure most patients.
This is it: using a combination of just two antiviral drugs, either Sofosbuvir and Ledipasvir (in one tablet called Harvoni®) for genotype 1a or 1b, or Sofosbuvir (Sovaldi®) and generic ribavirin together for genotype 2 or 3, 90 to 100% of all patients can be cured! Other companies will be introducing similar, very effective products soon.
Good riddance!!!
Three Hepatitis C treatment terms to know:

- **SVR12** - (Sustained Virologic Response, week 12) - this is the accepted **definition of cure**. It means at 12 weeks after completion of therapy, the HCV remains non-detectable. Very rare to relapse after that time period.

- **Treatment naïve** - patient has never been treated before

- **Treatment experienced** - the patient has been treated with but not cured previously with dual therapy (interferon and ribavirin) or triple therapy (interferon, ribavirin and a protease inhibitor). These patients may not respond as quickly to the new therapies as a treatment naïve patient, and may therefore require a longer course of medication to achieve SVR.
Interferon free, one pill daily, oral regimens with 98 to 99% cure rates in treatment naïve patients – no need for ribavirin for genotype 1a or 1b

Sofosbuvir/Ledipasvir (Harvoni®)
Therapy for genotype 2 and 3 treatment-naive patients

- **Genotype 2**: 12 weeks of Sofosbuvir and ribavirin – 95% SVR12
- **Genotype 3**: 24 weeks of Sofosbuvir and ribavirin – 93% SVR12

Note: Need to monitor for anemia while on ribavirin and adjust the dose as needed
Monitoring patients on therapy

- Be sure the patient has the entire course of planned therapy pre-approved by the insurance company before starting so no interruption occurs.
- Emphasize compliance, compliance and compliance. No excuses for missing any dose.
- I order a CBC, chem panel and HCV Quantitative PCR test at day # 28. Must be less than lower limit of quantitation (<12 to <25 copies based on lab cut-off), but ok to still be detectable at less than this cut-off.
- If on ribavirin for genotypes 2 or 3, I would also get a CBC at week 2 to be sure not severely anemic. A drop of about 2 to 3 grams of Hbg. by 4 weeks is actually a good sign of drug activity. I get a monthly CBC on these patients. It is ok to drop the ribavirin dose 200 to 400mg if needed.
- Complete the prescribed regimen and get a end of treatment HCV quantitative viral load and chem panel.
- Get a 4 week and 12 week HCV quantitative PCR to see if SVR12 achieved.
Case 1- Reluctant 62 year old with remote drug abuse history

- **HPI** - 62 year old male seen for routine exam. Remote hx of drug use in his 20’s, none since. He tells you he attempted to donate blood a few years ago. After that, he got a letter from Blood Bank telling him his HCV antibody test is positive, and suggesting discussing this with his doctor. Heard from friends that interferon was actually cancer chemotherapy so he did not pursue evaluation, as “treatment was worse than the disease.” Does not follow-up till now after reading that there are new HCV meds on the market. Drinks 1 to 2 glasses of wine with dinner. Wife of 32 years is HCV negative.

- **PMH** - Has hypertension, mild Type 2 DM.

- **PE** - no palmer erythema, no spider angiomata, liver edge 2 to 3 cm below RCM, no spleen.
Case 1 - Questions

- What test would confirm he has active Hepatitis C?
- It is an active infection, so what is the utility now of each of the following tests in evaluating your patient?
  - CBC
  - Chemistry panel, PT/INR
  - Fe/TIBC
  - Genotype
  - Ultrasound and AFP
  - HIV, HAV IgG, HBV Sag and Sab
Case 1-Lab results

Platelets: 158,000
AST/ALT: 54/72
Albumin: 3.8, T. bilirubin: 0.9mg/dl
INR: nl
Fe/TIBC: 34%
AFP: 8.2
Genotype: 1a
HCV viral load: 2,400,000 copies/ml
HIV: neg, HAV IgG+: HBV Sag-/Sab-
APRI score: (54/31)/148 = 1.1 (fibrosis, possible cirrhosis)
Ultrasound: mild, enlarged heterogeneous liver, no masses or portal hypertension
Case 1- Treatment Approach

What steps would you recommend next for the patient?

What treatment regimen would you prescribe?

What if the insurance company wants documentation of progressive liver disease first before authorizing treatment?
Case 2 – depressed female with advanced liver disease

**HPI:** 58 year old female asks you if you know much about the new HCV drugs she has seen advertised. She tells you she was probably infected in her 30’s by sharing needles with her ex-husband who later died of HCV. She was finally diagnosed positive in 2011 when she applied for life insurance. She was then seen by a GI physician who ordered a liver biopsy showing Stage 3 disease and genotype 2 HCV. He recommended interferon therapy, but she was reluctant to take it because she was worried her chronic depression would be exacerbated by the interferon. She stopped drinking in 2011 after her diagnosis.
exam

- spider angioma, palm erythema present
- Liver edge down 3 cm RCM, relatively smooth edge, no spleen tip
labs

- WBC - 3,600. platelets -112,000
- AFP - 12.2
- Ultrasound – nodular liver without mass, borderline spleen enlargement
- AST/ALT - 46/58
- APRI score - 1.3
- HIV – neg, HAV total – neg, HBV Sab+
Your recommendations

- Does she need a liver biopsy?
- What complications are she at risk for with untreated Hepatitis C?
- Is her depression a contraindication to treatment?
- After referring her to a GI doctor for screening upper endoscopy to evaluate for varices, what treatment regimen would you prescribe?
- If she was 28 years old now, what side-effect of ribavirin would be of prime concern?
Go for it!

- Send me HIPPA-ok patient information thru ECHO website and how I can contact you to discuss the case, or better bring the case to ECHO clinic for group discussion
- Excellent website for up to the minute treatment advice. A collaborative effort from GI and Infectious Disease organizations.  [www.hcvguidelines.org](http://www.hcvguidelines.org)  
  (Click on “Access the Full Report” on the home page)