HCV ECHO Case Recommendations

Session 4: February 24, 2025

Case Recommendations and Considerations:

CATEGORY	RECOMMENDATIONS	Relevant Presentation Question or Concern	REFERENCES/ RESOURCE LINKS
History	• The patient's history matters- if the patient had a documented sustained virologic response at 12 weeks after treatment completion and subsequently presents with detectable HCV RNA, then this is likely a re-infection. • However, there may be no documentation of SVR at 12 weeks. If a patient presents with a genotype different from that of their prior infection, we can assume this is re-infection and not treatment failure. • If the history of the patient's prior treatment appears chaotic or inconsistent and no documentation exists of undetectable viral loads, consider treatment failure.	1. For patients with active IV drug use and prior treated HCV infection who now present with positive HCV RNA, when do you consider re-infection vs. treatment failure?	
Physical Exam	•		

HCV ECHO Case Recommendations

Diagnostic evaluation	• The re-infection rate for HCV is very low. It's between 3% to 5%. • HCV re-infection is the detection of HCV RNA in a patient who was previously treated for chronic HCV and had a documented sustained virologic response at 12 weeks. • All lab tests are imperfect. HCV virus tests have a lower limit of detection (LLD) for the virus, around 15 IU/mL (1.2 log10 IU/mL). • It used to be that qualitative tests had a lower LLD than the quantitative tests, but today's tests are comparable. • For the patient in today's discussion, if he had an undetectable quantitative HCV RNA in 2020, then he had cleared the virus (and not failed treatment) at that time.	1. What is HCV re-infection and how common is it? 2. Does the qualitative hepatitis C RNA test have a lower limit of detection compared to the quantitative test?	https://microbiology.testcatalog.org/show/HCVQN
Medication Therapy & Adjustments	• For patients with active IV drug use, there are multiple reasons to treat blood borne HCV. These include forestalling the potential for a patient to act as a vector for the spread of HCV to others through needle sharing, tattoos, or sexual contact. • Treat the patient similar to how you would treat a patient who was never treated before. Even if the patient presents with the same genotype as the previous episode of HCV, it does not mean that the patient is re-infected with the same virus. Treatment should be started as soon as possible, leveraging support services for patients at high risk with limited support. • HCV resistance is a characteristic of the virus, not of the patient. If the patient was previously treated and achieved SVR, that virus population has been eliminated. Any new infection would be from a different virus that was not exposed to any drug treatment.	1. For a patient with active IV drug use and HCV re-infection after treatment, do we treat the patient again despite ongoing substance use? 2. How do you treat a patient with HCV re-infection? 3. Is there a risk of cultivating resistance in a patient who was previously treated for HCV? 4. Should you wait for HCV genotype results before you start treatment? 5. What if the history were more ambiguous and treatment failure is highly considered?	

	Resistance would not be an issue in that case. ● For patients with limited social support who are high-risk, start treatment as soon as they are ready. Current agents are pan-genotypic and treatment can be started even while waiting for the final genotype results to return. ● For the rare patient who is considered to have failed treatment, further thought regarding the optimal treatment regimen is needed and they may need a longer course of treatment. Consider consultation with a specialist for these exceptional patients.		
Vaccination	●		
Social Determinants of Health (SDOH)	● It is important to be mindful of systemic bias and to try to avoid stigmatizing patients. This can be a common experience described by patients who currently use injectable drugs or have a history of substance use. ● Patients may have varied reasons for not being able to adhere to their follow-up schedules and this behavior may not necessarily indicate that they have neglected to take care of themselves. ● Ensure all patients like this know about the syringe exchange programs and endorse their use. ● Use care navigators and coordinator staff to support treatment and follow-up. ● Clinicians must try to develop a therapeutic relationship with patients. Be present, find out their goals and try to get done as much as possible when patients show up for their visit, in order to practically expedite HCV care.	1. How do you maximize care for patients with social risk factors?	

HCV ECHO Case Recommendations

Behavioral Health	•		
Screening	•		
Risk Reduction	•		
Other	•		

HCV ECHO Case Recommendations

Didactic on Fibrosis and Cirrhosis Evaluation in HCV:

1. **Why is it important to evaluate fibrosis and cirrhosis in HCV?**

Advanced fibrosis, stage 3 or higher, or cirrhosis can lead to hepatocellular carcinoma (liver cancer, HCC). Delay in fibrosis staging has been shown to reduce the likelihood of achieving HCC cure. A study in 2023 showed that every 6 month's delay in fibrosis staging led to a 5% reduction in starting HCV treatment and 7% reduction in achieving SVR. (Without having seen this study, a finding like this could have been explained by insurance practices that require staging prior to authorizing treatment, even with a positive HCV RNA test.) Current guidelines recommend all patients with HCV to undergo fibrosis evaluation and to treat all patients with an HCV RNA positive test result.

2. **How do you assess fibrosis/ cirrhosis? What are the expected laboratory findings?**

Evaluation starts with a good history and physical exam. With stage 3 or 4 fibrosis or with compensated cirrhosis, patients are often asymptomatic and physical findings may not be very evident.

Findings can be more evident for patients with decompensated cirrhosis who may present with the stigmata of advanced liver disease: sarcopenia, seen as thinning of the arms and legs sometimes with an enlarged abdomen, spider angioma, palmar erythema, jaundice or yellowing of the skin, scleral icterus (yellowing of the white portion of the eyes), caput medusae or visible blood vessels on the umbilical area, asterixis, ankle clonus or encephalopathy.

Laboratory work-up may show reduced hepatic synthetic function seen as low albumin and/or a prolonged protime with elevated INR. Labs can reflect patterns of fibrosis in the liver and altered spleen function seen as low platelets. Sometimes anemia, with increased red cell distribution width, and/or leukopenia are seen.

Liver enzymes can be normal. In patients with cirrhosis, ALT may be found to be lower than AST but both can be in the normal range.

There are also serum markers of fibrosis that are proprietary. Examples are the Enhanced Liver Fibrosis (ELF) index or Fibrosure, however insurance coverage may be an issue.

3. What scoring systems can be used to assess for fibrosis or cirrhosis?

FIB-4 score is a commonly used scoring system. It was initially developed for HIV/Hepatitis C co-infected patients but has since been validated for other causes of advanced liver disease. It is easy to use, as it has only 4 variables: age, AST, ALT, and platelets. There are many calculators available on-line.

The cut-off is around 1.45, which can be used to rule out advanced fibrosis, however, it is not reliable to monitor regression of fibrosis after treatment for hepatitis C.

Another easy-to-use scoring system is called APRI which is an AST to platelet ratio index. A score >2 rules-in cirrhosis while a score <1 rules-out cirrhosis. A score of 1-2 is indeterminate.

The APRI and FIB-4 scores have been found to perform similarly. Some studies have shown that the APRI score performs poorly in comparison to transient elastography [1-2]. A cost-effectiveness study has shown that the APRI and FIB-4 scoring systems are not as cost effective as transient elastography [3-4]. The upfront cost of the machine may ultimately outweigh the cost of lab draws for every patient necessary to compute for either score.

Other scoring systems exist that are not as widely used.

4. What is elastography?

The principle is similar to using an ultrasound machine. Using a probe, sound waves are transmitted through and “bounced back” by the liver. Using a timed algorithm, a stiffness score is calculated and described in units of “kilopascals”, a measure of pressure.

This describes the degree of fibrosis. It has a good sensitivity and specificity in determining fibrosis. Limitations include cost, availability, and the need to train staff to conduct the scan. Certain conditions can produce inaccurate results such as the patient’s body habitus, increased liver enzymes, or conditions like iron deposition, all of which can mimic a stiff liver.

The degree of steatosis can be measured, as well, using the Controlled Attenuation Parameter [5].

Transient elastography is available from a dedicated device under the brand name, “Fibroscan”.

Transient elastography results may be falsely negative immediately after HCV treatment.

Another type of elastography used to check liver stiffness is Sheer Wave Elastography (SWE). A transducer delivers high-intensity pulses that produce shear waves, which are used to calculate a score. SWE is available as an add-on device to traditional ultrasound devices.

5. **Does a prolonged fasting state (e.g. Ramadan) produce inaccurate results?**

Not necessarily. In the example of Ramadan, individuals fast from sunrise to sunset but eat a lot of food thereafter, which may be calorie dense as well. Unless there are metabolic changes associated with the prolonged fasting state, then the effect of fasting is negligible.

6. **What if transient elastography is not available but an alternative modality such as shear wave elastography is available?**

This test may be more operator dependent [6] and is not as well validated in comparison to transient elastography [7-9]. It is, of course, better than nothing and can be useful if it is the imaging available. If the test supports other objective data that the patient may have liver fibrosis, then this can be confirmatory. Note that the cut-offs are different compared to transient elastography.

7. **How often does a transient elastography need to be repeated?**

Those with cirrhosis or with stage 3 or 4 fibrosis need periodic imaging and AFP testing for the early detection of HCC in these patients at risk. For those with stages 0, 1, or 2 fibrosis, periodic screening is not indicated unless there is some reason to suspect additional processes that could result in progression. Be cautious about repeating the test too early, close to the end of HCV treatment, where TE or SWE may show a false regression of fibrosis.

8. **Is liver biopsy necessary in the detection of fibrosis/cirrhosis?**

Liver biopsy is the gold standard as it can assess both inflammatory activity and fibrosis stage. However, it is an invasive test, variable in sampling (resulting in false negatives). Cost and availability can be limiting factors. It is not routinely recommended unless non-invasive testing is inconclusive.

HCV ECHO Case Recommendations

Reference:

1. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, Sun Y, Xuan SY. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology* 2011; **53**(3): 726-736 [PMID: 21319189 DOI: 10.1002/hep.24105]

2. Ajao S, Roach D, Chan KH, Thimmanagari K, Muhanna A, Mutyala M, Lakasanni S, Slim J. The Roles of Fibrosis Index Based on Four Factors and Aspartate Transaminase-to-Platelet Ratio Index Scoring Systems as an Alternative to Transient Elastography Liver Stiffness in Liver Fibrosis Staging in Human Immunodeficiency Virus and Hepatitis C Virus Co-Infected Patients. *Gastroenterology Research; Vol 14, No 4, Aug 2021* 2021

3. Serra-Burriel M, Graupera I, Torán P, Thiele M, Roulot D, Wai-Sun Wong V, Neil Guha I, Fabrellas N, Arslanow A, Expósito C, Hernández R, Lai-Hung Wong G, Harman D, Darwish Murad S, Krag A, Pera G, Angeli P, Galle P, Aithal GP, Caballeria L, Castera L, Ginès P, Lammert F; investigators of the LiverScreen Consortium. Transient elastography for screening of liver fibrosis: Cost-effectiveness analysis from six prospective cohorts in Europe and Asia. J Hepatol. 2019 Dec;71(6):1141-1151. doi: 10.1016/j.jhep.2019.08.019. Epub 2019 Aug 27. PMID: 31470067.

4. Vilar-Gomez E, Lou Z, Kong N, Vuppalanchi R, Imperiale TF, Chalasani N. Cost Effectiveness of Different Strategies for Detecting Cirrhosis in Patients With Nonalcoholic Fatty Liver Disease Based on United States Health Care System. *Clinical Gastroenterology and Hepatology* 2020; **18**(10): 2305-2314.e2312 [DOI: 10.1016/j.cgh.2020.04.017]

5. Pu K, Wang Y, Bai S, Wei H, Zhou Y, Fan J, Qiao L. Diagnostic accuracy of controlled attenuation parameter (CAP) as a non-invasive test for steatosis in suspected non-alcoholic fatty liver disease: a systematic review and meta-analysis. *BMC Gastroenterology* 2019; **19**(1): 51 [DOI: 10.1186/s12876-019-0961-9]

6. Fu J, Wu B, Wu H, Lin F, Deng W. Accuracy of real-time shear wave elastography in staging hepatic fibrosis: a meta-analysis. *BMC Medical Imaging* 2020; **20**(1): 16 [DOI: 10.1186/s12880-020-0414-5]

7. Losurdo G, Ditonno I, Novielli D, Celiberto F, Iannone A, Castellaneta A, Dell'Aquila P, Ranaldo N, Rendina M, Barone M, Ierardi E, Di Leo A. Comparison of Transient Elastography and Point Shear Wave Elastography for Analysis of Liver Stiffness: A Prospective Study. *Diagnostics (Basel)* 2024; **14**(6) [PMID: 38535025 PMCID: PMC10968920 DOI: 10.3390/diagnostics14060604]

8. Atzori SM, Pasha Y, Maurice JB, Taylor-Robinson SD, Campbell L, Lim AKP. Prospective evaluation of liver shearwave elastography measurements with 3 different technologies and same day liver biopsy in patients with chronic liver disease. *Digestive and Liver Disease* 2024; **56**(3): 484-494 [DOI: https://doi.org/10.1016/j.dld.2023.10.020]

9. Vidili G, Arru M, Meloni P, Solinas G, Atzori S, Maida I. Comparison of 2D Shear Wave Elastography and Transient Elastography in Non-Invasive Evaluation of Liver Fibrosis in Hepatitis C Virus-Related Chronic Liver Disease. *Journal of Clinical Medicine* 2024; **13**(14).

PLEASE NOTE that case consultations and recommendations for the HBV ECHO do not create or otherwise establish a provider-patient relationship between any participant, Hawaii Learning Groups, and/or any other clinician on the HBV ECHO faculty.