Appropriate Testing for Hepatitis C Virus (HCV) Infection

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SYNOPSIS AND RELEVANCE
The goal of this module is to allow participants to determine if HCV testing (serologic, viral load, and genotyping) is being appropriately performed in their laboratory and, if needed, to apply intervention(s) that will improve utilization. Potential assessments include:

- Are positive serologic HCV assays being unnecessarily repeated?
- Are all initially serologically positive patients receiving an HCV RNA test (ie, HCV viral load) and a genotype assessment?
- Are repetitive HCV genotyping tests being performed on the same patient without evidence of a new infection?

OBJECTIVES
After completing this module, participants should be able to:
1. Determine when clinicians should order HCV serologic studies, viral loads and genotyping tests.
2. Identify the limited circumstances in which HCV serologic testing should be repeated.
3. Assess the appropriate HCV testing algorithm for newly diagnosed patients, to include:
   a. The benefits of appropriately following the initial positive HCV serologic test with an HCV viral load and genotyping study.
   b. The consequences of failure to follow-up HCV serologic studies with an HCV viral load assay and genotyping study.
   c. The consequences of unnecessary repetitive serologic studies and HCV genotyping.
4. Identify the limited circumstances in which HCV genotyping should be repeated.
5. Learn and be able to discuss strategies to influence the correct ordering of HCV tests.

BACKGROUND
Joint guidelines for the testing, management and treatment of patients with HCV infections are available from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.[1] These recommendations are consistent with those provided by the Centers for Disease Control and Prevention.[2] The recommendations from these guidelines concerning HCV testing for diagnosis and management are summarized below.

Individuals with behaviors, exposures and conditions associated with an increased risk of HCV should be tested. It has also been recommended that individuals born between 1945 and 1965, who have not had prior testing, should be tested.[3,4] Annual testing is recommended for individuals who continue to participate in high-risk activities.

Serologic studies are the initial tests that should be performed in most instances. These are used to detect individuals who have been infected by HCV. Positive serologic studies should be confirmed by a sensitive HCV RNA test (ie, HCV viral load testing).

A repeat HCV serologic study or HCV RNA testing is recommended for persons suspected of having liver disease, if the initial serologic studies were negative and the exposure occurred within the past six months. HCV RNA testing should be considered, rather than or in addition to serologic studies, in immunocompromised individuals.

Primary HCV RNA testing is also recommended for individuals at risk for reinfection after either spontaneous or treatment-related viral clearance, since the anti-HCV serologic assays are expected to remain positive.

It is recommended that a baseline HCV viral load be obtained prior to the initiation of therapy. HCV genotyping is also recommended to guide therapy.

Individuals who have had positive serologic studies for HCV, but a negative HCV RNA test (ie, viral load) should be informed that they do not have evidence of current (active) HCV infection.

The uniform implementation of these guidelines will produce substantial benefits for the laboratory, the medical facility, and patients:
- Fewer patients will be lost to follow up and remain untreated.
- More patients with HCV will receive a baseline viral load prior to the initiation of therapy.
- More patients with HCV will receive HCV genotyping to guide therapy.
- Workload will be reduced for laboratory staff (phlebotomists, clinical laboratory scientists) by eliminating and reducing unnecessary HCV assays, adding time for other activities.

INSIGHTS
The diagnostic assessment of a patient with suspected HCV infection, who has never been previously infected by HCV, should:
- Begin with serologic studies, in most instances.
- Include a sensitive HCV RNA test for the initial assessment, if the patient is immunocompromised.

Notes:
A. Repeat the HCV serologic studies or HCV RNA testing for persons suspected of having liver disease if the initial serologic studies are negative and the exposure occurred within the past six months.

B. Perform primary HCV RNA testing, rather than HCV serologic studies, for individuals at risk for re-infection after either spontaneous or treatment-related viral clearance, since the anti-HCV serologic assays are expected to remain positive regardless of the infection status.

C. Perform HCV viral load (ie, RNA test) to determine the presence of active HCV replication and to obtain a baseline prior to therapy.

D. Perform HCV genotyping to guide therapy, upon discovery of an initial, active infection (ie, positive HCV serology and/or positive HCV RNA test).

INTERVENTIONS
1. Provide ordering clinicians with educational information about the recommended testing algorithm for the diagnosis and management of patients with HCV infection. Note that one-time educational interventions are not effective for sustaining improvements and that ongoing education or other interventions should be considered.

2. Review standing orders, panels, reflex testing workflows, and diagnostic aids that contain HCV-associated tests to confirm that they are appropriately designed and used. Modify or eliminate them as needed to improve utilization.

3. Consider using the hospital or laboratory information systems to develop reflex algorithms, and once these are approved by institutional leadership, use to assure that initially-positive HCV serologic studies are automatically followed by an HCV RNA test, and that initially-positive HCV RNA tests are followed by an HCV genotyping assay.

4. Create a best practice alert, such as a notification or soft stop, whenever a second HCV serologic study is ordered on a previously positive patient. The clinician may override the alert at the point of computer order entry.

5. Alternatively, create a hold (also referred to as a hard-stop which is an intervention that requires permission to override) on the order whenever a second HCV serologic study is ordered on a previously positive

patient. This type of intervention cannot be overridden at the point of order entry, so information must be provided regarding how the test can be obtained, if there is a medically valid reason for repeating the studies. An example of a medically valid reason would be because of clinical suspicious of a testing error (eg, specimen mix up).

6. Create a best practice alert, such as notification or soft stop, whenever a second HCV genotyping study is ordered on a patient for whom HCV genotyping has previously been performed. The clinician may override the alert at the point of computer order entry.

7. Create a laboratory-based algorithm that assures that an HCV viral load of sufficient quantity is present before proceeding to HCV genotyping.

8. Review clinical ordering patterns. If a relatively high number of repeat HCV serologic studies on previously positive patients and/or repeat HCV genotyping requests are identified among specific clinicians or locations, then a focused examination to uncover potential utilization problems may be helpful. Alternatively, selective feedback to clinicians about ordering practices relative to peers (eg, physician score cards) may also lead to improved utilization.

INTERVENTION ANALYSIS

Once an issue is discovered concerning inappropriate test ordering, an assessment of the scope of the issue should   be undertaken (ie, the degree of the problem), an intervention should be made, and this should be followed by another assessment to determine the effectiveness of the intervention. The following are suggestions of impact analyses that could be conducted for inappropriate HCV-associated testing; these may not be applicable for all practice settings.

Duplicate HCV Serologic Testing (See **Appendix A**):
- Determine the total number of first time positive HCV serologic tests performed over a previous time period (eg, 1-12 months, depending on frequency of testing and ease of data access). (A1, A3)
- Determine the number of duplicate HCV serologic tests within a time frame in months. (A2)
- Calculate the potential opportunity to reduce testing volume (A4).
- Implement interventions to stop or reduce duplicate HCV serologic testing.
- After interventions have been implemented, perform follow-up studies to assess the impact on the reduction of unnecessary HCV serologic studies. (A5, A7, A8)
- Determine the relative decrease in duplicate testing pre- and post-intervention. (A9).

Inappropriate Reflex Testing: Failure to Perform HCV Viral Load and/or Genotyping Testing After Initial Diagnosis (See **Appendix B**)
- Determine the number of individuals with an initial serologic diagnosis of HCV who did *not* receive reflex HCV viral load testing and/or HCV genotyping performed over a previous time period (B1-B3).
- Implement interventions to ensure that individuals with an initial diagnosis of HCV infection (ie, an initial positive HCV serologic result) receive baseline HCV viral load and HCV genotyping.
- After interventions have been implemented, perform follow-up studies to assess the impact of assuring that appropriate reflex HCV viral loads and genotyping studies are performed on patients with an initial diagnosis of HCV (B4-B8).
- Performing the appropriate reflex testing will aid clinicians in the diagnosis and treatment of HCV and help avoid patients who are lost to follow-up. These are patient care, quality, and patient safety issues.

Duplicate/Unnecessary HCV Genotype Testing (See **Appendix C**)
- Determine the total number of HCV genotyping tests ordered (C1) within a specified time period (C4).
- Among the total number of tests (C1), determine the number with a previously ordered HCV genotype (C2).
- Among the total number of tests (C1), also determine the number without a sufficiently high viral load to perform HCV genotype testing (C3).
- Implement interventions to ensure that HCV genotyping is not performed on individuals with an undetectable HCV viral load. This is usually done within the laboratory.
- After interventions have been implemented, perform follow-up studies to assess the impact of not performing duplicate HCV genotyping studies, and assuring that HCV genotyping studies are only

performed if an adequate HCV viral load is present (C6, C7).
- Determine actual volume change (C9).

QUESTIONS AND ANSWERS

QUESTION 1
What is the role of serologic studies for an initial diagnosis of HCV infection?
A. These assays are used to detect patients who are or have been infected with HCV.
B. The clearance of antibodies (ie, a positive test which becomes negative) is used to determine which patients have been cured.
C. The level of the antibodies present is used to determine the HCV viral load
D. The type of antibody response determines the genotype of HCV present
E. The presence of an IgG response without IgM is indicative of an early, acute infection.

The correct answer is A. Serologic studies (ie, antibody tests) are the tests used to determine if a patient has been infected by HCV. If the patient has previously had HCV and been cured (ie, achieved a sustained undetectable HCV viral load), then the HCV RNA test (ie, HCV viral load) would be used, if re-infection were suspected.
B is incorrect. A positive antibody response persists even after cure, so serologic studies cannot be used to determine if the immune system and/or therapy have effectively cleared the virus. The HCV viral load is used for this purpose.
C is incorrect. An RNA test, not a serologic test, is used to determine the HCV viral load.
D is incorrect. There is no correlation between the type of antibody response and the infecting HCV genotype.
E is incorrect. The presence of an IgG response without IgM is indicative of a remotely acquired infection. Ongoing viral replication would be determined by HCV viral load testing.

REFERENCE
HCV guidance: recommendations for testing, managing, and treating hepatitis C. AASLD-IDSA. Updated October 24, 2022. Accessed April 14, 2023. http://www.hcvguidelines.org/full-report/initial-treatment-hcv-infection

QUESTION 2
What is the primary purpose of HCV viral load testing?
A. To detect an initial HCV infection.
B. To determine the amount of virus present.
C. To establish the genotype of the virus present.
D. To determine if multiple HCV genotypes are present.
E. To measure the amount of antibodies produced against HCV.

The correct answer is B. The primary purpose of the initial HCV viral load testing is to determine the baseline amount of virus present. This test will be useful to follow while the patient is undergoing therapy. The viral load should diminish and eventually become undetectable for patients who are cured.
A is incorrect. Serologic studies are the most commonly used to detect initial HCV infection. An RNA test may be used in patients who are immunocompromised, or those who have previously had an HCV infection and are thought to possibly be re-infected.
C is incorrect. HCV viral load testing does not provide genotypic information. .
D is incorrect. HCV viral load testing does not provide genotypic information.
E is incorrect. Serologic studies, not HCV viral load studies, determine the presence of antibodies directed against HCV.

REFERENCE
HCV guidance: recommendations for testing, managing, and treating hepatitis C. AASLD-IDSA. Updated October 22, 2022. Accessed April 14, 2023.http://www.hcvguidelines.org/full-report/initial-treatment-hcv-infection

QUESTION 3
Why is HCV genotype testing performed?
A. To determine if the patient has been cured.
B. To establish the amount of virus present

C. To determine if the patient is co-infected with HIV
D. To guide therapy decisions
E. To detect an initial HCV infection

The correct answer is D. The current HCV therapies are based on the infecting HCV genotype.
A is incorrect. Cure is determined by the demonstration of a sustained viral load that is undetectable.
B is incorrect. The HCV viral load determines the amount of virus present.
C is incorrect. HIV serologic/antigenic studies would be necessary to determine if a patient were co-infected with HIV.
E is incorrect. HCV serology should be used to detect the initial infection with HCV.

REFERENCE
HCV guidance: recommendations for testing, managing, and treating hepatitis C. AASLD-IDSA. Updated October 24, 2022. Accessed April 14, 2023.http://www.hcvguidelines.org

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4. Smith BD, Beckett GA, Yartel A, Holtzman D, Patel N, and Ward JW. Previous exposure to HCV among persons born during 1945-1965. *Am J Public Health.*2014;104(3):474-481.doi:10.2105/AJPH.2013.301549
5. Recommended testing sequence for identifying ccurrent hepatitis C virus (HCV). Centers for Disease Control and Prevention. Accessed April 14, 2023. http://www.cdc.gov/hepatitis/hcv/pdfs/hcv_flow.pdf

APPENDICES
Collect data in the tables below during predetermined number of months periods (eg, 1 month, 3 months) before and after implementing interventions. In these appendices, the number 12 refers to the number of months in the year used to estimate an annual figure.

APPENDIX A: DUPLICATE HCV SEROLOGIC TESTING

Pre intervention	
Total number of first-time positive HCV serologic studies, within a defined time period	A1
Total number of duplicate positive HCV serologic tests within same time period	A2
Time period in months	A3
Potential annual volume change opportunity	
Annual unnecessary duplicate testing volume: A1*(12/A3) - (A2)*(12/A3) = A4	A4
Implement intervention	
Post intervention (determine A5 like A2, but after the intervention)	
Total number of first-time positive HCV serologic studies, within a defined time period	A5
Total number of duplicate positive HCV serologic tests within time period	A6
Post intervention time period in months	A7
Annual unnecessary duplicate testing volume A5*(12/A7) – A6(12/A7) = A8	A8
Percent change in duplicate testing post intervention = A4-A8/A4 x 100% = A9	A9%

APPENDIX B: INAPPROPRIATE REFLEX TESTING: FAILURE TO PERFORM HCV VIRAL LOAD AND/OR GENOTYPING TESTING AFTER INITIAL DIAGNOSIS

Total number of first-time positive HCV serologic studies without HCV viral load testing within a defined time period	B1

Total number or individuals with a first time positive HCV viral load test without HCV genotyping within same defined time period	B2
Time period within months	B3
Potential Annual Value Opportunity	
Potential to implement best practices: B1 + B2 * (12/B3)	
Implement intervention	
Post Intervention	
Total number of first-time positive HCV serologic studies without HCV viral load testing within a defined time period	B4
Total number or individuals with positive HCV viral load test without HCV genotyping within same defined time period	B5
Post intervention time period in months	B6
Change in annual confirmatory HCV RNA testing = B1 * (12/B3) – B4 * (12/B6) x 100% =B7%	B7%
Change in annual HCV genotype testing = B2 * (12/B3) – B5* (12/B6) x 100% = B8%	B8%

APPENDIX C: UNNECESSARY/DUPLICATE HCV GENOTYPE TESTING

Unnecessary tests	
Total number of HCV genotyping tests within a specified time period	C1
Total number of patients in C1 with a previously ordered HCV genotype test	C2
Total number of patients in C1 with an HCV viral load that is below the recommend quantity to perform HCV genotype testing	C3
Time period in months	C4
Potential annual value opportunity	
Potential reduction in annual test volume = (C2 + C3) * (12/C4) = C5	C5
Implement intervention	
Post Intervention	
Total number of HCV genotypes not performed because the patient had a previous HCV genotyping assay performed.	C6
Total number of HCV genotypes not performed because of an insufficient HCV viral load.	C7
Post intervention time period within months	C8
Change in annual unnecessary genotype tests = C5 – (C6 + C7) *(12/C8) x 100% = C9	C9%