Review of the Hepatitis C Testing Algorithm in NYS

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Objectives
- Describe the laboratory tests used to diagnose hepatitis C virus infection and how we interpret their results
- Discuss the recent update to laboratory testing guidelines for hepatitis C
- Explain the benefits and challenges of implementing the recommended HCV testing algorithm

What are the diagnostic markers of hepatitis C virus infection?
- As HCV replicates in the liver, the hepatocytes lyse, causing liver enzymes and HCV virus particles to spill into the blood
- HCV RNA is detectable in blood by ~1 to 2 wks
- Antibodies generally detectable by 6 to 8 weeks
  - Abs can take several months; >97% of persons have detectable antibodies at 6 months after exposure
- ~80% of people who become infected will have no notable symptoms during the acute phase

In some cases, HCV infection will resolve on its own
- Virus will be cleared by the body
- RNA will become undetectable
- Liver enzymes return to normal levels
- Antibodies will persist

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In most cases, hepatitis C becomes a chronic infection

- Signified by detectable HCV RNA > 6 months after onset of infection
  - Virus levels in the blood may be quite high
  - Anti-HCV antibodies are present
  - Liver enzymes may fluctuate, but there may be no noticeable symptoms for many years

All chronically infected people carry virus in their blood and have the potential to transmit

The lab testing guidelines didn’t meet the needs of today

- New testing recommendations were fueled by new treatment options
  - Goal is to reduce the burden of HCV-related liver disease and prevent onward transmission by treating the currently infected population
  - Laboratory testing guidelines needed to shift toward identifying current infections

2003 laboratory guidelines emphasized HCV antibody testing

- Enzyme immunoassay (EIA) used for antibody screening
- Confirmation of reactive screening result was needed
  - Either by RIBA or signal-to-cut off ratio of EIA
- RNA testing was presented as optional supplemental test
- Testing sequence frequently stopped once antibody status was determined

New HCV Testing Recommendations
2013 HCV Laboratory Testing Guidelines

- Algorithm was designed to identify people with current (active) HCV infection
- Antibody confirmation is no longer included
- Guidelines incorporate changes in the availability of FDA-approved HCV tests
  - 1st HCV rapid test rec’d CLIA waiver in 2011
    - POC, visual interpretation, no signal-to-cut off
  - RIBA test for HCV antibody confirmation was discontinued in 2013

Recommended Testing Sequence

- Testing begins with an HCV Screening Test
  - This is an FDA-approved immunoassay designed to screen for anti-HCV antibodies
  - This may be a laboratory-based immunoassay (e.g. EIA) or a rapid/POC test
  - Only one FDA-approved rapid test
    - CLIA-waived for whole blood collected by fingerstick or venipuncture

How do we interpret the HCV Screening Test results?

- ‘Nonreactive’ means no antibodies to HCV were detected
  - No further action is warranted unless recent exposure is suspected
- A ‘Reactive’ result can indicate:
  - Possible current HCV infection
  - Past (resolved) HCV infection
  - Biologic false positive result (non-specific)

HCV Diagnostic Test (RNA) is needed to detect current infection

- If the HCV Screening Test is reactive, an HCV Diagnostic Test (aka HCV RNA test) should be performed next
  - No additional testing is performed to confirm HCV antibodies
- Ideally, the laboratory reflexes directly to an HCV RNA test
- If reflex RNA testing is not possible, an HCV RNA test should be ordered ASAP

How do we interpret the HCV diagnostic test results?

- If RNA is ‘Detected’, current HCV infection is present
  - Person should be referred for appropriate care and treatment services for HCV infection and related conditions
- If RNA is ‘Not detected’, the interpretation is “No current HCV infection”
  - A previous, resolved infection is not ruled out

If the HCV RNA test is negative what are the next steps?

- No further testing is required, unless
  - Exposure within past 6 months is suspected
  - Clinical signs of Hepatitis C are present
  - Specimen handling was unsuitable for RNA test
- If one of these exceptions exists, HCV RNA testing should be repeated
- If there is a reason to distinguish between a past, resolved infection and a false positive antibody result, testing with a 2nd (different) antibody test can be performed

Several FDA-approved HCV RNA tests are available

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Manufacturer</th>
<th>Intended Use</th>
<th>LOD/LLOQ</th>
<th>Specimen Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERSANT HCV RNA Qualification Assay</td>
<td>Siemens</td>
<td>Qualitative</td>
<td>12/12 IU/mL</td>
<td>Serum or Plasma</td>
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<tr>
<td>VERSANT HCV RNA Assay/AMPLICOR HCV RNA Qualification Assay</td>
<td>Siemens</td>
<td>Qualitative</td>
<td>9.6 IU/mL</td>
<td>Serum or Plasma</td>
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<tr>
<td>AMPLICOR HCV Test, v2.0</td>
<td>Roche</td>
<td>Qualitative</td>
<td>50 IU/mL</td>
<td>Serum or Plasma</td>
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<tr>
<td>COBAS AmpliPrep/COBAS Taqman HCV Test, v2.0</td>
<td>Roche</td>
<td>Qualitative</td>
<td>15/15 IU/mL</td>
<td>Serum or Plasma</td>
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<tr>
<td>COBAS TaqMan HCV Test</td>
<td>Roche</td>
<td>Quantitative</td>
<td>20/25 IU/mL</td>
<td>Serum or Plasma</td>
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<tr>
<td>VERSANT HCV RNA 3.0 bDNA</td>
<td>Siemens</td>
<td>Detection</td>
<td>988/1100 IU/mL</td>
<td>Serum or Plasma</td>
</tr>
</tbody>
</table>

Modified from APHL’s “Testing for Hepatitis C Viral Infections: Frequently Asked Questions”
Implementation of reflex RNA testing at laboratories

- Laboratories are required to adhere to the package insert of FDA-approved tests
  - A modification to the package insert constitutes off-label use of an FDA-approved device
- HCV viral load tests (quantitative RNA) are not approved to aid in diagnosis
  - Labs may conduct validation of a viral load test to allow its use in a diagnostic algorithm
  - The NYSDOH is developing guidelines to assist labs in the validation and approval process
- Reflex testing is available at some clinical labs now and more are expected to add this option

Hepatitis C cases must be reported to the DOH

- Reporting of acute and chronic hepatitis C cases is mandated under the NYS Sanitary Code (10NYCRR 2.10,2.14)
- Physicians (or designees) report using the Universal Reporting Form
  - Form PD-16 (NYC) or Form DOH-389 NYC (rest of NYS)
  - Report to the local Health Department in the county where the client lives
- Laboratories report via the Electronic Clinical Laboratory Reporting System (ECLRS)

Check the specimen collection instructions for your lab

- Specimen collection instructions may differ by lab depending on the test kits in use
- Different options may apply if reflex testing is available
  - A single blood specimen may be acceptable for antibody and RNA testing
  - Two separate specimens, one for screening and one for RNA, may be needed at the time of initial testing
- If the OraQuick HCV rapid test is performed from a fingerstick and is reactive, a blood specimen must be collected by venipuncture for RNA testing

Summary

- New HCV laboratory guidelines were developed to identify currently infected persons
- All persons with a reactive HCV antibody screening test should receive an HCV RNA test ASAP
- Reflexing directly to HCV RNA testing is the recommended practice for laboratories but limitations among FDA-approved RNA tests may delay implementation
QUESTIONS?

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