Hepatitis C Screening Guideline Development Group

Background to recommendations 22 and 23: What test should be used for HCV screening and what should the frequency of testing be for those at ongoing risk of HCV infection?

The purpose of this document is to provide the background information to the formulation of recommendations by the Guideline Development Group (GDG).

Not all evidence in this document is presented in the National Clinical Guideline.

The National Clinical Guideline is available from: http://health.gov.ie/national-patient-safetyoffice/ncec/national-clinical-guidelines/

Please note, that this document is being made available for information purposes only. It should not be reproduced or cited. Please refer to the National Clinical Guideline for the final evidence analysis, value judgements and recommendations.

Contents

History of development of the recommendation

Date	Process	Outcome
02/06/2015	Recommendations from quality appraised national and international guidelines reviewed	Agreed to adopt/adapt recommendations
14/12/2016	GDG subgroup meeting to undertake considered judgement process	Formulation of recommendation
24/01/2017	Review of subgroup recommendation by GDG	Recommendation accepted
25/04/2017	Consultation feedback reviewed by GDG	No changes to recommendation
June – July 2017	Editing	Recommendation reworded in final editing process

Considered judgement process

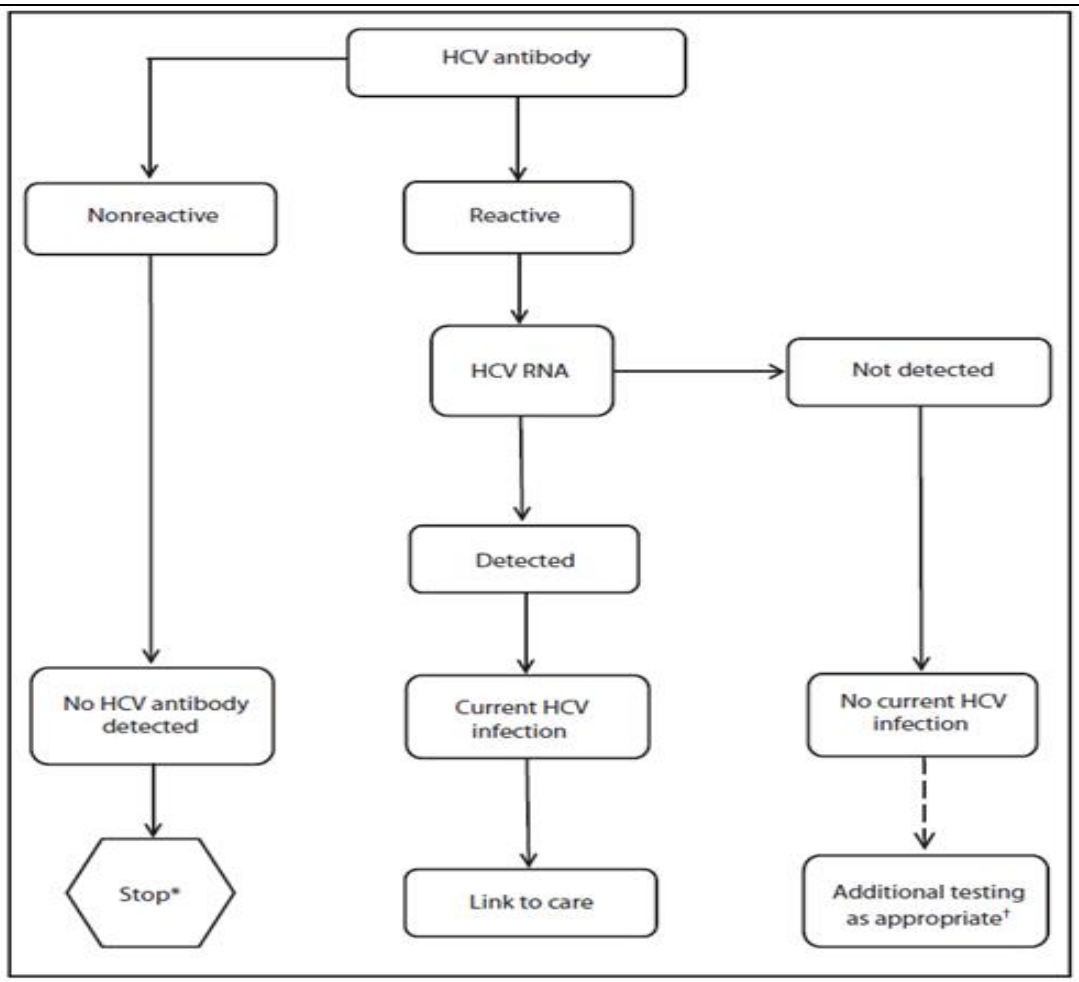
The considered judgment form completed by the GDG subgroup in formulating the recommendations is presented below. Please note the final wording of the recommendation may have changed after review of the GDG, after the consultation process, or during the editing process.

Date: 20 January 2017

Attendees: NOF, CDG, JC, SD, ER, LT

Table 1: Considered judgement form

1. What is the question being addressed?
Q4. How should screening be implemented for each group for which screening is recommended, including: **d. what test should be used, what should the screening sequence process be, how frequently should those who remain at risk be screened?** Testing following injuries that involve possible exposure to HCV is not being considered within this question, please refer to the EMI guidelines (www.emitoolkit.ie)
2. What evidence is being considered to address this question and why? (This section will explain the approach taken to address this question and what GDG members are being asked to consider)
Other international and national guidelines are considered. The guidelines below address the general approach to screening for HCV, including the type of test, the sequence of testing and the frequency of retesting. Some of the guidelines address specific testing situations or populations such as immunocompromised individuals, those with HIV infection, babies born to HCV positive women, acute HCV infections and reinfection after treatment or spontaneous clearance. The test and timing of testing for children born to infected mothers has been considered by a separate subgroup. The considered judgement form for this recommendation is attached for reference. Viral load and genotype testing are not being considered as these are not within the scope of the guideline.
3. What is the body of evidence? Source of evidence: (tick all that apply) Guidelines ã Primary literature Ĭ Other ã ; specify: Economic literature
Current Guidelines **CDC MMWR 2013 (1)** This is a clear and up to date guideline on the question of type or test and sequence of testing and the recommendations are presented in a clear algorithm and table. This 3 page guideline is attached(page 362-365) or available here and we recommend the group review this document in its entirety. (HIQA quality score 121) ***Summary and algorithm of CDC MMWR 2013*** Testing for HCV infection begins with either a rapid or a laboratory-conducted assay for HCV antibody in blood. A nonreactive HCV antibody result indicates no HCV antibody detected. A reactive result indicates one of the following: 1) current HCV infection, 2) past HCV infection that has resolved, or 3) false positivity. A reactive result should be followed by NAT for HCV RNA. If HCV RNA is detected, that indicates current HCV infection. If HCV RNA is not detected, that indicates either past, resolved HCV infection, or false HCV antibody positivity.



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differen□ate past, resolved HCV infec□on from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

WHO, 2016 (2) – WHO Guidelines on hepatitis B and C testing (awaiting publication)

Which serological assays to use?

- To test for exposure to HCV infection in adults and children (>18 months of age), an HCV serological assay (antibody or antibody/antigen) using either rapid diagnostic test (RDT) or laboratory-based immunoassay format that meets minimum safety, quality and performance standards (with regard to both analytical and clinical sensitivity and specificity) is recommended.
- In setting where there is limited access to laboratory infrastructure and testing and/or in populations where access to rapid testing would facilitate linkage to care and treatment, RDTs are recommended

Strong recommendation, low/moderate quality of evidence

Testing strategy for detection of antibodies to HCV

- In adults and children older than 18 months, a single serological assay for initial detections of exposure to HCV is recommended prior to supplementary nucleic acid testing (NAT) for evidence of current chronic infection

Conditional recommendation, moderate quality of evidence

Detection of viraemic HCV infection

- Directly following a positive HCV antibody serological test, the use of quantitative or qualitative NAT for detection of HCV RNA is recommended as the preferred strategy to diagnose HCV viraemic infection

Strong recommendation, moderate/ low quality of evidence

- An assay to detect HCV core (p22) antigen, which has comparable clinical sensitivity to NAT, is an alternative to NAT diagnose HCV viraemic infection

Conditional recommendation, moderate/low quality of evidence

WHO, 2016 (3)- Guidelines for the screening, care and treatment of persons with HCV infection

Type of test and sequence

It is recommended that HCV serology testing be offered to individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure/behaviour. Strong recommendation, moderate quality of evidence

Note: Information on WHO prequalified serological diagnostic tests for HCV infection are regularly updated at: http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en

It is suggested that nucleic acid testing for the detection of HCV RNA be performed directly following a positive HCV serological test to establish the diagnosis of chronic HCV infection, in addition to nucleic acid testing for HCV RNA as part of the assessment for starting treatment for HCV infection. Conditional recommendation, very low quality of evidence

Type of test if HIV positive

Persons who are infected with both HIV and HCV can have false-negative HCV serological test results. This may occur in up to 6% of persons with HIV who undergo testing using a second-generation anti-HCV enzyme immunoassay (EIA), but may occur more often among persons with advanced immunosuppression due to HIV and during early HCV infection . As the range of CD4 counts in persons with a false-negative anti-HCV antibody test was so different in the various studies, it was not possible to suggest a specific CD4 cut-off level below which all those with a negative anti-HCV antibody test should have HCV RNA testing performed.

Type of test if previously infected

For PWID - those previously infected with HCV should be retested using RNA testing, as the antibody remains positive.

Frequency of testing

In the United States and western Europe, it is recommended that all persons with HIV infection be screened for HCV at the time of enrolment into HIV care, and that those who are not infected with HCV but practice behaviours that place them at risk for HCV infection, such as injection drug use, be retested annually.

For PWID, repeated screening is required in individuals at ongoing risk, and the possibility of reinfection after spontaneous clearance or successful treatment should also be considered.

(World Health Organization, Guidelines for the screening, care and treatment of persons with HCV infection). HIQA Quality Score of 148

AASLD, 2016 (4)

Type of test and sequence

- An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive RNA test. Class I, Level A
- Among persons with a negative anti-HCV test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months; testing for HCV RNA can also be considered in persons who are immunocompromised. Class I, Level C
- Among persons suspected of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive. Class I, Level C
- If found to have positive results for anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR), persons should be informed that they do not have evidence of current (active) HCV infection. Class I, Level A
- Quantitative HCV-RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of vireamia (i.e. baseline viral load). Class I, Level A

Frequency of testing

- Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV. Class IIA, Level C

(American Association for the Study of Liver Diseases, Recommendations for Testing, Managing, and Treating Hepatitis C). HIQA Quality Score of 134.5

SIGN, 2013 (5)

Type of test and sequence

Background evidence: Detection of viral ribonucleic acid (RNA) by nucleic acid tests (NAT, usually using reverse transcriptase polymerase chain reaction; RT PCR) indicates current infection. Detection of antibodies indicates resolved or current infection. Nucleic acid testing sensitive enough to detect 50-100 IU/ml of virus must be performed to detect current infection. Viral RNA can be detected as early as one to two weeks after infection, whereas antibody can be detected at seven to eight weeks after infection. Antibody to infection may not be generated, particularly if the individual is immune-suppressed. Following acute infection, HCV RNA may oscillate between positive and negative for several months. Results from samples taken at this time may be misleading. In an individual positive for HCV antibody, but negative for HCV RNA, a second sample should be tested to confirm the initial diagnosis, especially as the date of infection is unknown in most cases.

Individuals with a positive HCV antibody test and repeatedly negative RNA do not require further active management of HCV infection. Since HCV is a serious communicable disease, after an initial laboratory diagnosis, a second sample should be taken from the patient to confirm correct identification of the original sample.

Frequency of testing

Anyone who has a negative HCV test but remains at risk of infection should be offered further testing on an annual basis. GRADE D

(Scottish Intercollegiate Guidelines Network, Management of Hepatitis C A National Clinical Guideline). HIQA Quality Score of 127.7

BHIVA, 2013(6)

Type of test and sequence

- It is recommended that all patients who are anti-HCV positive are tested for HCV-PCR and, if positive, genotyped.
- Patients who have experienced a recent high risk exposure (e.g. unprotected sex between men [especially in the context of concurrent STI, high-risk sexual practice, and recreational drug use] or shared injection drug equipment) but have normal transaminases are recommended to test for anti HCV and this is repeated 3 months later.
- It is recommended that the HCV-PCR should be repeated after 1 month if initially negative and if any potential exposure was less than 1 month before the first test, or the transaminases remain abnormal with no known cause.

Type of test if previously infected

- When past spontaneous clearance or successful treatment has occurred, HCV-PCR should be performed.

Type of test if HIV positive

- For HIV positive persons, it is recommended that patients who have repeated high-risk exposures but persistently normal transaminases are screened with anti-HCV and HCV-PCR, or HCV-PCR alone if previously successfully treated for or spontaneously have cleared infection and are HCV antibody positive, at 3–6-monthly intervals.

Frequency of testing

It is recommended that patients have an HCV antibody test when first tested HIV antibody positive and at least annually if they do not fall into one of the risk groups that increased frequency of testing require.

(British HIV Association, British HIV Association Guidelines for the Management of Hepatitis Viruses in Adults Infected with HIV) HIQA Quality Score of 121.7

BAASH, 2006 (7)

Type of test and sequence

Antibody-negative patients do not require further testing unless recent infection is suspected, or there is a strong suspicion of infection in an immunocompromised patient in whom persistent infection has occasionally been reported without detectable antibody. In patients with abnormal liver function tests serum HCV-RNA may be the

only test that is positive during acute HCV infection, or rarely in immunosuppressed patients.

Frequency of testing

Repeat screening should be offered to contacts with an HCV-infected partner who continues to be exposed to infection. The optimum frequency has not been defined but may be every 6-12 months. Repeat screening should be offered for other groups considered to be at risk. No frequency of screening has been defined, but annual testing may be considered. (British Association for Sexual Health and HIV, BASHH Sexually Transmitted Infections: UK National Screening and Testing Guidelines) HIQA Quality Score of 121.5

US Preventive Services Taskforce, 2013 (8)

Type of test and sequence

Anti HCV antibody testing followed by confirmatory PCR testing accurately identifies patients with chronic HCV infection.

Frequency of testing

Persons with continued risk of exposure should be screened periodically. Evidence on how often screening should occur in these persons is lacking

(United States Preventive Services Taskforce, Screening for Hepatitis C Virus Injection in Adults). HIQA Quality Score of 117

KASL, 2014 (9)

Type of test and sequence

Anti-HCV should be tested in patients suspected of having acute or chronic HCV infection. HCV RNA should be tested in patients with a positive anti-HCV test for the purpose of confirmative diagnosis. Even with negative anti-HCV, HCV RNA testing is required when acute HCV infection is suspected or in the presence of unexplained liver disease in immunosuppressed patients. HCV RNA assay should be conducted in patients having idiopathic liver disease even with negative anti-HCV or in patients with positive anti-HCV.

(The Korean Association for the Study of the Liver, KASL Clinical Practice Guidelines: Management of Hepatitis C). HIQA Quality Score of 111

BASHH, 2015 (10)

Type of test and sequence

A screening antibody or antibody/antigen test such as an Enzyme immunoassay (EIA) or other immunoassay is initially performed and RNA detection confirms active infection In HIV+ patients with a low CD4 count (<200 cells/mm 3) the EIA may be negative and HCV RNA detection may be needed for diagnosis. Chronic infection is confirmed if an HCV RNA assay is positive six months after the first positive test. All patients should have a viral RNA test to confirm viraemia and the HCV genotype should also be identified. (British Association for Sexual Health and HIV, United Kingdom National Guideline on the Management of the Viral Hepatitides A, B & C 2015) HIQA Quality Score of 97

SASLT, 2012 (11)

Type of test and sequence

Patients with suspected HCV infection should be tested for anti-HCV by an up-to-date (currently, third generation) ELISA test.

Type of test if immunosuppressed

Immunosuppressed patients may require a test for HCV RNA, if hepatitis is present, but anti-HCV antibodies are undetectable. (Saudi Association for the Study of Liver diseases and Transplantation, SASLT Practice Guidelines: Management of Hepatitis C Virus Infection). HIQA Quality Score of 95.3

EASL 2014 (12)

Type of test and sequence

Anti-HCV antibodies are the first line diagnostic test for HCV infection. In the case of suspected acute HCV or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation. If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method. Anti-HCV positive, HCV-RNA negative individuals should be retested for HCV RNA 3 months later to confirm true convalescence.

Frequency of testing

People who inject drugs should be routinely and voluntarily tested for HCV antibodies and if negative, they should be continuously tested every 6-12 months. (European Association for the Study of the Liver, Clinical Practice Guidelines: Management of Hepatitis C Virus Infection). HIQA Quality Score of 92

EMCDDA, 2010 (13)

Type of test and sequence

The standard screening test is the HCV antibody (anti-HCV) ELISA test. A positive test should be confirmed by using a nucleic acid amplification test (PCR-test), or if this is negative with a recombinant immunoblot assay, RIBA. A positive antibody test alone is evidence of previous exposure to the HCV virus, but gives no indication of whether the virus is still present. The window period is four to six months.

Frequency of testing

For individuals who are ongoing injecting drug users or involved in ongoing high-risk sex (e.g. sex work or male-to-male sex with multiple partners) this risk is usually very high (it should be noted that a client may intentionally or unintentionally under-report the frequency of risk behaviours) and frequent re-examination and re-testing are recommended to reduce the period of undiagnosed carriership after infection and thus the risk of infecting others. For practical reasons and taking into account these considerations, it is recommended that examination and testing is offered to IDUs at least once every six to 12 months. (European Monitoring Centre for Drugs and Drug Addiction, Guidelines for Testing HIV, Viral Hepatitis and Other Infections in Injecting Drug Users) HIQA Quality Score of 91

Dublin Area Hepatitis C Initiative Group, Ireland, 2004 (14)

Type of test and sequence

To determine if patients are anti-HCV positive, labs should use RIBA assay or another EIA to confirm presence of anti-HCV.

Frequency of testing

If continued potential exposure to the virus is an issue, then repeat testing should be offered at intervals of 12 months. (Dublin Area Hepatitis C Initiative Group, Hepatitis C Among Drug Users: Consensus Guidelines on Management in General Practice). HIQA Quality Score of 85.5

IUSTI/WHO Euro, 2010 (15)

Type of test and sequence

A screening antibody test such as an enzyme immunoassay (EIA) or other immunoassay is initially performed and RT-PCR for RNA is used to confirm active infection. In HIV-positive patients with a low CD4 count (200 cells/mm3) the EIA may occasionally be negative and an RT-PCR may be needed for definitive diagnosis. An antibody test may not become positive for three or more months after acute HCV infection but a test for HCV-RNA will be positive after only two weeks. Chronic infection is confirmed if an HCV-RNA assay is positive six months after the first positive test. Patients with low-level viraemia may require HCV-RNA levels testing on two or more occasions to confirm infection. (The International Union Against Sexually Transmitted Infections/WHO Europe, European Guideline for the Management of Hepatitis B and C Virus Infections). HIQA Quality Score of 66.3

NICE, 2013(5) (16)

Type of test and sequence

Ensure service specifications specify that laboratory services providing hepatitis B and C testing automatically test samples that are positive for HCV antibody for the presence of HCV virus (for example, using a polymerase chain reaction [PCR] assay), or refer the sample to a laboratory which can perform this test.

Frequency of testing

GPs/ Drugs Services should offer annual testing for HCV to people who test negative for HCV but remain at risk of infection (The National Institute for Health and Care Excellence, Hepatitis B and C: Ways to Promote and Offer Testing to People at Increased Risk of Infection). HIQA Quality Score of 148

Economic studies

Linas et al estimated the cost effectiveness of screening for acute HCV infection in HIV infected MSM (17) . All patients had a HCV Ab test at enrolment, followed by one of 10 screening strategies involving symptoms-based screening, or screening with LFTs, HCV Ab, or HCV RNA in various combinations and intervals. A societal perspective was used. Costs and utilities were discounted at a rate of 3% per year. The model assumed 81% of detected acute cases started treatment. Chronic cases also had treatment. The incremental cost effectiveness ratio (ICER) with 6 monthly LFTs and an annual HCV Ab test compared to symptom base screening was $43,700 (€41,704 when inflated and converted to Irish Euro) per QALY when treated with pegylated interferon and ribavirin and $57,800 (€55,160) when a protease inhibitor was added to treatment. Three monthly LFTs compared to symptom based screening had an ICER of $129,700 (€123,776) and $229,000 (€218,541), while

three monthly RNA and LFTs had ICERs of $1,700,000 €1,622,354) and $1,400,000(€1,336,056) when treatment was PEG/RBV and PEG/RBV/PI respectively. All other strategies dominated.
4. What is the quality of the evidence? To be considered if primary literature was reviewed.
4.1. How reliable are the studies in the body of evidence? **If there is insufficient evidence to answer the key question go to section 11. Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.**
Recommendations are contained in a number of good quality guidelines
4.2. Are the studies consistent in their conclusions – comment on the degree of consistency within the available evidence. Highlight specific outcomes if appropriate. If there are conflicting results highlight how the group formed a judgement as to the overall direction of the evidence
In general there is a high degree of consistency between the available guidelines as above. There is inconsistency in the type of screening test recommended in the older guidelines. Antigen testing is mentioned in some guidelines and not others. Guidelines that refer to the need for regular retesting in those at continuing risk of infection vary slightly in their recommendations. Some are not definite about the interval while others recommend an interval of 6 months or 12 months or 6-12 months. The MMWR algorithm is consistent with the main recommendation in all the other guidelines.
4.3. Generalisability – are the patients in the studies similar to our target population for this guideline? is it reasonable to generalise
Yes
4.4. Applicability - Is the evidence applicable to Ireland? Is the intervention/ action implementable in Ireland?
Yes
4.5. Are there concerns about publication bias? Comment here on concerns about all studies coming from the same research group, funded by industry etc
Not applicable
5. Additional information for consideration
5.1. Additional literature if applicable e.g. Irish literature
Nil
5.2. Relevant national policy
Nil
5.3. Epidemiology in Ireland if available and applicable
Not relevant
6. Potential impact of recommendation
6.1. Benefit versus harm **What factors influence the balance between benefit versus harm? Take into account the likelihood of doing harm or good. Do the desirable effects outweigh the undesirable effects?**
The guideline will ensure a standardised approach to the sequence of testing. The main benefit of the recommendation is likely to be in relation to the frequency of retesting in those who initially test negative but are at continuing risk, as currently they may not always be offered further testing.
6.2. What are the likely resource implications and how large are the resource requirements? Consider cost effectiveness, financial, human and other resource implications
The sequence of testing recommended is likely to be similar to what is already in practice in most laboratories, so there will not be resource implications. The frequency of re-testing may have some resource implications in settings where clients are offered testing at

entry, e.g. prisons, drug treatment clinics, but frequent re-testing may not always be carried out in those who remain at risk.

6.3. Acceptability – Is the intervention/ option acceptable to key stakeholders?

Yes

6.4. Feasibility - Is the intervention/action implementable in the Irish context?

Yes, in general. However, the recommendation for frequent re-testing may be difficult in settings where staff resources are limited.

6.5. What would be the impact on health equity?

The availability of national guidelines will ensure standardisation of clinical and laboratory practice throughout the country.

7. What is the value judgement? How certain is the relative importance of the desirable and undesirable outcomes? Are the desirable effects larger relative to undesirable

For population groups at continuing risk of infection, frequent re-testing will ensure early detection and linkage to care**.**

8. Final Recommendations

√ Strong recommenda□on
□ Condi□onal/ weak recommenda□on

Text:
Proposed HCV Testing Sequence*

Individuals being investigated for evidence of HCV infection should be screened with an anti-HVC antibody or combined HCV antigen/antibody EIA screening assay

1. If this initial test is negative, and recent infection is not suspected, then no further testing is indicated**

2. If the initial HCV EIA is reactive (positive), then the sample should be tested for the presence of HCV antigen, or HCV RNA

(a) If the individual tests positive for HCV antigen or HCV RNA, then the results should be reported with an interpretive comment along the lines of "consistent with active HCV infection"
(Proceed to 3 and 3(i) below)

(b) If an individual tests HCV antibody positive, but antigen/RNA negative, then a second anti-HCV assay (either a second EIA, or an immunoblot) should be performed to confirm the screening assay result

(i) If the second anti-HCV assay confirms the initial result, then the results should be reported with an interpretive comment along the lines of "consistent with HCV infection at some time" or "HCV serology suggestive of resolved infection"
(Proceed to 3 and 3(ii) below)

(ii) If the second anti-HCV assay does not confirm the initial result, then further testing should be performed with a view to resolving the discordant result profile: the further testing should be performed at a laboratory with sufficient expertise and experience to provide a resolution

3. All individuals testing positive for active or resolved HCV infection should have a second serum sample drawn to confirm their HCV diagnosis

(i) Those individuals testing positive for active infection should also have a sample drawn for HCV RNA (if not already performed) and HCV genotyping

(ii) Those individuals with evidence of a resolved HCV infection (i.e. antigen/RNA negative) should also have a further sample drawn after 6-12 months for HCV RNA testing to confirm their resolved infection status

*Each individual centre can develop its own HCV screening algorithm in accordance with those recommended by the CDC or PHE SMI

**In certain patient groups, initial testing should routinely incorporate HCV antigen or RNA testing. Those are: immunocompromised individuals; children (born to HCV-infected mothers) in the first 18 months of life; individuals previously treated for HCV infection; sources of needle-sticks; and those at risk of recent infection in whom an antibody response might not yet have developed (RNA testing should be performed 6 weeks post-exposure)

- Individuals who initially test HCV negative but who remain at risk of HCV infection should be offered further testing on an annual basis.

9. Justification

A standard approach to the sequence of testing will ensure that testing is carried out with maximum efficiency and will minimise the risk of missed diagnoses or inappropriate testing.

For population groups at continuing risk of infection, frequent re-testing will ensure early detection and linkage to care.

10. Implementation considerations

Each individual centre can develop its own HCV screening algorithm in accordance with those recommended by the CDC or PHE SMI

11. Recommendations for research

List any aspects of the question that have not been answered and should therefore be highlighted as an area in need of further research.

12. What is the quality of the evidence? To be considered if primary literature was reviewed.

12.1. How reliable are the studies in the body of evidence?

If there is insufficient evidence to answer the key question go to section 11. Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

Recommendations are contained in a number of good quality guidelines

12.2. Are the studies consistent in their conclusions – comment on the degree of consistency within the available evidence. Highlight specific outcomes if appropriate. If there are conflicting results highlight how the group formed a judgement as to the overall direction of the evidence

In general there is a high degree of consistency between the available guidelines as above. There is inconsistency in the type of screening test recommended in the older guidelines. Antigen testing is mentioned in some guidelines and not others. Guidelines that refer to the need for regular retesting in those at continuing risk of infection vary slightly in their recommendations. Some are not definite about the interval while others recommend an interval of 6 months or 12 months or 6-12 months. The MMWR algorithm is consistent with the main recommendation in all the other guidelines.

12.3. Generalisability – are the patients in the studies similar to our target population for this guideline? is it reasonable to generalise

Yes
12.4. Applicability - Is the evidence applicable to Ireland? Is the intervention/ action implementable in Ireland?
Yes
12.5. Are there concerns about publication bias? Comment here on concerns about all studies coming from the same research group, funded by industry etc
Not applicable
13. Additional information for consideration
13.1. Additional literature if applicable e.g. Irish literature
Nil
13.2. Relevant national policy
Nil
13.3. Epidemiology in Ireland if available and applicable
Not relevant
14. Potential impact of recommendation
14.1. Benefit versus harm What factors influence the balance between benefit versus harm? Take into account the likelihood of doing harm or good. Do the desirable effects outweigh the undesirable effects?
The guideline will ensure a standardised approach to the sequence of testing. The main benefit of the recommendation is likely to be in relation to the frequency of retesting in those who initially test negative but are at continuing risk, as currently they may not always be offered further testing.
14.2. What are the likely resource implications and how large are the resource requirements? Consider cost effectiveness, financial, human and other resource implications
The sequence of testing recommended is likely to be similar to what is already in practice in most laboratories, so there will not be resource implications. The frequency of re-testing may have some resource implications in settings where clients are offered testing at entry, e.g. prisons, drug treatment clinics, but frequent re-testing may not always be carried out in those who remain at risk.

14.3. Acceptability – Is the intervention/ option acceptable to key stakeholders?

Yes

14.4. Feasibility - Is the intervention/action implementable in the Irish context?

Yes, in general. However, the recommendation for frequent re-testing may be difficult in settings where staff resources are limited.

14.5. What would be the impact on health equity?

The availability of national guidelines will ensure standardisation of clinical and laboratory practice throughout the country.

15. What is the value judgement? How certain is the relative importance of the desirable and undesirable outcomes? Are the desirable effects larger relative to undesirable

For population groups at continuing risk of infection, frequent re-testing will ensure early detection and linkage to care.

16. Final Recommendations

√ Strong recommendation
□ Condi□onal/ weak recommenda□on

Text:
Proposed HCV Testing Sequence*

Individuals being investigated for evidence of HCV infection should be screened with an anti-HVC antibody or combined HCV antigen/antibody EIA screening assay

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2. If the initial HCV EIA is reactive (positive), then the sample should be tested for the presence of HCV antigen, or HCV RNA

(a) If the individual tests positive for HCV antigen or HCV RNA, then the results should be reported with an interpretive comment along the lines of “consistent with active HCV infection”

(Proceed to 3 and 3(i) below)

(b) If an individual tests HCV antibody positive, but antigen/RNA negative, then a second anti-HCV assay (either a second EIA, or an immunoblot) should be performed to confirm the screening assay result

(i) If the second anti-HCV assay confirms the initial result, then the results should be reported with an interpretive comment along the lines of "consistent with HCV infection at some time" or "HCV serology suggestive of resolved infection"
(Proceed to 3 and 3(ii) below)

(ii) If the second anti-HCV assay does not confirm the initial result, then further testing should be performed with a view to resolving the discordant result profile: the further testing should be performed at a laboratory with sufficient expertise and experience to provide a resolution

3. All individuals testing positive for active or resolved HCV infection should have a second serum sample drawn to confirm their HCV diagnosis

(i) Those individuals testing positive for active infection should also have a sample drawn for HCV RNA (if not already performed) and HCV genotyping

(ii) Those individuals with evidence of a resolved HCV infection (i.e. antigen/RNA negative) should also have a further sample drawn after 6-12 months for HCV RNA testing to confirm their resolved infection status

**Each individual centre can develop its own HCV screening algorithm in accordance with those recommended by the CDC or PHE SMI*

***In certain patient groups, initial testing should routinely incorporate HCV antigen or RNA testing. Those are: immunocompromised individuals; children (born to HCV-infected mothers) in the first 18 months of life; individuals previously treated for HCV infection; sources of needle-sticks; and those at risk of recent infection in whom an antibody response might not yet have developed (RNA testing should be performed 6 weeks post-exposure)*

- Individuals who initially test HCV negative but who remain at risk of HCV infection should be offered further testing on an annual basis.

17. Justification

A standard approach to the sequence of testing will ensure that testing is carried out with maximum efficiency and will minimise the risk of missed diagnoses or inappropriate testing.
For population groups at continuing risk of infection, frequent re-testing will ensure early detection and linkage to care.

18. Implementation considerations

Each individual centre can develop its own HCV screening algorithm in accordance with those recommended by the CDC or PHE SMI

19. Recommendations for research
List any aspects of the question that have not been answered and should therefore be highlighted as an area in need of further research.

Review by GDG

Date: 23/02/2017

Recommendation accepted

Consultation feedback and review by GDG

Please see *Report of the consultation process* for feedback received.

No material change to recommendation.

Final recommendation

Recommendation 22

22.1. Individuals being investigated for evidence of HCV infection should be screened with an anti-HCV antibody or combined HCV antigen/antibody EIA screening assay*.

22.2. If the initial HCV EIA is reactive (positive), then the sample should be tested for the presence of HCV antigen, or HCV-RNA, to test for current infection.

22.3. Current infection should be confirmed on a second sample and HCV-RNA should be performed (if not already performed) and HCV genotyping should be carried out.

22.4. Those individuals with evidence of a resolved HCV infection (i.e. anti-HCV positive and antigen/ RNA negative) should have a further sample drawn after six to 12 months for HCV-RNA testing to confirm their resolved infection status.

*In certain patient groups, initial testing should routinely incorporate HCV-antigen or HCV-RNA testing.Those are: immunocompromised individuals; children (born to HCV-infected mothers) in the first 18 months of life; individuals previously treated for HCV infection; sources of needle-sticks; and those at risk of recent infection in whom an antibody response might not yet have developed (HCV-RNA testing should be performed six weeks post-exposure)

Quality/level of evidence: moderate; good consistency between existing high quality guidelines
Strength of recommendation: strong

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Appendices

Evidence search and results

International and national guidelines

HCV guidelines identified, reviewed, and quality appraised as described in the National Clinical Guideline.

Grey literature

Nil used.

Primary literature

Nil.