Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle-income countries

PICO 2: Screening

A systematic review of immediate HCV RNA testing following HCV Antibody compared with HCV RNA testing at time of assessment for HCV therapy

Conducted by the Burnet Institute, Melbourne and Health Protection Scotland, Glasgow
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BACKGROUND

The World Health organization estimates that between 130 and 150 million people are chronically infected with hepatitis C virus (HCV) worldwide (World Health Organisation, 2012, Woodall et al., 1994). People with untreated HCV are at increased risk of liver cirrhosis, hepatocellular carcinoma, and liver-related mortality (Villano et al., 1997). HCV RNA testing, which generally follows a positive anti-HCV antibody test in a clinical setting, allows the detection of current HCV infection, thus indicating individuals for treatment and care options (Rongey et al., 2009, Scott et al., 2006, Piasecki et al., 2004). This review investigates the optimal time at which to perform HCV RNA tests in order to establish the presence of current infection, and to reduce morbidity and mortality associated with HCV infection.


METHODS

PICO question:
Population: People who are HCV antibody positive
Intervention: HCV RNA testing at the time of receipt of a positive HCV antibody result
Comparison: HCV RNA test in the context of HCV care as part of assessment for HCV therapy
Outcomes: Number of cases of HCV transmission, number achieving sustained virological response (SVR) to HCV treatment, number of cases of decompensated liver diseases/hepatocellular carcinoma/liver-related deaths/all-cause mortality, quality of life
Study type/limits: Experimental or observational studies published between 1994 and the present

Search strategy:
A systematic review was conducted by searching databases (Ovid MEDLINE, Ovid EMBASE, LILACS, the Cochrane Library (CENTRAL and DARE)), unpublished/ongoing research presented at international HCV conferences, conference proceedings and registries from EASL, AASLD, APASL, and ClinicalTrials.gov, reference lists of all relevant articles and reviews, and other relevant articles identified during the conduct of the other systematic reviews.

Search terms were broad and were combinations of free text and medical subject heading terms (MeSH, Emtree), briefly summarized as: HCV AND HCV RNA test AND Antibodies (see Appendix I).

Conduct of the review:
The review process followed the Cochrane methodology for conducting a systematic review and the PRISMA guidelines on reporting. Two reviewers assessed all search results, in order to include those studies that met population, intervention, comparison and at least one outcome criteria. The bibliographic records and abstracts were used to filter studies that clearly did not meet the inclusion criteria. Full articles were then obtained and assessed to confirm eligibility of potentially relevant studies.

Quality appraisal:
The review process followed the Cochrane methodology for conducting a systematic review and the PRISMA guidelines on reporting. The review was prospectively registered with the systematic reviews registry PROSPERO (University of York). The review was be carried out by a primary and secondary reviewer. The Cochrane Risk of Bias Tool was used to assess any RCTs and observational studies were assessed using the Newcastle-Ottawa (N-O) checklist (Reeves et al., 2011). N-O
assesses each study in terms of the risk of bias in the representativeness of the study cohort, the comparability of the exposed and non-exposed participants, and the ascertainment of study outcomes.

Data extraction:
The primary reviewer and secondary reviewer acted to extract data independently. We aimed to stratify data according to:

- Study characteristics: country, study design, study objectives, funding source;
- Study population (people with HCV antibodies, population at risk of HCV);
- Participant details (age, sex, ethnicity);
- Setting (GP, hospital, alcohol and drug services, harm reduction services, sexual health clinics, high/medium/low income country);
- Inclusion/exclusion criteria for study;
- Sample size;
- Intervention group (selection and characteristics of intervention group);
- Intervention (HCV RNA testing upon receipt of positive HCV antibody result, delivered by healthcare professional/drug support worker/ancillary staff, year or time period of intervention delivered, costs of delivery);
- Control group (selection and characteristics of control group);
- Control (HCV RNA test in the context of HCV care as part of assessment for HCV therapy);
- Analysis (number offered intervention, number accepted intervention, reason for refusal, time to follow-up, study data collection method, statistical analysis, primary outcomes of study, secondary outcomes of study);
- Results (number of cases of HCV transmission, number of cases achieving sustained virological response (SVR) to HCV treatment, number of cases of decompensated liver diseases/hepatocellular carcinoma/liver-related deaths/all-cause mortality, quality of life in the intervention group compared to the comparison group).

To fulfil the inclusion criteria, studies needed to present i) original research, ii) have populations of individuals testing positive to anti-HCV antibodies, iii) include an intervention of HCV RNA testing at the time of receipt of a positive anti-HCV antibody result, and iv) have a comparison where individuals received HCV RNA testing in the context of HCV care as part of assessment for HCV therapy, and v) include at least one of the following outcomes: number of cases of HCV transmission, number achieving sustained virological response (SVR) to HCV treatment, number of cases of
decompensated liver diseases/hepatocellular carcinoma/liver-related deaths/all-cause mortality, or quality of life.

**GRADE process:**

The quality of the body of evidence for each outcome of interest was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. GRADE rates the quality of evidence for each outcome of interest as high, moderate, low or very low, depending on a number of criteria. These include study design, study quality, study consistency (the similarity of estimates of effect across studies) and study directness (the extent to which the evidence is relevant to the population, intervention, and outcome of interest).
RESULTS

The number of citations screened was 2454 from which 2427 citations were excluded, due to incorrect population (n=1908) or incorrect intervention (n=343) (see study flow chart, Figure 1). From the remaining abstracts, a further 19 citations were excluded after title and abstract review because they involved the incorrect study design (such as modelling papers, or non-original research) (Cipriano et al., 2012, Annicchiarico et al., 2012, Galloppo and Galloppo, 2010, Vogel and Rockstroh, 2010, Matteoni and Younossi, 1999), incorrect study population (such as not anti-HCV positive individuals) (Fan et al., 2004, Gugenheim et al., 1994, Ndimbie et al., 1995, Pujol et al., 1994, Zhang et al., 2006), or incorrect intervention (RNA testing at baseline) (Aniszewska et al., 2009, Iqbal et al., 2011, Keating et al., 2005, Malina et al., 1996, McDonald et al., 2012, Shah et al., 2012, Strasak et al., 2011, Tobler et al., 2010, Woodall et al., 1994).

Eight articles were obtained for full-text appraisal (Allison et al., 2012, Ohkoshi et al., 1995, Piasecki et al., 2004, Rongey et al., 2009, Scott et al., 2006, Rein et al., 2012, Sheth et al., 2012, Yoshino and Kasai, 1996). No studies matched the complete inclusion criteria as all lacked a comparison arm and were primarily designed to address other research questions. Since the aims were different, these studies did not directly report on the outcomes of interest specified in the PICO. Therefore, no studies were included for qualitative or quantitative assessment and in the absence of any directly relevant studies, neither narrative synthesis nor meta-analysis could be performed.

Given that no studies were found to be relevant, we searched widely through systematic reviews, comment papers, and other study types and in order to capture relevant studies. This included widening the search topic to include comparisons of RNA testing at any time versus no RNA testing, as opposed to testing “early” (at receipt of anti-HCV-Ab test) versus “late” (in the context of care as part of assessment for HCV treatment). This also yielded no further citations of primary studies or systematic reviews.

Despite not meeting the complete PICO inclusion criteria, those articles appraised at full-text review stage are summarised in Table 1 for their potential for any indirect evidence related to the question.
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**Figure 1: Flowchart for systematic review**

No of Records identified through database searches (Embase, Medline, Cochrane, LILACS, ClinicalTrials.gov, AASLD, EASL, APASL (N=3647) ➔

Duplicates removed (n=1193) ➔

Number of records screened (n=2454) ➔

Number of records excluded (n=2427):
- Reviews/case reports (n=75)
- Animal studies (n=1)
- Papers prior to 1994 (n=1)
- Incorrect population (n=1908)
- Incorrect intervention – laboratory studies (n=343)
- Incorrect intervention – not early vs late RNA (n=99) ➔

Number of articles assesses for eligibility by title/abstract (n=27) ➔

Number of studies included (n=0) ➔

Number of full-text articles excluded (n=8):
- No comparison:
  - HCV-RNA testing at the time of receipt of a positive antibody result (n=4) (Rongey et al., 2009, Scott et al., 2006, Sheth et al., 2012, Rein et al., 2012)
  - HCV RNA testing in the context of HCV care (n=4) (Allison et al., 2012, Piasecki et al., 2004, Ohkoshi et al., 1995, Yoshino and Kasai, 1996)
### Table 1: Characteristics of studies among anti-HCV positive individuals receiving RNA testing, without direct comparison group, for potential indirect evidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allison et al. (2012)</td>
<td>Anti-HCV positive blood donors</td>
<td>HCV RNA in all patients</td>
<td>HCV related cirrhosis; risk factors for HCV acquisition</td>
<td>Aimed to describe risk factors for HCV acquisition and predictors of liver disease (cirrhosis) in a US blood donation service. All individuals tested for RNA in the study regardless of timing of infection. Found after mean 25 years of HCV infection, histologic outcomes were mild and 20% had spontaneously cleared.</td>
</tr>
<tr>
<td>Ohkoshi et al. (1995)</td>
<td>Anti-HCV positive undergoing annual liver function testing</td>
<td>HCV RNA test in all patients</td>
<td>HCV natural history, patient characteristics</td>
<td>Aimed to better define HCV natural history in one town in Japan. Among 63 subjects, 50 (79.4%) HCV RNA detected in serum and 40 (80%) of the 50 subjects with HCV RNA had abnormal LFTs. Six of 50 (12%) had ultrasonographic findings suggestive of cirrhosis. Concludes the viremic patients had low rates of progressive liver disease.</td>
</tr>
<tr>
<td>Piasecki et al. (2004)</td>
<td>Anti-HCV positive (RNA+ and RNA – patients)</td>
<td>HCV RNA testing for spontaneous clearance</td>
<td>HCV RNA spontaneous clearance</td>
<td>Aimed to define the role of alcohol, race, and HCV or HIV co-infection on natural HCV clearance. Likelihood of spontaneous clearance of HCV may be influenced by alcohol and viral co-infactions. For indirect evidence, study provides information on prevalence of RNA testing immediately after anti-HCV ab testing.</td>
</tr>
<tr>
<td>Rein et al. (2012)</td>
<td>Outpatients tested for anti-HCV</td>
<td>HCV RNA testing after receipt of anti-HCV positive test</td>
<td>RNA testing pattern/predictors</td>
<td>Investigating effectiveness of one-time HCV screening for people born 1945-65. Data collected from medical records for anti-HCV antibody testing and HCV RNA testing. Evidence of low HCV RNA testing rates among anti-HCV positive. Evidence suggesting that RNA testing is not being performed in the population in which it is indicated.</td>
</tr>
<tr>
<td>Rongey et al. (2009)</td>
<td>Anti-HCV positive US veterans</td>
<td>HCV RNA testing (with and without routine HCV RNA testing in anti-HCV positive individuals)</td>
<td>RNA test being performed</td>
<td>Aimed to determine factors influencing HCV RNA testing in US anti-HCV-positive veterans. Perceived eligibility for treatment may influence the decision to order an RNA test. Patients with abnormal transaminases, presence of non-HCV hepatitis or compensated liver disease all significantly more likely to receive HCV RNA testing, while patients aged over 65 years and illicit drug users were significantly less likely. Results of the study include predictors of RNA testing and suggest significant underutilization of RNA testing, where treatment eligibility is used as a prompt for performing HCV RNA testing.</td>
</tr>
<tr>
<td>Scott et al. (2006)</td>
<td>Anti-HCV positive</td>
<td>HCV RNA testing soon after anti-HCV diagnosis</td>
<td>Frequency of RNA spontaneous clearance</td>
<td>Aims to determine frequency of spontaneous HCV RNA clearance during chronic HCV infection. Found annualized clearance rate of 0.74% per person-year (95% CI, 0.30%-1.53%). Concluded clearance is a surprisingly frequent event and is associated with low HCV RNA titres at baseline.</td>
</tr>
<tr>
<td>Sheth et al. (2012)</td>
<td>Patients identified with CHC in</td>
<td>Anti-HCV or RNA testing</td>
<td>Characteristics of incident HCV cases</td>
<td>Description of characteristics of an incident cohort of patients with CHC. Investigated anti-HCV antibody and HCV RNA testing within 60 days prior to index date, and also quantitative</td>
</tr>
</tbody>
</table>
There is insufficient evidence to draw conclusions for the optimal timing at which HCV RNA tests should be performed in a GRADE evidence profile matching this PICO question (Table 2). However, there was some indirect evidence suggesting that HCV RNA testing is underutilized in populations in which it is indicated (Rein et al., 2012, Rongey et al., 2009, Sheth et al., 2012, Yoshino and Kasai, 1996). Rongey et al. (2009) found that predictors of receipt of an RNA test among a cohort of anti-HCV-positive US Veterans included patients with abnormal transaminases, the presence of non-HCV hepatitis, and decompensated liver disease, while those aged over 65 years, and illicit drug users were significantly less likely to be HCV RNA tested. The relative risk of receiving RNA testing in Rongey et al. is summarised in Table 4.

Table 2: GRADE Evidence summary – HCV RNA testing performed immediately after anti-HCV diagnosis compared with RNA testing in context of HCV care/treatment among anti-HCV positive individuals

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of participants (Studies) Follow up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV transmission</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained Virological Response</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver-related morbidity</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3: Summary of other quantitative evidence of risk of receiving HCV RNA test

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of participants (Studies)</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the association between age &gt;65 and receiving a test for HCV RNA?</td>
<td>13,257 (1 study) 5 years</td>
<td>Very low¹</td>
<td>0.79 (0.69-0.92)</td>
<td>(Rongey et al., 2009)</td>
</tr>
<tr>
<td>Outcome: receipt of RNA test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is the association of illicit drug use on RNA testing?</td>
<td>13,257 (1 study) 5 years</td>
<td>Very low¹</td>
<td>0.94 (0.91-0.97)</td>
<td>(Rongey et al., 2009)</td>
</tr>
<tr>
<td>Outcome: receipt of RNA test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is the association of abnormal transaminases on RNA testing?</td>
<td>13,257 (1 study) 5 years</td>
<td>Very low¹</td>
<td>1.1 (1.03-1.20)</td>
<td>(Rongey et al., 2009)</td>
</tr>
<tr>
<td>Outcome: receipt of RNA test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is the association of non-HCV hepatitis on RNA testing?</td>
<td>13,257 (1 study) 5 years</td>
<td>Very low¹</td>
<td>1.07 (1.02-1.14)</td>
<td>(Rongey et al., 2009)</td>
</tr>
<tr>
<td>Outcome: receipt of RNA test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is the association of decompensated liver disease (cirrhosis) on RNA testing?</td>
<td>13,257 (1 study) 5 years</td>
<td>Very low¹</td>
<td>1.2 (1.1-1.3)</td>
<td>(Rongey et al., 2009)</td>
</tr>
<tr>
<td>Outcome: receipt of RNA test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Evidence ranked very low due to single observational study data; N-O quality appraisal of study, 5 out of maximum 9 points.
CONCLUSIONS

Further studies are needed to further investigate the appropriate timing of HCV RNA testing. Prospective cohort studies of individuals after diagnosis of HCV may provide this evidence as randomised trials of early versus later RNA testing are highly unlikely to gain ethical approval in settings where RNA testing is readily available.

Implications for clinical practice
While no conclusive evidence is available, four studies conducted in high income settings indicated HCV RNA testing is underused in chronic HCV diagnosis and suggest routine HCV RNA testing for HCV antibody positive individuals in order to confirm active HCV infection. There is no direct evidence on whether the timing of RNA testing is associated with clinical outcomes including transmission, mortality, morbidity or quality of life.

Implications for research
Further research into the optimal timing of RNA testing is warranted to determine with early testing compared to delayed testing has any association or impact patient important outcomes including HCV transmission, morbidity, mortality and quality of life.
REFERENCES


PUJOL, F. H., GUZMAN-BLANCO, M., PLAZ, J., ROJAS, O., BEKER, B. & BEKER, S. 1994. Usefulness of the PCR technique (polymerase chain reaction) in the follow-up of patients infected with hepatitis C virus. Preliminary communication. [Spanish] Utilidad de la Tecnica de PCR
PICO 2 (Screening): When should HCV RNA tests be performed?

(reaccion en cadena de la polimerasa) en el seguimiento de pacientes infectados con el virus de la hepatitis C. Comunicacion preliminar. G.E.N, 48, 121-123.


APPENDIX 1: Search syntax for electronic databases

MEDLINE
1524 citations
1. Hepacivirus*.ti,ab,hw.
2. HCV.ti,ab,hw.
3. Hepatitis C.ti,ab,hw.
4. HepC.ti,ab,hw
5. Hep C.ti,ab,hw
6. 1 or 2 or 3 or 4 or 5 or 6
7. Exp polymerase chain reaction
8. (assess* or diagnos* or test or tests or testing or tested).ti,ab
9. 8 and 9
10. ((RNA or ribonucleic acid or nucleic acid) adj3 (assess* or diagnos* or test or tests or testing or tested)).ti,ab
11. ((PCR or polymerase chain reaction) adj3 (assess* or diagnos* or test or tests or testing or tested)).ti,ab
12. 10 or 11 or 12
13. Exp Antibody/
14. (ab or antibody* or anti HCV).ti,ab
15. 14 or 15
16. 7 and 13 and 16
17. Limit 14 to yr="1994-current"

EMBASE
2041 citations
1. Exp hepatitis C/
2. Hepacivirus*.ti,ab,hw
3. HCV.ti,ab,hw
4. Hepatitis C.ti,ab,hw
5. HepC.ti,ab,hw
6. Hep c.ti,ab,hw
7. 1 or 2 or 3 or 4 or 5 or 6
8. Exp Polymerase Chain Reaction/
9. (assess* or diagnos* or test or tests or testing or tested).ti,ab
10. 8 and 9
11. ((RNA or ribonucleic acid or nucleic acid) adj3 (assess* or diagnos* or test or tests or testing or tested)).ti,ab
12. ((PCR or polymerase chain reaction) adj3 (assess* or diagnos* or test or tests or testing or tested)).ti,ab
13. 10 or 11 or 12
PICO 2 (Screening): When should HCV RNA tests be performed?

14. Exp Antibody/
15. (ab or antibody* or anti HCV).ti,ab
16. 14 or 15
17. 7 and 13 and 16
18. Limit 14 to yr="1994-Current" citations

COCHRANE
29 Citations

1. MeSH descriptor: [Hepatitis C] explode all trees
2. Hepacivirus:ti,ab,kw
3. HCV:ti,ab,kw
4. Hepatitis c:ti,ab,kw
5. HepC:ti,ab,kw
6. Hep C:ti,ab,kw
7. #1 or #2 or #3 or #4 or #5 or #6
8. MeSH descriptor: [Polymerase Chain Reaction] explode all trees
9. (assess* or diagnos* or test or tests or testing or tested):ti,ab
10. #8 and #9
11. ((RNA or ribonucleic acid or nucleic acid) near/3 (assess* or diagnos* or test or tests or testing or tested)):ti,ab
12. ((PCR or polymerase chain reaction) near/3 (assess* or diagnos* or test or tests or testing or tested)):ti,ab
13. #10 or #11 or #12
14. MeSH descriptor: [Antibodies] explode all trees
15. (ab or antibody* or anti HCV):ti,ab
16. #14 or #15
17. #7 and #13 and #16

LILACS
43 Citations

("HCV RNA testing") OR ("HCV PCR testing") and ("antibodies" or "antibody")

ClinicalTrials.gov
1 Citation

"HCV RNA testing" OR "HCV PCR testing"