WHO/HIV/2014.28

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
18 June 2013

Review Members

Ms Katherine Hall	Burnet Institute, Melbourne
Ms Rachel Sacks-Davis	Burnet Institute, Melbourne
Dr Joseph Doyle	Burnet Institute, Melbourne
Dr Esther Aspinall	Health Protection Scotland, Glasgow
Prof Sharon Hutchinson	Caledonian University, Glasgow
Prof Margaret Hellard	Burnet Institute, Melbourne

Review Advisory Group

Dr Mark Stoove	Burnet Institute, Melbourne
Prof David Goldberg	Health Protection Scotland, Glasgow
Prof Stanley Luchters	Burnet Institute, Melbourne
Dr Alexander Thompson	St Vincent's Hospital, University of Melbourne
Dr Stefan Wiktor	WHO Global Hepatitis Program, Geneva
Mr Tim Nguyen	WHO Global Hepatitis Program, Geneva
Dr Bryce Smith	Centre for Disease Control and Prevention, Atlanta
Dr Yngve Falck-Ytter	Case Western Reserve University, Cleveland
Ms Rebecca Morgan	Centre for Disease Control and Prevention, Atlanta

Contents

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 PROPSPERO (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 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, Galoppo and Galoppo, 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.

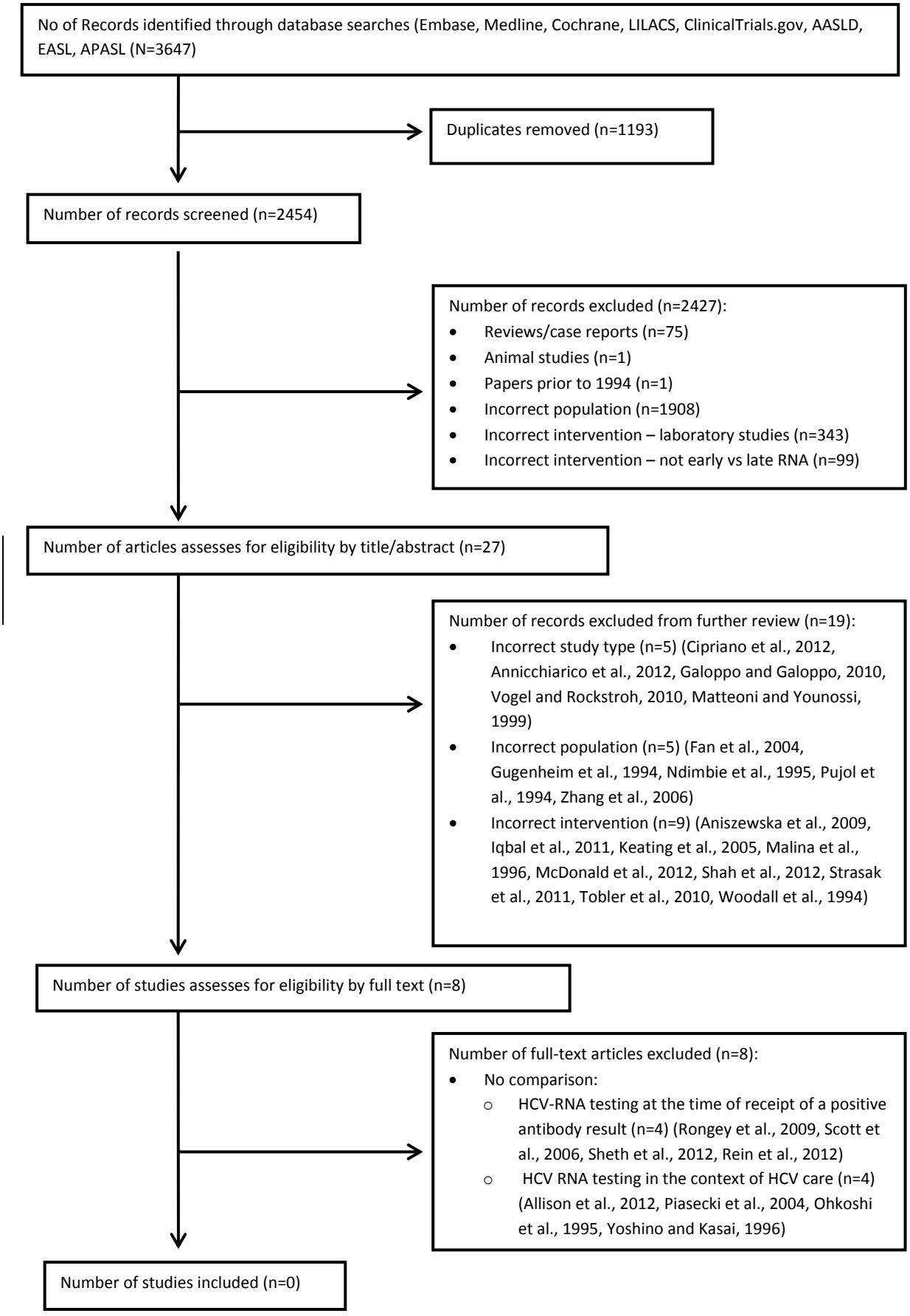

Figure 1: Flowchart for systematic review

Table 1: Characteristics of studies among anti-HCV positive individuals receiving RNA testing, without direct comparison group, for potential indirect evidence

Study	Population	Intervention	Outcomes	Comments
Allison *et al. (*2012) **Setting:** Blood donation service, US **Study type:** Retrospective cohort	Anti-HCV positive blood donors	HCV RNA in all patients No comparison	HCV related-cirrhosis; risk factors for HCV acquisition	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.
Ohkoshi *et al.* (1995) **Setting:** One township, Japan **Study type:** Retrospective cohort	Anti-HCV positive undergoing annual liver function testing	HCV RNA test in all patients No comparison arm	HCV natural history, patient characteristics	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 viraemic patients had low rates of progressive liver disease.
Piasecki et al. (2004) **Setting:** Medical centre, US **Study type:** prospective cohort	Anti-HCV-positive (RNA+ and RNA – patients)	HCV RNA testing for spontaneous clearance	HCV RNA spontaneous clearance	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-infections. For indirect evidence, study provides information on prevalence of RNA testing immediately after anti-HCV-ab testing.
Rein et al. (2012) **Setting:** Four large primary care service providers, US **Study type:** Retrospective cohort	Outpatients tested for anti-HCV	HCV RNA testing after receipt of anti-HCV positive test No comparison arm	RNA testing pattern/predictors	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.
Rongey et al. (2009) **Setting:** Veteran facilities, US **Study type:** Retrospective cohort	Anti-HCV-positive US veterans	HCV RNA testing (with and without routine HCV RNA testing in anti-HCV-positive individuals) No comparison arm	RNA test being performed	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 decompensated 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.
Scott *et al.* (2006) **Setting:** Outpatients, Alaska, US **Study type:** prospective cohort	Anti-HCV positive	HCV RNA testing soon after anti-HCV diagnosis No comparison arm	Frequency of RNA spontaneous clearance	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.
Sheth et al. (2012) **Setting:** Patients identified with CHC in	Patients with CHC	Anti-HCV or RNA testing No comparison	Characteristics of incident HCV cases	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

various clinical and non-clinical settings, US **Study type:** retrospective study		arm		RNA testing after treatment initiation. Indirect evidence suggesting that RNA testing is not being performed in the population in which it is indicated, resulting in potential misdiagnosis.
Yoshino and Kasai (1996) **Setting:** Medical clinic, Japan **Study type:** Retrospective cohort	Anti-HCV-positive patients receiving annual liver function examinations	HCV RNA testing in context of long-term care No comparison arm	HCV transmission routes	Aimed to investigate initial HCV transmission routes among anti-HCV positive/ HCV-RNA negative cases compared to HCV-RNA positive cases. Indirect evidence suggesting that RNA testing is not being performed in the population in which it is indicated.

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

Outcomes	**No of participants (Studies)** Follow up	**Quality of the Evidence (GRADE)**	**Relative Effect (95% CI)**	**Anticipated absolute effects**
HCV transmission	No data			
Sustained Virological Response	No data			
Adverse events	No data			
Liver-related morbidity	No data			
Mortality	No data			
Quality of Life	No data			

Table 3: Summary of other quantitative evidence of risk of receiving HCV RNA test

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

[1]Evidence 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

ALLISON, R. D., CONRY-CANTILENA, C., KOZIOL, D., SCHECHTERLY, C., NESS, P., GIBBLE, J., KLEINER, D. E., GHANY, M. G. & ALTER, H. J. 2012. A 25-year study of the clinical and histologic outcomes of hepatitis C virus infection and its modes of transmission in a cohort of initially asymptomatic blood donors. *Journal of Infectious Diseases,* 206**,** 654-661.

ANISZEWSKA, M., KOWALIK-MIKOLAJEWSKA, B., POKORSKA-LIS, M. & MARCZYNSKA, M. 2009. Spontaneous clearance of HCV-RNA in children with vertically acquired HCV infection. *Experimental and Clinical Hepatology,* 5**,** 15-18.

ANNICCHIARICO, B. E., SICILIANO, M. & GASBARRINI, A. 2012. Chronic hepatitis C virus infection: clinical picture and treatment possibilities. *Giornale italiano di nefrologia,* 29 Suppl 54**,** S103-108.

CIPRIANO, L. E., ZARIC, G. S., HOLODNIY, M., BENDAVID, E., OWENS, D. K. & BRANDEAU, M. L. 2012. Cost Effectiveness of Screening Strategies for Early Identification of HIV and HCV Infection in Injection Drug Users. *PLoS ONE,* 7.

FAN, W. M., ZHU, W. F., ZHANG, S. Y., WANG, Q. X., YIN, L. M., WAN, H., GAO, Y., TIAN, X. L., YU, M., JIN, J., XU, X. Y., WEI, L. & ZHUANG, H. 2004. [Nine-year follow-up of hepatitis C virus infection in a rural area of Hebei province, China]. *Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal],* 84**,** 392-6.

GALOPPO, M. & GALOPPO, C. 2010. Management of hepatitis C virus infection in childhood. *Annals of hepatology : official journal of the Mexican Association of Hepatology,* 9 Suppl**,** 98-102.

GUGENHEIM, J., BALDINI, E., MAZZA, D., FABIANI, P., ST PAUL, M. C., GOUBAUX, B., OUZAN, D. & MOUIEL, J. 1994. Recurrence of hepatitis C virus after liver transplantation. *Transplant international : official journal of the European Society for Organ Transplantation,* 7 Suppl 1**,** S224-226.

IQBAL, M., MAC NICHOLAS, R., MCNULTY, C., HEGARTY, J. & MC CORMICK, A. 2011. Long-term follow up of patients with spontaneous clearance of hepatitis C. *Journal of Hepatology,* 54**,** S460.

KEATING, S., COUGHLAN, S., CONNELL, J., SWEENEY, B. & KEENAN, E. 2005. Hepatitis C viral clearance in an intravenous drug-using cohort in the Dublin area. *Irish Journal of Medical Science,* 174**,** 37-41.

MALINA, L., ZDARSKY, E., HAVLICKOVA, M. & STRANSKY, J. 1996. Detection of HCV RNA in anti-HCV positive patients with chronic hepatic porphyria. *Casopis lekaru ceskych,* 135**,** 427-429.

MATTEONI, C. A. & YOUNOSSI, Z. M. 1999. In diagnosing hepatitis C, which patient needs which test? *Cleveland Clinic journal of medicine,* 66**,** 529-530.

MCDONALD, S. A., HUTCHINSON, S. J., CAMERON, S. O., INNES, H. A., MCLEOD, A. & GOLDBERG, D. J. 2012. Examination of the risk of reinfection with hepatitis C among injecting drug users who have been tested in Glasgow. *International Journal of Drug Policy,* 23**,** 353-357.

NDIMBIE, O. K., NEDJAR, S., KINGSLEY, L., RIDDLE, P. & RINALDO, C. 1995. Long-term serologic follow-up of hepatitis C virus-seropositive homosexual men. *Clinical and Diagnostic Laboratory Immunology,* 2**,** 219-224.

OHKOSHI, S., TAWARAYA, H., KUWANA, K., HARADA, T., WATANABE, M., HIGUCHI, S., KOJIMA, H., KAMIMURA, T. & ASAKURA, H. 1995. A retrospective study of hepatitis C virus carriers in a local endemic town in Japan. A possible presence of asymptomatic carrier. *Digestive Diseases & Sciences,* 40**,** 465-71.

PIASECKI, B. A., LEWIS, J. D., REDDY, K. R., BELLAMY, S. L., PORTER, S. B., WEINRIEB, R. M., STIERITZ, D. D. & CHANG, K. M. 2004. Influence of alcohol use, race, and viral coinfections on spontaneous HCV clearance in a US veteran population. *Hepatology,* 40**,** 892-899.

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

(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.

REEVES, B. C., DEEKS, J. J., HIGGINS, J. P. T., WELLS, G. A. & ON BEHALF OF THE COCHRANE NON-RANDOMISED STUDIES METHODS GROUP 2011. Including non-randomized studies. *In:* HIGGINS, J. P. T. & GREEN, S. (eds.) *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011].* The Cochrane Collaboration.

REIN, D. B., WAGNER, L. D., BROWN, K. A., FALLON, M. B., KRAUSKOPF, K., MASSOUD, O. I. & SMITH, B. D. 2012. Current practices of hepatitis C antibody testing and follow-up evaluation in primary care settings: A retrospective study of four large, primary care service centers. *Hepatology,* 56**,** 1094A.

RONGEY, C. A., KANWAL, F., HOANG, T., GIFFORD, A. L. & ASCH, S. M. 2009. Viral RNA Testing in Hepatitis C Antibody-Positive Veterans. *American Journal of Preventive Medicine,* 36**,** 235-238.

SCOTT, J. D., MCMAHON, B. J., BRUDEN, D., SULLIVAN, D., HOMAN, C., CHRISTENSEN, C. & GRETCH, D. R. 2006. High rate of spontaneous negativity for hepatitis C virus RNA after establishment of chronic infection in Alaska natives. *Clinical Infectious Diseases,* 42**,** 945-952.

SHAH, D. P., GRIMES, C. Z., BROWN, E. & HWANG, L. Y. 2012. Demographics, socio-behavioral factors, and drug use patterns: What matters in spontaneous HCV clearance? *Journal of Medical Virology,* 84**,** 235-241.

SHETH, S. D., VERA-LLONCH, M., LYNCH, J., WERTHER, W. & RUBIN, R. 2012. Characterization of a cohort of incident hepatitis c patients in the US (2005-2010): Comorbidities, use of medications and diagnostic tests. *Pharmacoepidemiology and Drug Safety,* 21**,** 91.

STRASAK, A. M., KIM, A. Y., LAUER, G. M., DE SOUSA, P. S., GINUINO, C. F., FERNANDES, C. A., VELLOSO, C. E., DE ALMEIDA, A. J., DE OLIVEIRA, J. M., YOSHIDA, C. F., SCHULZE ZUR WIESCH, J., PARANHOS-BACCALA, G., LANG, S., BRANT, L. J., ULMER, H., STROHMAIER, S., KALTENBACH, L., LAMPE, E. & LEWIS-XIMENEZ, L. L. 2011. Antibody dynamics and spontaneous viral clearance in patients with acute hepatitis C infection in Rio de Janeiro, Brazil. *BMC infectious diseases,* 11**,** 15.

TOBLER, L. H., BAHRAMI, S. H., KAIDAROVA, Z., PITINA, L., WINKELMAN, V. K., VANDERPOOL, S. K., GUILTINAN, A. M., COOPER, S., BUSCH, M. P. & MURPHY, E. L. 2010. A case-control study of factors associated with resolution of hepatitis C viremia in former blood donors. *Transfusion,* 50**,** 1513-1523.

VILLANO, S. A., VLAHOV, D., NELSON, K. E., LYLES, C. M., COHN, S. & THOMAS, D. L. 1997. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. *J Clin Microbiol,* 35**,** 3274-7.

VOGEL, M. & ROCKSTROH, J. K. 2010. Treatment of acute hepatitis C in HIV infection. *The Journal of antimicrobial chemotherapy,* 65**,** 4-9.

WOODALL, D. W., GODENICK, M. & VALAINIS, G. T. 1994. Hepatitis C experience at a community teaching hospital. *Journal of Family Practice,* 39**,** 257-261.

WORLD HEALTH ORGANIZATION 2012. Fact sheet No. 164, July 2012. World Health Organization.

YOSHINO, I. & KASAI, M. 1996. Analysis of cases of negative HCV-RNA with positive anti-HCV. [Japanese]. *Acta Hepatologica Japonica,* 37**,** 412-416.

ZHANG, Y., LI, J., LIU, Y. F., ZHAO, H. W. & TIAN, G. S. 2006. Significance of blood HCV RNA screening in the prevention of post-transfusion hepatitis C. [Chinese]. *Zhonghua shi yan he lin chuang bing du xue za zhi = Zhonghua shiyan he linchuang bingduxue zazhi = Chinese journal of experimental and clinical virology,* 20**,** 70-72.

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

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"