Hepatitis C Screening Guideline Development Group
Background to recommendation 16: People on renal dialysis or who have had a kidney transplant

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/

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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 existing recommendations
19/01/2017	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: 20/01/2017
Attendees: NOF, CDG, JC, SD, ER, LT

Table 1: Considered judgement form

1. What is the question being addressed? Present PICO if relevant

Should people on renal dialysis or who have had renal dialysis in the past be screened?

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)

Irish national guidelines on the prevention of blood borne viruses (BBV) within the healthcare setting and other guidelines on prevention of BBV in dialysis settings, and international hepatitis C recommendations.

3. What is the body of evidence?

Source of evidence: (tick all that apply)
Guidelines √
Primary literature □
Other □ ; specify: _____

Irish guidelines

National Standing Advisory Committee on the Prevention of Transmission of Blood-Borne Diseases in the Health-Care Setting, 2014

- **Haemodialysis**
  - **Before starting:** Testing for HCV should include antibody to hepatitis C (anti-HCV), PCR for HCV RNA (HCV RNA), and alanine aminotransferase (ALT). In addition, HCV antigen (Ag) testing may be helpful if the result may be available more quickly than that of an RNA test
  - **While on HD:** ALT monthly, 3 monthly HCV Ag (Abbott Architect) OR HCV RNA, anti-HCV. If HCV Ag (Abbott Architect) is being performed, annual HCV RNA in not required for any patient provided that HCV RNA was not detected during initial laboratory screening.
  - **Resolved HCV infection**: HCV Ag OR HCV RNA, and ALT monthly.
  - **Patients who are immunosuppressed** *(*including those who are on immunosuppressive therapy for a renal transplant) may only have HD in the multi-bedded unit when anti-HCV and RNA negative results are….(i.e. a negative HCV Ag test is not sufficient – a negative RNA test is required)
- **Treated/ on treatment:**
  - Patients who attain a SVR to anti-viral treatment should be regarded as having resolved HCV infection and in accordance with the "Blood borne viruses in haemodialysis, CAPD and renal transplantation 2010" they can be dialysed in the multi-bedded unit but tested monthly for HCV antigen OR HCV RNA.
  - Patients who are HCV RNA negative at the end of treatment (ETR) can either be

- Dialysed in an isolation room, if the facilities available, until a SVR is confirmed OR
- Dialysed in the multi-bedded unit but tested for HCV Ag OR HCV RNA EVERY TWO WEEKS until SVR.

- **Dialysed abroad**
  - Re-admitted patients who have been dialysed abroad for a period of 2 weeks or less should be tested for HBsAg, HCV Ag (Abbott Architect) OR HCV RNA, anti-HCV and HIV Ag/Ab before their first HD session on return but it is not necessary to have negative results before coming HD
  - For re-admitted patients who have been dialysed abroad for 2 weeks or more, a negative HBsAg, HCV Ag (Abbott Architect) **OR** HCV RNA, anti-HCV and HIV Ag/Ab must be available before HD in the multi-bedded unit.
- **Renal Transplant Patients**
  - Consideration should be given to testing all renal transplant patients on a one-off basis for the following at 3 months post- transplant: Anti-HCV and HCV RNA or HCV Ag
  - For patients transplanted before the introduction of above: it is advisable that all patients currently with a functioning kidney transplant, unless known to be HCV infected, be tested on a one-off basis for anti-HCV and HCV RNA, to out-rule the possible acquisition of HCV infection through past treatment for renal failure.
- **CAPD/CCPD**
  - Before starting: ±Anti-HCV, HCV Ag (Abbott Architect), HCV RNA and HIV Ag/Ab.
  - Regular testing on CAPD/CCPD: Annual anti-HCV, HCV Ag (Abbott Architect) OR HCV RNA

(*Blood Borne Viruses in the haemodialysis, CAPD and renal transplantation setting, July 2014 (1)*)

Advice issued by National Standing Advisory Committee on Blood Borne Viruses, 2008

- All patients having a kidney transplant should be test for hepatitis C by the HCV combi test (combined antigen-antibody) or anti-HCV test, AND HCV RNA at 3 months post transplant
- For patients transplanted before the introduction of the above – all patients with a currently functioning kidney transplant, unless already known to be HCV infected, should be tested on a one-off basis by the HCV combi test (combined antigen-antibody) or anti-HCV test, AND HCV RNA to out rule the possible acquisition of hepatitis C infection through past treatment for renal failure

(Issued in letter from Dr Kevin Kelleher to Consultant Nephrologists)

International dialysis/ renal guidelines

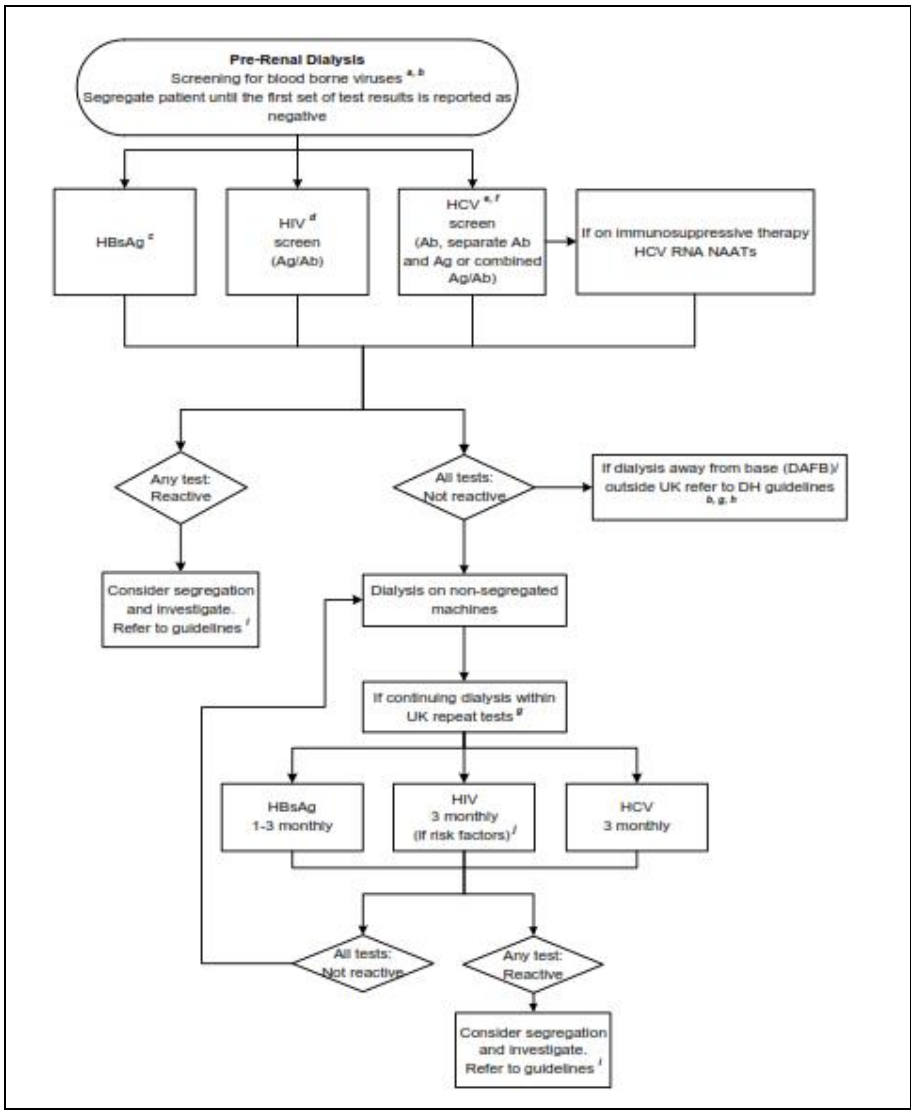
UK Department of Health 2002, Good Practice Guidelines for Renal Dialysis/Transplantation Units Prevention and Control of Blood-borne Virus Infection (2)

- Patients admitted or re-admitted to a unit should be tested for HBsAg, and HCV and HIV antibody, unless they have been tested in the month before admission. Additionally, patients who are HCV antibody negative and are immunosuppressed, have undergone a renal transplant, or are being admitted from a unit where there has been a recent HCV transmission, should be tested for HCV RNA.
- Re-admitted patients who have been dialysed outside the UK should be tested and found negative for HBsAg, HCV antibody and HCV RNA before being dialysed in the main unit. A risk assessment of potential BBV exposure overseas should also be carried out, and where exposure is considered likely, enhanced surveillance for one or more BBVs should be instituted. This should involve testing for HBsAg 2-weekly for 3 months and/or for HCV RNA 2-weekly for 3 months.
- Peritoneal dialysis patients or kidney transplant recipients returning to haemodialysis treatment should be

tested for HBsAg and HCV antibody unless they have been tested in the month before re-admission. As an antibody test result may not be reliable in immunosuppressed patients, transplant patients who are found to be HCV antibody negative should also be tested for HCV RNA before being dialysed in the main unit.

- Patients should be tested for HBsAg and HCV antibody (and HCV RNA if they are HCV antibody negative and immunosuppressed, have undergone a renal transplant, or are being admitted from a unit where there has been a recent HCV transmission). A risk assessment for the likelihood of HIV infection should be carried out, and HIV antibody testing undertaken if indicated.
- Patients who are being treated in dialysis units…should be tested for HCV antibody every 3 months

Public Health England, NHS 2015 UK Standards for Microbiology Investigations Blood Borne Virus Testing in Dialysis Patients(3)



Footnotes:

a) If more than 1 month since negative tests for BBV.

b) Local risk assessment should be carried out based on the patient's history, including where and when dialysed if

outside the UK.

e) Refer to V 5 - Investigation of Hepatitis C Infection by Antibody Testing or Combined Antigen/Antibody Assay.

f) In addition to HCV Ab testing consider HCV Ag/HCV NAAT at start of dialysis and annually.

Renal Association, 2009 (4)

- We recommend that patients on regular hospital haemodialysis should be tested for HCV antibody at least every 6 months.
- We recommend that testing for HCV antibody should be by third generation ELISA.

(*The Renal Association; Blood Borne Virus Infection*)

Kidney Disease: Improving Global Outcomes. KDIGO, 2008 (5)

- It is suggested that CKD patients be tested for HCV. (Weak)
- Testing for HCV should be performed in patients on maintenance hemodialysis (CKD Stage 5D) and kidney transplant candidates. (Strong)
- Patients on hemodialysis should be tested when they first start hemodialysis or when they transfer from another hemodialysis facility. (Strong)
- In hemodialysis units with a low prevalence of HCV, initial testing with EIA (if positive, followed by NAT) should be considered (Moderate)
- In hemodialysis units with a high prevalence of HCV, initial testing with NAT should be considered. (Moderate)
- For patients on hemodialysis who test negative for HCV, retesting every 6–12 months with EIA should be considered. (Moderate)

(*Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of Hepatitis C in chronic kidney disease* (2008))

CDC 2001 (aspects updated 2016)(6)

- Routinely test all chronic hemodialysis patients for HBV and HCV infection
- Routine HCV testing should include use of both an EIA to test for anti-HCV and supplemental or confirmatory testing with an additional, more specific assay
- Use of RT-PCR for HCV RNA as the primary test for routine screening is not recommended because few HCV infections will be identified in anti-HCV negative patients.
- HCV-Negative Patients. Monthly ALT testing will facilitate timely detection of new infections and provide a pattern from which to determine when exposure or infection might have occurred. In the absence of unexplained ALT elevations, testing for anti HCV every 6 months should be sufficient to monitor the occurrence of new HCV infections.

(*CDC; Recommendations for preventing transmission of infections among chronic hemodialysis patients* (2001)).

International hepatitis C guidelines

AASLD, 2013 Any patients who has ever undergone long term haemodialysis should be offered screening for HCV. (*American Association for the Study of Liver Diseases, Recommendations for Testing, Managing, and Treating Hepatitis C (7)*). HIQA Quality Score of 134.5

SIGN, 2013 People on haemodialysis should be offered testing for HCV. (Scottish Intercollegiate Guidelines Network,

Management of Hepatitis C A National Clinical Guideline). HIQA Quality Score of 127.7

KASL, 2016 Anti-HCV testing should be offered to plan further treatment and management in patients preparing for kidney replacement therapy, such as dialysis or kidney transplantation. Any persons undergoing haemodialysis should be offered screening for HCV. (The Korean Association for the Study of the Liver, KASL Clinical Practice Guidelines: Management of Hepatitis C (8)). HIQA Quality Score of 111

CDC, 1998 Any persons who were ever on chronic (long-term) haemodialysis should be offered testing for HCV. (*Center for Disease Control and Prevention, Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease (9)*). HIQA Quality Score of 98

SASLT, 2012 Whoever has undergone haemodialyisis should be offered screening for HCV. (*Saudi Association for the Study of Liver diseases and Transplantation, SASLT Practice Guidelines: Management of Hepatitis C Virus Infection (10)*). HIQA Quality Score of 95.3

NASPGHAN, 2012 Any persons who have ever been on haemodialysis should be offered screening for HCV. In dialysis patients, it is desirable to perform the HCV antibody test at least once every 6 months even if HCV antibody is negative on the initial test. (*North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, NASPGHAN Practice Guidelines: Diagnosis and Management of Hepatitis C Infection in Infants, Children, and Adolescents (11)*). HIQA Quality Score of 88

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.

N/A

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

There is consistency internationally that patients on haemodialysis should be offered regular screening for HCV. The protocol for screening these patients for HCV in Ireland is detailed in national guidelines. Additionally some guidelines state that patients who were ever on dialysis should be screened for HCV.

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

Yes this is the accepted norm internationally.

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

See recommendations from *Blood-Borne Viruses in the Haemodialysis, CAPD and Renal Transplantation Setting July 2014* in section 3

5.3. Epidemiology in Ireland if available and applicable

In the National Hepatitis C Database (for infection acquired through blood and blood products), there are 26 patients who were on renal dialysis for extended periods of time and who may have been infected with hepatitis C in this way. However, the majority of these patients also had multiple blood transfusions before routine HCV screening was introduced and many also had renal transplants, so it is not possible to definitively identify the source of their infection. (Personal communication from database files – Niamh Murphy HPSC. Database website: www.hcvdatabase.ie).

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?

Benefits:

- Detection of HCV infected patients and prevention of transmission within the dialysis unit
- Enables HCV treatment for the identified case
- Screening of historic renal transplant recipients will detect cases possibly infected prior to routine screening and the implementation of the current standards of infection prevention control standards.

Harms:

- Opportunity cost

6.2. What are the likely resource implications and how large are the resource requirements?

Consider cost effectiveness, financial, human and other resource implications

Screening of new and current dialysis patients is current practice and will not have additional resource implications. Screening of historic renal transplant recipients may require some additional resources. These patients will still be attending care so the resource implications are unlikely to be large.

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

Transmission of hepatitis C within the healthcare setting is not considered acceptable. Therefore, any interventions which reduce this risk are likely to be acceptable.

Screening post transplant may cause concern that transmission will be linked to the transplant or surgery. However, the purpose is to detect any cases of transmission from dialysis prior to transplant.

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

Screening of new or current dialysis patients is current practice in Ireland. Once off screening post transplant was recommended by the National Standing Advisory committee in a letter to consultant nephrologists in 2008. It is not known if this advice was implemented.

6.5. What would be the impact on health equity?

Patients in renal failure or post transplant are a vulnerable population with sometimes complex healthcare needs which could be further complicated by hepatitis C infection.

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

Comprehensive screening of patients before starting haemodialysis is important in order to appropriately manage infected patients so as to minimise the risk of transmission to others in the dialysis unit. Regular screening while on dialysis will also detect any transmission events early and allow the appropriate action to be taken.
It is possible for transmission to occur during dialysis just prior to renal transplant. In order to detect any such event one off screening post transplant is considered justified.
There may be people who were on dialysis, and successfully transplanted who were potentially infected prior to the current standards of screening, and infection prevention and control being implemented.

8. Final Recommendations

√ Strong recommendation
□ Conditional/ weak recommendation

Text:

- Patients commencing, or on maintenance, haemodialysis or peritoneal dialysis should be screened according to the current recommendations of the Standing National Advisory Committee on the Prevention of Transmission of Blood-Borne Diseases in the Health-Care Setting and any ensuing updates from this committee
- Current recommendation from the National Advisory Committee include:
- Before starting haemodialysis patients should be tested for anti-HCV, HCV RNA and alanine aminotransferase (ALT). In addition, HCV antigen (Ag) testing may be helpful if the result may be available more quickly than that of an RNA test
- While on HD, patients who have no history of HCV infection should have a monthly ALT; 3 monthly HCV Ag (Abbott Architect) OR HCV RNA; and an annual HCV RNA**.** If HCV Ag (Abbott Architect) is being performed, annual HCV RNA in not required for any patient provided that HCV RNA was not detected during initial laboratory screening.
- Patients with resolved HCV infection should have monthly LT and HCV Ag OR HCV RNA while on HD
- In patients who are immunosuppressed *(*including those who are on immunosuppressive therapy for a renal transplant) a negative RNA test is required prior to dialysis in a multibed unit.
- Patients who have been treated for HCV infection and attain a SVR should be regarded as having resolved HCV infection and tested monthly for HCV antigen OR HCV RNA.
- Patients who are HCV RNA negative at the end of treatment (ETR) can either be
    - Dialysed in an isolation room, if the facilities available, until a SVR is confirmed OR
    - Dialysed in the multi-bedded unit but tested for HCV Ag OR HCV RNA EVERY TWO WEEKS until SVR.
- Patients on CAPD/CCPD should be screened for anti-HCV, HCV Ag (Abbott Architect), HCV RNA and annual anti-HCV, HCV Ag (Abbott Architect) OR HCV RNA

- The following are now recommended for renal transplant patients rather than a recommendation to consider:
  - All patients having a kidney transplant should be test for hepatitis C by the HCV combi test (combined antigen-antibody) or anti-HCV test, AND HCV RNA at 3 month post transplant
  - For patients transplanted before the introduction of the above, unless already known to be HCV infection, should be testing on a one-off basis by the HCV combi test (combined antigen-antibody) or anti-HCV test, AND HCV RNA to out rule the possible acquisition of hepatitis C infection through past treatment for renal failure

9. Justification

In the absence of strict infection prevention and control practices, including appropriate screening, the dialysis setting is a high risk environment for hepatitis C and other BBV transmission. Detection of cases prior to commencing HD will ensure the appropriate procedures are followed to prevent transmission. In patients on haemodialysis, HCV infection is associated with an increased risk for all-cause and liver-related mortality. Detection of cases will also enable the patient to receive appropriate treatment either pre or post transplant as indicated.

Regular screening while on dialysis will also detect any transmission events early and allow the appropriate action to be taken.

It is possible for transmission to occur during dialysis just prior to renal transplant. In order to detect any such event one off screening post transplant is recommended. One off screening is also recommended for those who were on dialysis, and successfully transplanted prior to screening, and the current infection prevention and control standards being implemented.

10. Implementation considerations

Annual audit of compliance with these recommendations should be undertaken by each unit.

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.

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 17

17.1. Patients commencing, or on maintenance, haemodialysis or peritoneal dialysis should be screened according to the current recommendations of the National Standing Advisory Committee on the Prevention of Transmission of Blood-Borne Diseases in the Health-Care Setting and any ensuing updates from this committee.

17.2. All patients having a kidney transplant should be tested for HCV by a combined antigen-antibody test, or anti-HCV test AND HCV-RNA at three months post-transplant.

17.3. Patients transplanted before the introduction of the above, unless already known to be HCV positive, should be tested on a one-off basis by a combined antigen-antibody test, or anti-HCV test AND HCV-RNA to out rule the possible acquisition of HCV infection through past treatment for renal failure.

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

Strength of recommendation: strong

References List

1. Subgroup of the Standing Advisory Committee on the Prevention of Transmission of Blood-Borne Diseases in the Health-Care Setting. Blood borne viruses in the haemodialysis, CAPD and renal transplantation setting, July 2014. Dublin: HSE HPSC; 2014. Available from: https://www.hpsc.ie/A-Z/Hepatitis/HepatitisC/Guidance/File,4374,en.pdf.
2. Good Practice Guidelines for Renal Dialysis/Transplant Units: Prevention and Control of Blood-Borne Virus Infection. Department of Health; 2002.
3. UK Standards for Microbiology Investigations; Blood Borne Virus Testing in Dialysis Patients Version 10 Issue 2. Public Health England; 2015. Available from: http://www.apsi.it/public/ufiles/smi/v10_2_en_150427.pdf.
4. Blood Borne Virus Infection. Renal Association; 2009.
5. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. 2008(109):S1-99.
6. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recomm Rep. 2001;50(Rr-5):1-43.
7. American Association for the Study of Liver Disease. HCV guidance: recommendations for testing, managing, and treating hepatitis C. AASLD; 2016. Available from: http://www.hcvguidelines.org/full-report/website-policies.
8. Korean Association for the Study of the Liver. KASL clinical practice guidelines: management of hepatitis C. Clin Mol Hepatol. 2014;20(2):89-136.
9. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998;47(Rr-19):1-39.
10. Alghamdi AS, Sanai FM, Ismail M, Alghamdi H, Alswat K, Alqutub A, et al. SASLT practice guidelines for the management of hepatitis C virus infection: summary of recommendations. Saudi J Gastroenterol. 2012;18(5):293-8.
11. Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA, et al. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr. 2012;54(6):838-55.

Appendices

Evidence search and results

International and national guidelines

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

Other guidelines reviewed

Dialysis guidelines identified by expert GDG members.

Grey literature

Nil used.

Primary literature

Nil used.