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PRACTICE

GUIDELINES

Assessment and management of cirrhosis in people older than 16 years: summary of NICE guidance

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Clinical identification of cirrhosis remains imperfect, especially in people with compensated disease who are often asymptomatic. There is considerable variation in practice across England and Wales with regard to who is tested for cirrhosis and the diagnostic tests used.[1] We provide guidance to aid diagnosis of cirrhosis, referral to specialist care for those at high risk of liver decompensation before they experience a defining event, and management of people with cirrhosis, including surveillance for and treatment of complications.

Liver disease is the third most common cause of premature death in the UK. In England and Wales 60 000 people (1 in 1000) have cirrhosis, and mortality rates have increased by 400% since the 1970s.[2] Liver biopsy was historically the standard test for the diagnosis of cirrhosis for all causes of liver disease. However, liver biopsy is associated with complications, such as pain and bleeding; it is an expensive test and is less acceptable to patients because of the morbidity associated with its use.[3] New diagnostic technologies such as transient elastography and acoustic radiation force impulse imaging can diagnose cirrhosis with >90% sensitivity, and mean that it is now practical and acceptable to offer testing to a greater number of people.

The Guideline Development Group (GDG) believe that

- Earlier diagnosis of cirrhosis may offer more opportunity for treatments, limiting disease progression and avoiding complications.
- These recommendations—particularly early diagnosis, effective surveillance, and early access to specialist care—will be measured by a long term reduction in hospital admissions and liver related mortality over the next 10-20 years.
- These recommendations—some of which will involve implementation costs for commissioners—are in the best interests of people with cirrhosis and will contribute significantly to the long term health of the nation.

This article summarises the most recent recommendations on the diagnosis and management of cirrhosis from the National Institute for Health and Care Excellence (NICE).[4]

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the GDG's experience and opinion of what constitutes good practice.

Diagnosis

Routine liver blood tests and ultrasound examinations are not sensitive for the detection of cirrhosis. Transient elastography and acoustic radiation force impulse use a form of ultrasound to send a sheer wave impulse through the liver and measure its "stiffness," which is a surrogate for fibrosis.[5] Their performance is established particularly in specialist settings, and the GDG does not expected it to differ in other settings assuming appropriate education is offered to non-specialists.

The infographic shows the recommended tests for detecting and monitoring cirrhosis

- Do not use routine laboratory liver blood tests to rule out cirrhosis. *[Based on cost effectiveness analysis, and the experience and opinion of the GDG]*

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Data supplements on bmj.com (see http://www.bmj.com/content/354/bmj.i2850?tab=related#datasupp)

Infographic of tests for detecting and monitoring cirrhosis
Authors' competing interests statements

What you need to know

- Offer testing for cirrhosis to those at higher risk, including those with:
  - Hepatitis C
  - Alcohol related liver disease
  - Non-alcoholic fatty liver disease and advanced liver fibrosis
  - Alcohol intake >50 units per week in men and >35 units in women for several months
- Non-invasive transient elastography or acoustic radiation force impulse imaging is the first line investigation
- Refer those with cirrhosis to a hepatologist

Related guidance from NICE

For people with hepatitis B or non-alcoholic fatty liver disease please follow alternate guidance:

- Hepatitis B (chronic): diagnosis and management (clinical guideline 165). 2013. www.nice.org.uk/guidance/cg165
- Non-alcoholic fatty liver disease (NAFLD) (NICE guideline 49). 2016. www.nice.org.uk/guidance/ng49

Review intravenous antibiotics prescriptions in line with the "Prescribing intravenous antimicrobials" section in NICE guideline NG15:

- Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NICE guideline 15). 2015. www.nice.org.uk/guidance/ng15

- Offer transient elastography to diagnose cirrhosis for: people with hepatitis C virus infection; men who drink >50 units of alcohol a week and women who drink >35 units per week and have done so for several months; and people diagnosed with alcohol related liver disease. *[Based on moderate to very low quality evidence from diagnostic accuracy studies, cost effectiveness analysis, and the experience and opinion of the GDG]*
- Offer either transient elastography or acoustic radiation force impulse imaging (whichever is available) to diagnose cirrhosis for people with non-alcoholic fatty liver disease and advanced liver fibrosis (as diagnosed by a score of ≥10.51 using the enhanced liver fibrosis test). (Also see the "Diagnosing advanced liver fibrosis" section in NICE guideline NG49 (Non-alcoholic fatty liver disease (NAFLD).[6]) *[Based on very low quality evidence from diagnostic accuracy studies, cost effectiveness analysis, and the experience and opinion of the GDG]*
- Consider liver biopsy to diagnose cirrhosis in people for whom transient elastography is not suitable. *[Based on cost effectiveness analysis, and the experience and opinion of the GDG]*
- Do not offer tests to diagnose cirrhosis for people who are obese (body mass index ≥30) or have type 2 diabetes unless they have non-alcoholic fatty liver disease and advanced liver fibrosis (as diagnosed by a score of ≥10.51 with the enhanced liver fibrosis test). *[Based on the experience and opinion of the GDG]*

Referral

- Refer people diagnosed with cirrhosis to a specialist in hepatology. *[Based on the experience and opinion of the GDG]*

Retesting

- Offer retesting (using the same diagnostic test as recommended above for each aetiology) every two years for:
  - People diagnosed with alcohol related liver disease
  - People with hepatitis C virus infection who have not shown a sustained virological response to antiviral therapy
  - People with non-alcoholic fatty liver disease and advanced liver fibrosis (diagnosed by score ≥10.51 with the enhanced liver fibrosis test). (Also see "Diagnosing advanced liver fibrosis" in NICE guideline NG49.[6])

  [Based on cost effectiveness analysis, and the experience and opinion of the GDG]

Monitoring

After review in secondary care, monitoring of cirrhosis—using blood test markers such as serum bilirubin, sodium, creatinine, international normalised ratio (INR), and α fetoprotein as well as ultrasound imaging and upper gastrointestinal endoscopy—will be undertaken as part of a shared care agreement between primary and secondary care services, dependent on local management pathways.

Risk of complications

- Calculate the Model for End-Stage Liver Disease (MELD) score every six months for people with compensated cirrhosis.
- Consider using a MELD score of ≥12 as an indicator that the person is at high risk of complications of cirrhosis.
- Refer people who have, or are at high risk of, complications of cirrhosis to a specialist hepatology centre.

  [Based on low to high quality observational studies and the experience and opinion of the GDG]

Hepatocellular carcinoma

- Offer ultrasound imaging (with or without measurement of serum α fetoprotein) every six months as surveillance for hepatocellular carcinoma in people with cirrhosis who do not have hepatitis B virus infection. *[Based on very low to moderate quality observational and randomised studies, cost effectiveness analysis, and the experience and opinion of the GDG]*
- Do not offer surveillance for hepatocellular carcinoma for people who are receiving end of life care. *[Based on the experience and opinion of the GDG]*

Oesophageal varices

- Offer upper gastrointestinal endoscopy, after a diagnosis of cirrhosis, to detect oesophageal varices. *[Based on the experience and opinion of the GDG]*
- For people in whom no oesophageal varices have been detected, offer surveillance with upper gastrointestinal endoscopy every three years. *[Based on cost effectiveness analysis and the experience and opinion of the GDG]*
- Offer endoscopic variceal band ligation for the primary prevention of bleeding for people with cirrhosis who have medium to large oesophageal varices. *[Based on very low to moderate quality randomised studies]*
- Offer prophylactic intravenous antibiotics for people with cirrhosis who have upper gastrointestinal bleeding. *[Based on very low to moderate quality randomised studies and the experience and opinion of the GDG]*

Ascites

- Consider a transjugular intrahepatic portosystemic shunt for people with cirrhosis who have refractory ascites. *[Based on very low to moderate quality randomised studies and the experience and opinion of the GDG]*
- Offer prophylactic oral ciprofloxacin or norfloxacin for people with cirrhosis and ascites with an ascitic protein concentration of ≤15 g/L, until the ascites has resolved. *[Based on very low to high quality randomised studies and the experience and opinion of the GDG.]*

Implementation

Several recommendations in this guidance require additional resources, which may present a barrier to their uptake.

- Currently only a small percentage of people who drink at harmful levels or who have non-alcoholic fatty liver disease and advanced liver disease are tested for cirrhosis.
- Although hepatocellular carcinoma surveillance is routinely offered, additional resources may be necessary to provide it every six months.
- Variceal banding is not routinely offered as a preventive measure in people with medium to large oesophageal varices.

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Competing interests: We declare the following interests based on NICE's policy on conflicts of interests (available at: www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/Code-of-practice-for-declaring-and-managing-conflicts-of-interest.pdf): BJH is a co-investigator on a national trial of stents for treating variceal haemorrhage that receives funding from the stent manufacturer and from the NIHR, has participated in research on biomarkers of portal hypertension, and received accommodation and travel expenses from Gilead to attend a “HCV and transplantation” preceptorship in 2015. The authors’ full statements can be viewed at: www.bmj.com/content/bmj/354/bmj.i2850/related#datasupp.

1 RightCare. The NHS atlas of variation in healthcare for people with liver disease: Reducing unwarranted variation to increase value and improve quality. 2013. www.rightcare.nhs.uk/index.php/atlas/liver-disease-nhs-atlas-of-variation-in-healthcare-for-people-with-liver-disease/.

2 Williams R, Aspinall R, Bellis M, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* 2014;384:1953-97. doi:10.1016/S0140-6736(14)61838-9 pmid:25433429.

3 European Association for Study of Liver Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015;63:237-64. doi:10.1016/j.jhep.2015.04.006 pmid:25911335.

4 National Institute for Health and Care Excellence. Assessment and management of cirrhosis (clinical guideline NG50). 2016. www.nice.org.uk/guidance/ng50.

5 Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003;29:1705-13. doi:10.1016/j.ultrasmedbio.2003.07.001 pmid:14698338.

6 National Institute for Health and Care Excellence. Non-alcoholic fatty liver disease (NAFLD) (clinical guideline NG49). 2016. www.nice.org.uk/guidance/ng49.

How patients were involved in the creation of this article

The Guideline Development Group included one patient representative and one representative from a national liver patient support group, who helped to formulate the recommendations summarised here.

Further information on the guidance

Methods

The guideline was developed by the National Clinical Guideline Centre using standard National Institute for Health and Care Excellence (NICE) methods (www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview). The guideline review process involved systematic literature searches to identify relevant evidence for the clinical and economic reviews. Results of intervention studies were compared using pairwise meta-analyses. Results of diagnostic studies were compared with a focus on the sensitivity and specificity of each diagnostic test, with a reference standard of liver biopsy. GRADE methodology was also applied to develop quality ratings for the body of evidence (www.gradeworkinggroup.org). A health economic model was developed to compare the cost effectiveness of different diagnostic testing strategies for cirrhosis and for the frequency of surveillance of complications.

A multidisciplinary team of healthcare professionals (forming the Guideline Development Group) was established to review and interpret the evidence and to develop the recommendations and research recommendations. The GDG comprised three consultant hepatologists, a general practitioner, two clinical nurse specialists, a principal research associate and honorary consultant physician, a lead pharmacist in hepatology, and two patient or lay members. Members with a potential conflict of interest relating to specific aspects of the guideline did not participate in these discussions.

The draft guideline then went through an external consultation with stakeholders. Stakeholders were invited to comment, and all comments were considered by the GDG when producing the final version of the guideline.

NICE has produced four different versions of the guidance: a full version; a summary version known as the “NICE guidance”; a pathway; and a version for people using NHS services, their families and carers, and the public (www.nice.org.uk/guidance/NG50/ifp/chapter/about-this-information). All these versions, together with tools to help with implementation of the guidance, are available from the NICE website (www.nice.org.uk/guidance/ng50). Further updates of the guidance will be produced as part of NICE’s guideline development programme.

Future research

- Can a risk tool to identify people who should be offered assessment for cirrhosis be developed from an existing population of people with cirrhosis?
- In people with small varices, should β blockers or alternative strategies to lower portal pressure be offered to reduce bleeding and liver related mortality?
- How often does antibiotic resistance occur in patients with previous spontaneous bacterial peritonitis who are taking long term prophylaxis?
- What is the quality of life benefit for people with cirrhosis and refractory ascites who choose transjugular intrahepatic portosystemic shunt over large volume paracentesis?
- What is the most clinically and cost effective volume replacer for patients with hepatorenal syndrome due to cirrhosis who are also receiving vasoactive drugs?
- In people with cirrhosis and an acute episode of hepatic encephalopathy secondary to a clearly identified, potentially reversible precipitating factor, does management of the precipitating event alone improve the hepatic encephalopathy without specific treatment?