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*Guidelines*

# Cirrhosis in over 16s: assessment and management—updated summary of NICE guidance

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**Box start**

**What you need to know**

- Non-selective beta blockers (NSBB) are likely to prevent or delay decompensation in people with cirrhosis and clinically significant portal hypertension
- NSBBs can be used safely in people with cirrhosis but need to be used with caution and should be started at low doses
- NSBBs are as effective as endoscopic variceal band ligation for preventing oesophageal variceal bleeding, and are more cost effective
- Routine prophylactic antibiotics are unlikely to be effective in preventing spontaneous bacterial peritonitis

**Box end**

Liver cirrhosis affects 110 people per 100 000 in the UK[1] and is closely linked with deprivation. The British Liver Trust[2] estimates premature deaths from liver disease to be four times higher in the most deprived areas compared with the most affluent. Early identification and management can delay decompensation events such as variceal bleeding, ascites, and hepatic encephalopathy, leading to longer, better quality life for people with liver disease.

In 2015, the National Institute for Health and Care Excellence (NICE) first published guidance on the assessment and early management of cirrhosis in people over 16. This article summarises updated 2023 recommendations, focusing on managing complications, and appraises new evidence related to the effectiveness of non-selective beta blockers (NSBB) for the primary prevention of decompensation in people with cirrhosis.[3] The new guidance also updates recommendations about prevention of variceal bleeding in people with cirrhosis and

medium or large oesophageal varices, and the primary prevention of spontaneous bacterial peritonitis in people with cirrhosis and ascites.

## 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 guideline committee's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italics in square brackets. Definitions of evidence certainty are given in box 1.

**Box start**

**Box 1 GRADE Working Group grades of evidence**

High certainty—we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Box end**

## Primary prevention of decompensation

NSBBs, most commonly carvedilol and propranolol, are frequently prescribed by clinicians to prevent oesophageal variceal bleeding. New evidence from a randomised controlled trial (RCT) in Spain[4] and from an individual patient data meta-analysis of four RCTs[5] showed that NSBBs could be useful in delaying or preventing decompensation, mainly by reducing incidence of ascites, in people with clinically significant portal hypertension. In both studies, patients with compensated cirrhosis who had clinically significant portal hypertension, as determined directly by measurement of hepatic venous pressure gradient or indirectly by assessing for presence of varices, received either an NSBB (propranolol, carvedilol *v* placebo in the RCT, or carvedilol *v* either placebo or endoscopic variceal band ligation in the individual patient data meta-analysis).

A review of the evidence showed that the risk of decompensation or death was numerically, but not statistically lower in patients who received an NSBB compared with placebo (relative risk (RR) 0.6, 95% confidence interval (CI) 0.34 to 1.04); carvedilol (RR 0.33 (0.1 to 1.12)), and for propranolol (RR 0.73 (0.39 to 1.37). The individual patient data

meta-analysis found a sub-distribution hazard ratio for decompensation of 0.506 (95% CI, 0.289 to 0.887) for carvedilol *v* control.[5] Overall, there was more evidence for use of carvedilol compared with propranolol because the individual patient data meta-analysis included patients who were treated with carvedilol only.

In the UK, direct measurement of hepatic venous pressure gradient, which was used to diagnose clinically significant portal hypertension in the RCT and in one of the trials within the individual patient data, is not undertaken in practice routinely. Therefore, the decision about whether a person is likely to have clinically significant portal hypertension remains a clinical one that might be informed by tests of liver stiffness, presence of collaterals or splenomegaly on ultrasound imaging, or biomarkers (for example, platelet count <150 or emerging tests such as osteopontin or Von Willebrand factor).

- For people who have cirrhosis and confirmed or suspected clinically significant portal hypertension (for example, as indicated by a hepatic venous pressure gradient of more than 10 mm Hg or the presence of small oesophageal varices), consider the following options for the primary prevention of decompensation:
  - Carvedilol as the first choice treatment because it has fewer side effects and a greater effect on portal vein pressure, or
  - Propranolol as the second choice treatment if carvedilol is contraindicated.

  *[Recommendations based on low to moderate quality evidence from a randomised controlled trial and an individual patient data meta-analysis, economic modelling results, and on the committee's experience and expertise]*

## Preventing bleeding from varices

Endoscopic band ligation remains the current standard practice for preventing bleeding from varices. Evidence from 18 RCTs that compared endoscopic variceal band ligation with NSBBs for preventing oesophageal variceal bleeding in people with medium or large varices was reviewed. All the trials used propranolol or carvedilol in the NSBB arm. There were no clinically significant differences between the two treatment modalities across multiple outcomes assessed, including mortality (pooled RR 0.99, 95%CI 0.83 to 1.58 from meta-analysis of six RCTs) and variceal bleeding (pooled RR 0.86, 95%CI 0.52 to 1.43 from meta-analysis of 10 studies).[6] The evidence, however, was rated low or very low confidence using GRADE assessment.

However, NSBB was much more cost effective than endoscopic band ligation. An economic analysis developed for this guideline, based on the outcomes of the evidence review, found little difference between band ligation and NSBBs regarding the impact on quality of life as a result of averted variceal bleeds and early mortality. However, band

ligation is a more expensive treatment option than NSBBs and requires additional resources for the endoscopic surveillance to detect new varices.

A person's lifestyle factors are therefore an important part of the treatment choice. Usually, most people would prefer an NSBB because it is less invasive. However, some people might not have a lifestyle where they could easily access daily medication, and therefore for those people, endoscopic band ligation might be their preferred option.

If the person with cirrhosis has medium or large oesophageal varices:

- Discuss the benefits and harms of all treatment options in line with NICE's guidelines on shared decision making[7] and patient experience in adult NHS services[6]
- Explain what treatment involves and ask about any potential barriers that could prevent the person from accessing treatment (for example, they may find it difficult to take tablets regularly because they are dependent on alcohol or are experiencing homelessness)
- For people with medium or large oesophageal varices, offer:
  - Carvedilol or propranolol, or
  - Endoscopic variceal band ligation, if either carvedilol or propranolol are not tolerated or contraindicated, or the person cannot take tablets regularly because of their circumstances.

    *[Recommendations based on very low and low quality evidence from randomised controlled trials, economic modelling results, and on the committee's experience and expertise]*

## Prescribing carvedilol and propranolol

In practice, clinicians tend to prefer carvedilol over propranolol because it has anti-adrenergic vasodilatory effects in addition to beta blockade that may make it more effective at reducing portal hypertension.

The recommendation to avoid carvedilol use in people with severe hepatic impairment was maintained in this update, in line with current licensing information in the British National Formulary (BNF)[8] However, the guideline committee acknowledged that carvedilol continues to be widely used in this patient group because both clinical experience and very low quality evidence suggest that it might be more effective than propranolol. Further review by the Medicines and Healthcare products Regulatory Agency is awaited.

- Be aware that:
  - Carvedilol and propranolol should be used with caution in people with cirrhosis because they can have a greater effect on heart rate and blood pressure
  - Carvedilol should be avoided in people with severe hepatic impairment (for example, in those with large volume or refractory ascites).
- When starting treatment with either carvedilol or propranolol in people with cirrhosis to prevent decompensation or bleeding from medium or large varices:
  - Use a low dosage (for example, 6.25 mg a day for carvedilol or 40 mg twice a day for propranolol) and

- Increase or decrease the dose depending on the results of heart and blood pressure monitoring.

  *[Recommendations based on prescribing advice from the BNF, the committee's expertise and experience in prescribing these drugs in people with cirrhosis, and the dosages used in the trial included in the evidence reviews]*

## Preventing spontaneous bacterial peritonitis

Updated evidence for the use of antibiotics to prevent spontaneous bacterial peritonitis (SBP) in people with ascites from a 2020 Cochrane network meta-analysis of 23 RCTs comparing the effectiveness of different antibiotics in preventing spontaneous bacterial peritonitis was reviewed.[9] Confidence in the evidence was assessed as being low and very low using GRADE, and overall the review did not show that antibiotics were effective at preventing spontaneous bacterial peritonitis. Consistent with the authors' conclusions, the guideline committee did not have enough confidence in the evidence to make a strong recommendation to not prescribe antibiotics.

Therefore, the existing recommendation was updated to make it clearer that clinicians should not give people with ascites antibiotics to prevent SBP routinely, but there were potential exceptions. There is no preferred choice of antibiotic.

- Do not routinely offer antibiotics to prevent SBP in people with cirrhosis and ascites.
- Consider antibiotics to prevent SBP only if:
  - The person is at high risk of developing SBP because they have severe liver disease (for example, they have an ascitic protein of 15 g per litre or less, a Child-Pugh score of more than 9, or a model for end-stage liver disease score of more than 16) or
  - The consequences of an infection could seriously impact the person's care, for example, if it could affect their wait for a transplant or a transjugular intrahepatic portosystemic stent insertion.
- When offering antibiotics to prevent SBP:
  - Follow local microbiological advice (in line with the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use[10])
  - Continue with treatment until the ascites is resolved.

    *[Recommendations based on very low and low quality evidence from a Cochrane network meta-analysis, and on the committee's experience and expertise]*

## Implementation

Use of NSBBs to prevent or delay decompensation is novel, not yet well established, and therefore uncommon practice in the UK. The recommendation may lead to an increase in prescriptions for this indication by specialists, with shared care oversight by primary care practitioners.

The updated recommendation of prescribing NSBBs to prevent variceal bleeding will reduce the number of endoscopic variceal band ligation procedures performed, thereby allowing clinician time and hospital resources to be more used for alternative procedures. Against this, the number of people who choose, or require, endoscopic variceal band ligation, and the impact on resources, remain unknown.

Concerns were raised that the contraindication for carvedilol use in severe hepatic dysfunction might lead to primary care physicians declining to prescribe it for people with cirrhosis who are eligible for this treatment. The aim of the updated recommendations is to increase appropriate prescribing of this medication by secondary care physicians and to inform primary care physicians that they may be asked to order repeat prescriptions.

## Future research

The guideline committee noted the BOPPP[11] and ASEPTIC trials,[12] which will provide useful evidence for future updates of these recommendations.

The guideline committee prioritised the following questions for further research:

- What is the effectiveness and cost effectiveness of endoscopic variceal band ligation plus a non-selective beta blocker compared with either of these interventions alone for preventing variceal bleeding in adults with cirrhosis and medium or large oesophageal varices?
- What is the clinical and cost effectiveness of antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with cirrhosis and ascites?
- What is the clinical and cost effectiveness of non-selective beta blockers for the primary prevention of decompensation in people with compensated cirrhosis and signs of clinically significant portal hypertension from non-invasive tests (such as tests to measure liver stiffness, or biomarkers)?

**Box start**

### Guidelines into practice

- How would you choose between different NSBBs for a patient with cirrhosis who you have assessed as being at high risk of decompensation?
- Under what circumstances would you prescribe antibiotics to prevent spontaneous bacterial peritonitis?

**Box end**

**Box start**

### Further information on the guidance

This guidance was developed by NICE's Guideline Development Team B and an expert committee in accordance with NICE guideline methodology (https://www.nice.org.uk/process/pmg20/chapter/introduction). The guideline committee (GC) was established by the Guideline Development Team, and incorporated an independent chair, a topic adviser (consultant hepatologist), and healthcare and allied healthcare professionals (two consultant hepatologists, a nurse specialist, a specialist pharmacist, and a consultant microbiologist) and two lay members.
The guideline is available at https://www.nice.org.uk/guidance/ng50

The GC identified relevant review questions and collected and appraised clinical and cost effectiveness evidence. Quality ratings of the evidence were based on GRADE methodology (www.gradeworkinggroup.org). These relate to the quality of the available evidence for assessed outcomes or themes rather than the quality of the study. The GC agreed recommendations for clinical practice based on the available evidence or, when evidence was not found, based on their experience and opinion using informal consensus methods. Original economic modelling was undertaken in priority areas not sufficiently addressed by the published cost effectiveness literature.
The scope and the draft of the guideline went through a rigorous reviewing process, in which stakeholder organisations were invited to comment; the GC took all comments into consideration when producing the final version of the guideline.
NICE will conduct regular reviews after publication of the guidance, to determine whether the evidence base has progressed significantly enough to alter the current guideline recommendations and require an update.
**Box end**

**Box start**
**How patients were involved in the creation of this article**
Committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.
**Box end**

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The guideline authors' full statements can be viewed at https://www.nice.org.uk/guidance/indevelopment/gid-ng10355/documents

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CC is the guarantor for this article.

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