

Cirrhosis in over 16s: assessment and management (update)

NICE guideline: methods

NICE guideline NG50

Methods

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Contents

Development of the guideline	5
What this guideline covers	5
What this guideline does not cover	5
Methods	6
Developing the review questions and outcomes	6
Reviewing research evidence	6
Review protocols	6
Searching for evidence	6
Selecting studies for inclusion.....	6
Incorporating published evidence syntheses	6
Methods of combining evidence.....	9
Data synthesis for intervention studies	9
Appraising the quality of evidence	10
Intervention studies (relative effect estimates).....	10
Interpretation of effect	12
Reviewing economic evidence.....	12
Inclusion and exclusion of economic studies	12
Appraising the quality of economic evidence.....	12
References.....	13

Development of the guideline

What this guideline covers

This guideline covers parts of section 1.3 of the guideline “Managing complications”.

It updates recommendations on

1. Endoscopic variceal band ligation vs. non-selective beta-blockers for the prevention of variceal bleeding in people with cirrhosis and medium/large oesophageal varices.
2. The primary prevention of spontaneous bacterial peritonitis using antibiotics in people with cirrhosis and ascites

And adds new recommendations on

3. The primary prevention of decompensation in people with compensated cirrhosis using non-selective beta-blockers.

What this guideline does not cover

This guideline does not update other sections of the guideline, nor does it update recommendations in section 1.3 relating to upper gastrointestinal bleeding, or transjugular intrahepatic portosystemic shunts for people with cirrhosis who have refractory ascites

Methods

This guideline was developed using the methods described in the [2022 NICE guidelines manual](#).

Declarations of interest were recorded according to the [NICE conflicts of interest policy](#).

Developing the review questions and outcomes

The 1 review question developed for this guideline was based on the key areas identified in the guideline [scope](#). It was drafted by the NICE guideline development team and refined and validated by the guideline committee.

The review question was based on the Population, Intervention, Comparator and Outcome [and Study type] (PICO[S]) framework.

Full literature searches, critical appraisals and evidence reviews were completed for the review question.

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the [PROSPERO register of systematic reviews](#).

Searching for evidence

Evidence was searched for each review question using the methods specified in the [2022 NICE guidelines manual](#).

Selecting studies for inclusion

All references identified by the literature searches and from the previous version of the guideline were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

Incorporating published evidence syntheses

If published evidence syntheses (including meta-analyses and network meta-analyses) were identified sufficiently early in the review process (for example, from

the surveillance review or early in the database search), they were considered for use as the primary source of data, rather than extracting information from primary studies. Syntheses considered for inclusion in this way were quality assessed to assess their suitability using the appropriate checklist, as outlined in

Table 1. Note that this quality assessment was solely used to assess the quality of the synthesis in order to decide whether it could be used as a source of data, as outlined in Table 2, not the quality of evidence contained within it, which was assessed in the usual way as outlined in the section on 'Appraising the quality of evidence'.

Table 1: Checklists for published evidence syntheses

Type of synthesis	Checklist for quality appraisal
Systematic review of quantitative evidence	ROBIS
Network meta-analysis	Modified version of the PRISMA NMA tool (see appendix K of ‘Developing NICE guidelines, the manual’)
Qualitative evidence synthesis	ENTREQ reporting standard for published evidence synthesis (https://bmcmmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-12-181) is the generic reporting standard for QES, however specific reporting standards exist for meta-ethnography (eMERGe [https://emergeproject.org/]) and for realist synthesis (RAMESES II [https://www.ramesesproject.org/]). If these reporting standards are not appropriate to the QES then an adapted PRISMA framework is used (see Flemming K, Booth A, Hannes K, Cargo M, Noyes J. Cochrane Qualitative and Implementation Methods Group guidance series-paper 6: reporting guidelines for qualitative, implementation, and process evaluation evidence syntheses. <i>Journal of Clinical Epidemiology</i> 2018; 97: 79-85).
Individual patient data meta-analysis	Checklist based on Tierney, Jayne F., et al. "Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use." <i>PLoS Med</i> 12.7 (2015): e1001855.

Each published evidence synthesis was classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each published evidence synthesis was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.

- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

The way that a published evidence synthesis was used in the evidence review depended on its quality and applicability, as defined in Table 2. When published evidence syntheses were used as a source of primary data, data from these evidence syntheses were quality assessed and presented in GRADE/CERQual tables in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were checked to ensure none of the data had been double counted through this process.

Table 2: Criteria for using published evidence syntheses as a source of data

Quality	Applicability	Use of published evidence synthesis
High	Fully applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted.
High	Partially applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted. For other sections not covered by the evidence synthesis, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the evidence synthesis, searches were undertaken as normal.

Methods of combining evidence

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. Network meta-analyses was considered in situations where there were at least 3 treatment alternatives. When there were 2 treatment alternatives, pairwise meta-analysis was used to compare interventions.

Pairwise meta-analysis

Pairwise meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 4.1.0. using the package 'metafor'. A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

A pooled mean difference was calculated for continuous outcomes (using the inverse variance method) when the same scale was used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences.

For continuous outcomes analysed as mean differences, change from baseline values were used in the meta-analysis if they were accompanied by a measure of spread (for example standard deviation). Where change from baseline (accompanied by a measure of spread) were not reported, the corresponding values at the timepoint of interest were used. If only a subset of trials reported change from baseline data, final timepoint values were combined with change from baseline values to produce summary estimates of effect. For continuous outcomes analysed as standardised mean differences this was not possible. In this case, if all studies reported final timepoint data, this was used in the analysis. If some studies only reported data as a change from baseline, analysis was done on these data, and for studies where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient derived from studies reporting both baseline and endpoint data, or if no such studies were available, assuming a correlation of 0.5 as a conservative estimate (Follman et al., 1992; Fu et al., 2013).. In cases where SMDs were used they were back converted to a single scale to aid interpretation by the committee where possible, and when it was considered useful for decision making.

Random effects models were fitted when significant between-study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken. For all other syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in

the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses were less heterogeneous (with $I^2 < 50\%$) the results from these subgroups were reported using fixed effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes.

For continuous outcomes expressed as a mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For relative risks and hazard ratios, where no other clinical decision threshold was available, a default clinical decision threshold for dichotomous outcomes of 0.8 to 1.25 was used. Odds ratios were converted to risk ratios before presentation to the committee to aid interpretation.

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials, non-randomised controlled trials and cohort studies (which were quality assessed using the Cochrane risk of bias tool or ROBINS-I) were initially rated as high quality while data from other study types were initially rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 3. These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 3: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	<p>Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.</p> <p>Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.</p> <p>Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.</p>
Indirectness	<p>Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.</p> <p>Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.</p> <p>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.</p>
Inconsistency	<p>Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic.</p> <p>Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded.</p>

GRADE criteria	Reasons for downgrading quality
	<p>Serious: If the I^2 was between 33.3% and 66.7%, or if the outcome only contained data from a single study, the outcome was downgraded one level.</p> <p>Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.</p>
Imprecision	<p>The outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID.</p> <p>Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.</p>
Publication bias	<p>Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.</p>

Interpretation of effect

A column was added to the GRADE summary of findings table for each outcome detailing an interpretation of effect based on the following criteria:

Pooled effect estimate and confidence intervals do not cross the line of no effect interpreted as '**Favours x**'.

Confidence intervals cross line of no effect interpreted as '**unable to differentiate**'.

Reviewing economic evidence

Inclusion and exclusion of economic studies

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included.

Appraising the quality of economic evidence

Economic studies identified through a systematic search of the literature were appraised using a methodology checklist designed for economic evaluations (NICE

guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 4.

Table 4 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 5.

Table 5 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

References

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