NICE National Institute for Health and Care Excellence

Appendix A: Summary of evidence from surveillance

2020 surveillance of Cirrhosis in over 16s: assessment and management (2016) NICE guideline NG50

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts was considered alongside the evidence to reach a view on the need to update each section of the guideline.

Diagnosis

Surveillance proposal

This section of the guideline should not be updated.

Risk factors and risk assessment tools

2020 surveillance summary

Risk factors

We identified 1 systematic review of case control and cohort studies (1) which considered alcohol consumption (see Table 1 below).

Table 1 – Risk factors and populations at risk of cirrhosis: alcohol consumption

Study	Type	Population	n	Confounders	Risk factor/ outcomes	Result
(1)	SR	women	(9 studies) 2.6million	NR	Women 5-6 drinks per day/ long-term abstainers (duration not specified)	RR = 12.44 (95% CI: 6.65 to 23.27)
(1)	SR	women	(9 studies) 2.6million	NR	Women ≥7 drinks per day/ long-term abstainers	RR = 24.58 (95% CI: 14.77 to 40.90)

Study	Type	Population	n	Confounders	Risk factor/ outcomes	Result
(1)	SR	men	(9 studies) 2.6million	NR	Men 5-6 drinks per day/ long-term abstainers	RR = 3.80 (95% CI: 0.85 to 17.02)
(1)	SR	men	(9 studies) 2.6million	NR	Men ≥7 drinks per day/ long-term abstainers	RR = 6.93 (95% CI: 1.07 to 44.99)

Abbreviations: SR - systematic review; RR – relative risk; CI – confidence interval; NR – not reported.

Risk assessment tools

In addition to outlining risk factors for people with an increased risk of cirrhosis, the guideline committee sought to identify people at risk of having cirrhosis before they developed evidence of liver decompensation and to determine whether there are any validated risk tools that identify these populations. At the time of guideline development, no validated risk tools were identified from the literature. Similarly, during the current surveillance review we did not identify any studies that validated risk tools that indicate populations at specific risk for cirrhosis.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

Recommendation 1.1.1 identifies populations at increased risk of cirrhosis and includes people who misuse alcohol. New evidence was identified from 1 systematic review which focused on alcohol consumption and investigated the association of factors relating to future development of cirrhosis. The systematic review identified a higher risk of cirrhosis in men and women who regularly drink alcohol; it also noted a higher risk in women than men, at the same alcohol consumption levels.

NICE guideline NG50 identifies an increased risk of cirrhosis in people who misuse alcohol. The new evidence is consistent with the guidance and no impact is anticipated.

New evidence is unlikely to impact on the guideline.

Diagnostic tests

2020 surveillance summary

Twenty-six prospective and retrospective diagnostic test accuracy (DTA) studies (including 9 systematic reviews of DTAs) were included in the current surveillance review covering 6 aetiologies of cirrhosis. Four studies covered autoimmune liver disease/hepatitis, 5 for hepatitis C population (HCV), 6 for non-alcoholic fatty liver disease (NAFLD) population, 2 for HCV/HIV co-infected population, 3 studies for chronic liver disease (CLD), 2 studies focused

on people who are obese and 4 studies for alcohol-related liver disease (ALD). Studies were identified across a range of diagnostic tests, although most provided data about imaging tests rather than blood/blood fibrosis tests.

Details and findings of the studies to diagnose cirrhosis for each aetiology, as reported in the study abstracts, are documented in Tables 2 to 6 below (where index test cirrhosis was assessed against biopsy as reference standard (Metavir F4 or equivalent)).

Note: The results in this section are based on the information that was available in journal abstracts. There was wide variation in reporting of useful data: some abstracts reported sensitivity/specificity, area under ROC or both (with reporting of 95% CI absent in many cases). Given that there were identified gaps in the evidence base in relation to certain aetiological groups we reported all available data, including where CIs were not provided, to establish if similar gaps in the evidence base persisted.

Summary of tests in hepatitis C population

We found 5 studies(2–6) which looked at the hepatitis C population (see Table 2 below). This included assessment of APRI, FIB-4 and enhanced liver fibrosis (ELF) blood fibrosis tests and assessment of fibroscan and real-time elastography imaging tests (no individual blood tests were available). Two studies also looked at HCV populations who had a sustained virological response to treatment. In all cases in the hepatitis C population a high sensitivity, specificity and overall good diagnostic accuracy based on the AUROC was reported.

Table 2 – Diagnostic tests: hepatitis C population

Study	Type	Aetiology	n	Index test	Cut off	Result
Blood fibrosis tests						
(4)	DTA(r)	HCV	575	APRI	0.65	sens 85.5% spec 77%
(5)	DTA(p)	HCV	106	APRI	NR	AUROC 1.0
(4)	DTA(r)	HCV	575	FIB-4	1.63	sens 91% spec 77%
(5)	DTA(p)	HCV	106	FIB-4	NR	AUROC 1.0
(4)	DTA(r)	HCV	575	APRI/FIB-4 combination	0.64/1.46	sens 81.5% spec 79%
(5)	DTA(p)	HCV	68	ELF	NR	AUROC 0.94
Imaging tests						
(5)	DTA(p)	HCV	51	ARFI	NR	AUROC 0.96

Study	Type	Aetiology	n	Index test	Cut off	Result
(2)	DTA(p)	HCV (sustained virological response)	121	ARFI	1.49 m/s	AUROC 0.981
(2)	DTA(p)	HCV	215	ARFI	1.49 m/s	AUROC 0.89
(6)	NR	HCV	90	Fibroscan	17.15 kPa	AUROC 0.98 sens 91.7% spec 98.3%
(5)	DTA(p)	HCV	107	Fibroscan	NR	AUROC 0.99
(3)	DTA(p)	HCV (sustained virological response)	118	R-T elastography	NR	AUROC 0.860

Abbreviations: DTA – diagnostic test accuracy (retrospective or prospective); SR - systematic review; CI – confidence interval; AUROC – area under the receiver operating characteristics; sens – sensitivity; spec – specificity; APRI - aspartate aminotransferase to platelet count ratio; ELF – enhanced liver fibrosis panel; R-T – real-time; ARFI - acoustic radiation force impulse; NR – not reported.

Summary of tests in NAFLD and obese populations

We found 8 studies(7–14) which looked at NAFLD and obese populations (see Table 3 below). This included assessment of fibroscan, ARFI, Shear wave, transient and magnetic resonance elastography imaging tests (no studies were identified that employed blood tests). Four of the studies were systematic reviews. In all cases in these populations a high sensitivity, specificity and overall good diagnostic accuracy based on the AUROC was reported. All studies reported a good diagnostic utility; one review(14) indicated that TE using the XL (extra-large) probes, rather than M (medium) probes, is likely to be more reliable in patients with obesity. A study(12) which compared performance found MRE (magnetic resonance elastography) to be more accurate than TE in NAFLD for diagnosis of cirrhosis.

Table 3 - Diagnostic tests: NAFLD and obese populations

Study	Type	Aetiology	n	Index test	Cut off	Result
Imaging tests in obese populations						
(7)	DTA(p)	Obese	97	ARFI	NR	AUROC 0.97 (overweight) AUROC 0.94 (obese)
(7)	DTA(p)	Obese	87	TE (M and XL probes)	NR	AUROC 0.97 (overweight) AUROC 0.92 (obese)

Study	Type	Aetiology	n	Index test	Cut off	Result
(14)	SR	Obese	1310 8 studies	TE (XL probes)	NR	sens 0.84 (95% CI 0.76 to 0.90) spec 0.78 (95% CI 0.70 to 0.84) AUROC 0.88
Imaging tests in NAFLD populations						
(8)	DTA(p)	NAFLD	291	ARFI	NR	AUROC 0.84
(8)	DTA(p)	NAFLD	291	FibroScan (M probe)	10.5/9.5 kPa	AUROC 0.87
(9)	DTA(p)	NAFLD	450	FibroScan (M or XL probe)	13.6 kPa	AUROC 0.89 (95% CI 0.84 to 0.93)
(10)	SR	NAFLD	698 (7 studies)	Fibroscan	NR	sens 96.2 % (95% CI: 94.5 to 97.8) spec 92.2% (95% CI: 89.9 to 94.6)
(11)	SR	NAFLD	1753 (11 studies)	TE	NR	AUROC 0.94 (95% CI 0.93 to 0.97)
(12)	DTA(p)	NAFLD	104	TE	NR	AUROC 0.69 (95% CI, 0.45-0.94)
(12)	DTA(p)	NAFLD	104	MRE	NR	AUROC 0.87 (95% CI, 0.71 to 1.00)
(13)	SR	NAFLD	232 9 studies	MRE	NR	AUROC 0.91 (95% CI, 0.76 to 0.95)
(8)	DTA(p)	NAFLD	291	SWE (supersonic)	10.5/9.5 kPa	AUROC 0.88
(11)	SR	NAFLD	982 (9 studies)	pSWE	NR	AUROC 0.95 (95% CI 0.93 to 0.97)

Abbreviations: TE – transient elastography; SWE – shear wave elastography; pSWE – point shear wave elastography; MRE - magnetic resonance elastography; DTA – diagnostic test accuracy (retrospective or prospective); SR - systematic review; CI – confidence interval; AUROC – area under the receiver operating characteristics; sens – sensitivity; spec – specificity; APRI - aspartate aminotransferase to platelet count ratio; ELF – enhanced liver fibrosis panel; R-T – real-time; ARFI - acoustic radiation force impulse; NR – not reported.

Summary of tests in ALD and chronic liver disease populations

We found 6 studies(15–21) which looked at ALD and chronic liver disease (CLD) populations (see Table 4 below). This included assessment of ARFI, ultrasonography, Shear wave and transient elastography imaging tests, with 1 study that employed red cell distribution width to platelet ratio blood tests.

Four of the studies were systematic reviews, including 1 Cochrane review of ultrasonography. The Cochrane review(16) only identified 2 studies and were not able to perform any analyses. In all studies in these populations a high sensitivity, specificity and overall good diagnostic accuracy based on the AUROC was identified for imaging tests.

Table 4 - Diagnostic tests: alcohol-related liver disease (ALD) and chronic liver disease (CLD) populations

Study	Type	Aetiology	n	Index test	Cut off	Result
Blood fibrosis tests in CLD populations						
(21)	SR	CLD	1800 study no. not reported	RPR	NR	sens 73.9% spec 76.8% AUROC 0.82
Imaging tests in CLD populations						
(20)	DTA(p)	CLD	127	SWE (2D)	13.1 kPa	AUROC 0.915
(19)	DTA(r)	CLD	102	TE combined with LiMAx	NR	sens 88.9% spec 84.6%
Imaging tests in ALD populations						
(18)	DTA(p)	ALD (detoxification)	83	ARFI	1.94 m/s	sens 92.3 (95% CI: 0.78 to 1.00) spec 81.6 (95% CI: 0.72 to 0.90) AUROC 0.89
(17)	SR	ALD	1026 10 studies	TE	18.6 kPa	AUROC 0.91 (95% CI 0.83 to 0.99)
(15)	SR	ALD	834 14 studies	TE	12.5kPa	sens 0.95 (95% CI, 0.87 to 0.98) spec 0.71 (95% CI, 0.56 to 0.82)
(16)	C-SR	ALD	205 2 studies	Ultra-sonography		no pooled data available

Abbreviations: RPR – red cell distribution width to platelet ratio; C-SR – Cochrane SR; LiMAx test - maximum liver function capacity; DTA – diagnostic test accuracy (retrospective or prospective); SR - systematic review; CI – confidence interval; AUROC – area under the receiver operating characteristics; sens – sensitivity; spec – specificity; APRI - aspartate aminotransferase to platelet count ratio; ARFI - acoustic radiation force impulse.

Summary of tests in autoimmune liver disease/hepatitis populations

We identified 4 studies(22–25) which looked at autoimmune liver disease/hepatitis populations (see Table 5 below). This included assessment of Shear wave and transient elastography imaging tests, as well as PC/CD, FIB-4, AAR and APRI blood fibrosis tests. One study(23) was a systematic review of DTAs. Overall, the studies in these populations reported

a mixed sensitivity, specificity results for SWE and good diagnostic accuracy based on the AUROC for the imaging tests and PC/SD. The systematic review identified that TE performed well in patients with AIH, in contrast to APRI and FIB-4 showed poor performance (no data reported in abstract). One study(24) reported a moderate sensitivity for pSWE, although the high specificity would result in few people without cirrhosis being incorrectly labelled with cirrhosis (false positive results).

Table 5 - Diagnostic tests: autoimmune liver disease/hepatitis populations

Study	Type	Aetiology	n	Index test	Cut off	Result
Blood fibrosis tests						
(22)	DTA(p)	AILD (AIH)	76	AAR	NR	AUROC 0.744
(22)	DTA(p)	AILD (AIH)	76	APRI	NR	AUROC 0.723
(23)	SR	AILD (AIH)	861 16 studies	APRI and FIB-4	NR	showed poor performance (no data reported in abstract)
(22)	DTA(p)	AILD (AIH)	76	FIB-4	NR	AUROC 0.795
(22)	DTA(p)	AILD (AIH)	76	PC/SD	NR	AUROC 0.968
Imaging tests						
(24)	DTA(p)	AILD (AIH)	49	pSWE (ElastPQ)	9.28kPa	sens 63.6% spec 86.8% AUROC 0.81 (95% CI, 0.65 to 0.96)
(25)	DTA(p)	AILD	114	SWE (2D)	16.3kPa	sens 87% spec 80.2% AUROC 0.86
(23)	SR	AILD (AIH)	861 16 studies	TE	NR	AUROC 0.89 (95% CI, 0.86 to 0.92)

Abbreviations: PC/SD - platelet count to spleen diameter ratio; AAR - alanine aminotransferase (ALT) ratio; AILD - autoimmune liver disease; AIH - autoimmune liver hepatitis; DTA – diagnostic test accuracy (retrospective or prospective); SR - systematic review; CI – confidence interval; AUROC – area under the receiver operating characteristics; sens – sensitivity; spec – specificity; APRI - aspartate aminotransferase to platelet count ratio; ELF – enhanced liver fibrosis panel; R-T – real-time; ARFI - acoustic radiation force impulse; SWE – shear wave elastography; pSWE – point shear wave elastography; NR – not reported.

Summary of tests in HIV/HCV populations

We identified 2 studies(26,27) which looked at HIV/HCV co-infection populations (see Table 6 below). This included assessment of fibroscan and transient elastography imaging tests, as well as FIB-4, FibroTest, hepascore, ELF and APRI blood fibrosis tests. One study(26) evaluated the performance TE and 6 blood fibrosis tests; TE (fibroscan) performed best in

that study. Overall, the studies in these populations reported a high sensitivity, specificity and overall good diagnostic accuracy based on the AUROC for TE.

Table 6 - Diagnostic tests: HIV/HCV populations

Study	Type	n	Index test	Cut off	Result
Blood fibrosis tests					
(26)	DTA(p)	105	APRI	NR	AUROC 0.89 (95% CI 0.84 to 0.93)
(26)	DTA(p)	105	ELF	NR	AUROC 0.82
(26)	DTA(p)	105	FIB-4	NR	AUROC 0.91
(26)	DTA(p)	105	FibroTest	NR	AUROC 0.84
(26)	DTA(p)	105	Hepascore	NR	AUROC 0.82
(26)	DTA(p)	105	hyaluronic acid	NR	AUROC 0.79
Imaging tests					
(27)	SR	756 6 studies	TE		sens 90 % (95% CI: 0.74 to 0.97) spec 87% (95% CI: 0.80 to 0.92)
(26)	DTA(p)	105	TE	NR	AUROC 0.97

Abbreviations: DTA – diagnostic test accuracy (retrospective or prospective); SR - systematic review; CI – confidence interval; AUROC – area under the receiver operating characteristics; sens – sensitivity; spec – specificity; APRI - aspartate aminotransferase to platelet count ratio; ELF – enhanced liver fibrosis panel; R-T – real-time; ARFI - acoustic radiation force impulse; TE – transient elastography; NR – not reported.

Intelligence gathering

Diagnostic tests

During the consultation in 2017 on NICE's draft quality standard liver disease (2017) QS152, stakeholder feedback raised the following issue that could have an impact on recommendations in NG50:

- Transient elastography values are often falsely raised (due to inflammation and alcoholic steatosis) during harmful drinking, regardless of fibrosis stage, and typically fall to more realistic values after 3-4 weeks of abstinence. If introduced at a national level, there is the risk of triggering many false positives, requiring unnecessary investigations.
- The finding of a low transient elastography value in a patient who is drinking at harmful levels can therefore lead to false reassurance and may reinforce problem behaviours if it appears there is no damage. Given the low proportion of people with alcohol misuse who access treatment for dependency, it may be more appropriate to advise that all patients

drinking at harmful levels should be offered treatment for their alcohol misuse rather than simply screening them for cirrhosis.

- Obesity can amplify the impact of alcohol consumption on the liver. Where alcohol is mentioned as a risk factor the threshold (units of alcohol per week) should be lowered for people BMI >35.

One expert raised 2 points concerning the enhanced liver fibrosis (ELF) test which is mentioned in the diagnosis section in NG50: it was queried whether the economic argument has altered compared with other comparable fibrosis tests; it was also noted there is patchy/poor uptake of ELF testing across UK with many areas not commissioning ELF testing at all. The expert also queried whether FIB-4 blood fibrosis tests, which can be calculated by GP-accessible tests without recourse to specialised tests, should be considered. In this context the following guideline was referred to for comparison and to check consistency: increased risk the management of abnormal liver blood tests.

Another expert queried whether recommendations 1.1.3 and 1.1.4 to 'offer transient elastography to diagnose cirrhosis' is being adopted countrywide.

One expert commented that recommendation 1.1.9, 'do not use routine laboratory liver blood tests to rule out cirrhosis', was too strong as routine blood tests can be used to exclude cirrhosis when used as part of an algorithm.

One expert queried the relevance of magnetic resonance elastography for diagnosis of cirrhosis within the guideline.

Impact statement

Diagnostic tests

Quality standard consultation 2017 feedback

Stakeholders submitted comments during the consultation of NICE's quality standard liver disease (2017) QS152 about the risk of raised transient elastography values during The considerations raised by the stakeholder had already been taken into account during the development of NG50, before publication in 2016. It was acknowledged that for both blood fibrosis tests and imaging tests, care needs to be taken when interpreting results in people who are actively drinking. Although diagnostic tests should be performed at the point of first contact, the tests should be repeated after a period of abstinence in this population subgroup. The committee also recommended that liver biopsy should be considered when transient elastography is not suitable (recommendation 1.1.5), for example in someone who has not abstained from alcohol for at least 6 weeks prior to testing, or where obesity may amplify the impact of alcohol consumption on the liver. In this respect, the issues raised by the stakeholder was addressed at the time of development of this guideline.

Regarding the stakeholder comment from the quality standard consultation, that it may be appropriate to advise that all patients drinking at harmful levels should be offered treatment for their alcohol misuse rather than simply screening them for cirrhosis, the NG50 guideline

should be read in conjunction with NICE's guidelines on alcohol-use disorders: prevention and alcohol-use disorders: diagnosis, assessment and management of harmful drinking (high-risk drinking) and alcohol dependence.. We will also ensure that the guidelines on the management of abnormal liver blood tests are considered during the next surveillance review of non-alcoholic fatty liver disease (NAFLD): assessment and management (NICE guideline NG49), to check for consistency.

Comments received during 2020 surveillance review

With regard to the topic expert query about the applicability of the ELF test in people with NAFLD for identifying advanced liver fibrosis and the availability of such tests locally, this recommendation mirrors the advice provided in non-alcoholic fatty liver disease (NAFLD): assessment and management (NICE guideline NG49). The recommendation to consider the ELF test, with a threshold of 10.51 to test for advanced fibrosis, is based on evidence that it was the most diagnostically accurate and also the most cost-effective test compared with all other testing and non-testing strategies. We will consider this issue at the next surveillance review of that guideline (likely to be in 2021). We have also noted that FIB-4 blood fibrosis tests, which can be calculated by GP-accessible tests without recourse to specialised tests, may be more readily available.

In relation to recommendations 1.1.3 and 1.1.4 which state, 'offer transient elastography to diagnose cirrhosis', one expert queried whether transient elastography to diagnose cirrhosis is being adopted countrywide. It is acknowledged that access to the 2 diagnostic tests recommended in NG50, transient elastography and acoustic radiation force impulse imaging, is currently varied across England - whilst the first is not available cross all hospitals, the latter is a newer technology that is not as widespread. Recommendations for these tests were based on a number of considerations, including that they ranked as the most cost-effective options available. NICE's quality standard liver disease (2017) QS152 recommends that commissioners commission non-invasive testing (transient elastography and acoustic radiation force impulse imaging) for cirrhosis, with a view to address any variability in access.

One expert commented that recommendation 1.1.9, 'do not use routine laboratory liver blood tests to rule out cirrhosis', was too strong as routine blood tests can be used to exclude cirrhosis when used as part of an algorithm. Combinations of these tests would be theoretically beneficial for the diagnosis of cirrhosis (in addition to advanced fibrosis), although no confirmatory evidence informed the development of the guideline or was identified during the current surveillance review. A further point to note, the recommendation does not refer to blood tests in the context of an algorithm but refers to blood tests as a stand-alone test to rule out cirrhosis.

Lastly, 1 expert queried whether MRE should be recommended in the guideline for diagnosis of cirrhosis. At the time of guideline development, no evidence was identified on MRE. The present review identified 2 studies of MRE tests in NAFLD populations; whilst the findings were promising further confirmatory evidence across other population groups would be required to impact current recommendations.

Impact of new evidence

Considering the new evidence for diagnostic tests for cirrhosis across the various aetiologies identified during the current surveillance review, the studies cover a range of diagnostic tests with many reporting high sensitivity, specificity and overall good diagnostic accuracy based on the AUROC. However, there were gaps in the new evidence: there were no studies of individual blood tests or blood fibrosis tests for NAFLD and ALD populations to detect cirrhosis, and this reflects similar gaps in the evidence that informed the development of the guideline. There was, however, limited new evidence in the HIV/HCV co-infection population which indicated TE performed better than blood tests; similar evidence was not available during guideline development.

When identifying the most appropriate non-invasive cirrhosis test, the committee that developed the guideline noted the practicality of recommending a common test for all aetiologies (and that there is an existing recommendation for people with hepatitis B in hepatitis B (chronic): diagnosis and management NICE guideline CG165). Taking these factors into account, the committee recognised that there was adequate evidence across all aetiologies to conclude that transient elastography (at the appropriate threshold for each aetiology) is a cost-effective option for the diagnosis of cirrhosis.

Considering the new evidence in this surveillance review and identified gaps in the evidence base, the rationale to recommend TE across all aetiologies because there is evidence of effectiveness and cost-effectiveness for this test still seems to hold. The committee also acknowledged that many people have multiple aetiologies (for example hepatitis C and ALD) and that recommendations should have some consistency across the different aetiologies for this reason. Also, of note, the new evidence in the HIV/HCV co-infection population seems to support the use of TE. Given these considerations there is no reason to amend the recommendations based on available new evidence.

New evidence is unlikely to change guideline recommendations.

Monitoring

Surveillance proposal

This section of the guideline should not be updated. However, 2 questions will be asked of stakeholders during consultation to help inform the final decision.

Risk of complications - risk assessment tools for predicting morbidity and mortality in compensated cirrhosis

2020 surveillance summary

Two studies (1 systematic review and 1 retrospective cohort study)(28,29) were identified which assessed the accuracy of risk assessment tools to predict mortality and liver-related morbidity in people with compensated cirrhosis (see Table 7). The retrospective cohort study(28) in people with ALD assessed the performance of blood fibrosis tests to assist the identification of people at risk of HCC. The systematic review(29) focused on prognostic accuracy of CTP, MELD, MELD-Na, and MESO index.

Table 7 Risk assessment tools for predicting morbidity and mortality in compensated cirrhosis

Study	Study Type	Index test	Aetiology	n	Follow-up	Outcome	Result
(28)	cohort (r)	modified fib-4	ALD	924	3 years	HCC	AUROC 0.71 (0.64 to 0.78)
(28)	cohort (r)	APRI	ALD	924	3 years	HCC	AUROC 0.61 (0.56 to 0.66)
(28)	cohort (r)	eLIFT	ALD	924	3 years	HCC	AUROC 0.56 (0.5 to 0.62)
(29)	SR	CTP	NR	2337 (14 studies)	3 month 6 month 12 month	Mortality	AUROC 0.86 (3 month) AUROC 0.91 (6 month) AUROC 0.72 (12 month)
(29)	SR	MELD	NR	2337 (14 studies)	3 month 6 month 12 month	Mortality	AUROC 0.78 (3 month) AUROC 0.83 (6 month) AUROC 0.75 (12 month)
(29)	SR	MELD-Na	NR	2337 (14 studies)	3 month 6 month 12 month	Mortality	AUROC 0.86 (3 month) AUROC 0.90 (6 month) AUROC 0.84 (12 month)
(29)	SR	CTP	NR	2337 (14 studies)	3 month	OV bleeding	AUROC 0.76
(29)	SR	MELD	NR	2337 (14 studies)	3 month	OV bleeding	AUROC 0.88

Abbreviations: Cohort(r) – Cohort study (retrospective); SR - systematic review; AUROC – area under the receiver operating characteristics; sens – sensitivity; spec – specificity; ALD - alcohol-related liver disease; OV - oesophageal varices; HCC - hepatocellular carcinoma; eLIFT - easy liver fibrosis test; CTP - Child-Turcotte-Pugh; MELD - Model for End-stage Liver Disease score; MELD-Na – MELD Sodium (modified risk tool); APRI - aspartate aminotransferase to platelet count ratio.

Intelligence gathering

One expert queried whether recommendation 1.2.2, which states 'calculate the Model for End-Stage Liver Disease (MELD) score every 6 months for people with compensated cirrhosis', should include the United Kingdom Model for End-Stage Liver Disease (UKELD) which predicts prognosis in CLD.

Impact statement

The guideline recommendation 1.2.2 states, 'calculate the Model for End-Stage Liver Disease (MELD) score every 6 months for people with compensated cirrhosis'. At the time of development there was limited good quality evidence overall, although the evidence available for MELD was superior to other approaches and the ease of use and relatively low costs of calculating MELD tipped in favour of this approach.

There was new evidence from 1 retrospective cohort study in predicting decompensation, which was limited to single decompensating event of HCC across 3 blood fibrosis tests. In all cases the tests had moderate accuracy in predicting the decompensating event.

A systematic review pooled results of CTP, MELD-Na and MELD to predict mortality and OV bleeding and reported AUROCs. Based on the findings MELD-Na has moderate to good accuracy in predicting the mortality of decompensated liver cirrhosis, it performs slightly better than CTP and MELD. In comparison with CTP, the systematic review found that MELD is better at predicting OV bleeding. All the reported AUROC values were greater than 0.7, which demonstrated that the CTP, MELD, MELD-Na, and MESO index have certain prognostic value. For predicting short-term mortality in variceal haemorrhage patients, the AUROC of MELD and CTP was 0.88 and 0.76, respectively.

During the current surveillance review no studies were identified that looked at the prognostic accuracy of the UKELD score in the prediction of mortality or decompensation in people with cirrhosis. We have not therefore been able to assess the suitability of this test.

Whilst the new evidence indicates that MELD-Na is promising the evidence is limited in its breadth and there is little new evidence reported on decompensating event outcomes. At the time of developing the guideline the committee noted that evidence on the prognostic accuracy decompensating events was a priority. Overall, MELD is a robust prognostic marker in people with compensated cirrhosis. Further confirmatory evidence is needed to trigger an update in this area of the guideline.

New evidence is unlikely to impact on the guideline.

Hepatocellular carcinoma - surveillance for the early detection of hepatocellular carcinoma (HCC)

2020 surveillance summary

When developing NG50 the guideline committee sought to compare the clinical and cost-effectiveness of different surveillance strategies (mode and timing)'

We found 1 study(30) that was relevant to this section of the guideline:

A retrospective study of 270 patients with confirmed cirrhosis identified that no surveillance, compared with 6 monthly ultrasound surveillance, was significantly associated with advanced HCC (multifocal or total diameter ≥6 cm) at diagnosis (odds ratio [OR] 8.1 (CI not reported)).

In addition, patients without HCC surveillance had a significantly shorter median survival compared with those who had HCC surveillance (27.4 vs 52.0 months, P=0.0006).

Intelligence gathering

One expert highlighted evidence from 1 study that demonstrates people who have hepatitis C virus and achieved a sustained virologic response following antiviral treatment continue to have a high risk for HCC: Increased Risk for Hepatocellular Carcinoma Persists Up to 10 Years After HCV Eradication in Patients With Baseline Cirrhosis or High FIB-4 Scores. Increased treatment and sustained virological response rates have been achieved with new direct acting antiviral drugs over the past 5 years (Hepatitis C in England and the UK, PHE 2019).

Also with regard to recommendation 1.2.4, 'offer ultrasound (with or without measurement of serum alpha-fetoprotein) every 6 months as surveillance for hepatocellular carcinoma (HCC) for people with cirrhosis who do not have hepatitis B virus infection', 1 expert queried the need for measurement of serum alpha-fetoprotein (AFP).

Impact statement

The current review identified 1 study which addressed the question, 'when and how frequently should surveillance testing be offered for the early detection of HCC in people with cirrhosis?' This single study which favoured 6-month surveillance over no surveillance using liver US for HCC in people with cirrhosis. This finding is consistent with recommendation 1.2.4 and will have no impact on the guideline.

One expert highlighted that surveillance of individuals with cirrhosis and hepatitis C virus that have subsequently cleared virus following antiviral treatment are at continued risk of HCC and should continue under the surveillance programme outlined in recommendation 1.2.4. As the guideline is focused on people with cirrhosis, it is anticipated that surveillance will continue if the person has cirrhosis, and therefore no impact is anticipated on the guideline. Populations without cirrhosis are beyond the scope of the current guideline.

Regarding the query, whether measurement of serum AFP is needed with US, the guideline review question assumes that the surveillance system uses liver ultrasound (with or without serum AFP testing). Furthermore, the purpose of the current surveillance review was not to assess diagnostic accuracy of ultrasound and AFP, or other approaches, for the diagnosis of hepatocellular carcinoma. However, we acknowledge that disagreement exists between using serum biomarker AFP as an additional test. In view of this we will track the following Cochrane systematic review and await publication: Abdominal ultrasound and alpha-fetoprotein for the diagnosis of hepatocellular carcinoma. It is anticipated that the findings of this review will help clarify practice in this area, given that it will assess the diagnostic accuracy of AFP alone, ultrasound alone, and combination of ultrasound and AFP in detecting HCC in people with CLD.

New evidence is unlikely to impact on the guideline.

Oesophageal varices - surveillance for the detection of varices

2020 surveillance summary

When developing NG50 the guideline committee recommended that all people with cirrhosis should be tested for the presence of varices using upper gastrointestinal endoscopy. The review question they wanted to address was, 'how frequently should surveillance testing using endoscopy be offered for the detection of oesophageal varices and isolated gastric varices in people with cirrhosis?'

No studies relevant to this review question were identified during the current surveillance review.

Expert comments suggested not all people with cirrhosis should automatically undergo invasive procedures using endoscopy for detection of varices given that half of these people have no identifiable oesophageal varices 10 years after the initial diagnosis of cirrhosis (see intelligence gathering section below). Therefore, we considered studies examining the accuracy of non-invasive tests for detection of varices that could be used to identify who should undergo more invasive endoscopy to check for varices in the population of people with confirmed cirrhosis.

Eight studies used non-invasive tests (with endoscopy as a reference standard) in patients with confirmed cirrhosis, to detect the presence or degree of varices. These studies were considered relevant to this section of the guideline and have potential to inform recommendations 1.2.7 and 1.2.8. Further details of the studies are reported in Tables 8, 9 and 10, below; they include 1 Cochrane systematic review(31), 4 systematic reviews(32–35) and 3 test accuracy studies(36–38). Whilst the studies cover different aetiologies and varices size identification, all studies assessed the predictive value of liver transient elastography, combined or not with platelet count, for the presence of oesophageal varices in patients with liver cirrhosis.

Table 8 Detection of varices - blood tests

Study	Type	Aetiology	n	OV size	Index test	Cut off	Result
(31)	C-SR	any	2054 (10 studies)	any	Platelet count	150,000/ mm3	sens 0.71 (95% CI: 0.63 to 0.77) spec 0.8 (95% CI: 0.69 to 0.88)

Abbreviations: C-SR - Cochrane systematic review; CI – confidence interval; sens – sensitivity; spec – specificity.

Table 9 Detection of varices - non-invasive imaging tests

Study	Type	Aetiology	n	OV size	Index test	Cut off	Result
(36)	DTA(p)	Non-viral	123	NR	Fibroscan (TE)	NR	AUROC 0.66

Study	Type	Aetiology	n	OV size	Index test	Cut off	Result
(36)	DTA(p)	HBV or HCV	123	NR	Fibroscan (TE)	NR	AUROC 0.704
(34)	SR	NR	2697 (15 studies)	any	Fibroscan (TE)	NR	AUROC 0.8262 sens 0.84 (95%CI: 0.81 to 0.86) spec 0.62 (95%CI: 0.58 to 0.66)
(34)	SR	NR	2697 (15 studies)	large	Fibroscan (TE)	NR	AUROC 0.8321 sens 0.78 (95%CI: 0.75 to 0.81) spec 0.76 (95%CI: 0.73 to 0.78)
(32)	SR	NR	4082 (32 studies)	any	TE	NR	sens 0.8 (95% CI: 0.78 to 0.86) spec 0.68 (95% CI: 0.62 to 0.74)
(32)	SR	NR	5221 (27 studies)	Substantial grade 2-3	TE	NR	sens 0.92 (95% CI: 0.83 to 0.96) spec 0.78 (95% CI: 0.7 to 0.85)
(31)	C-SR	any	1489 (13 studies)	any	Spleen length	110mm	sens 0.85 (95% CI: 0.75 to 0.91) spec 0.54 (95% CI: 0.46 to 0.62)
(33)	SR	NR	NR	any	Computed tomography	NR	AUROC 0.8975 sens 0.87 spec 0.95

Abbreviations: DTA – diagnostic test accuracy (retrospective or prospective); C-SR - Cochrane systematic review; SR - systematic review; CI – confidence interval; AUROC – area under the receiver operating characteristics; sens – sensitivity; spec – specificity; OV - oesophageal varices; TE – transient elastography.

Table 10 Detection of varices - non-invasive multi-component and blood fibrosis tests

Study	Type	Aetiology	n	OV size	Index test	Cut off	Result
(36)	DTA(p)	Non-viral	145	NR	APRI (AST to platelet ratio)	NR	AUROC 0.68
(36)	DTA(p)	HBV or HCV	145	NR	APRI (AST to platelet ratio)	NR	AUROC 0.703
(31)	C-SR	any	2637 (17 studies)	any	platelet count-to-spleen length ratio	909 (n/mm3)/mm	sens 0.93 (95% CI: 0.83 to 0.97) spec 0.84 (95% CI: 0.75 to 0.91)

Study	Type	Aetiology	n	OV size	Index test	Cut off	Result
(35)	SR	NR	NR	any	PSR (platelet count/spleen diameter ratio)	909	AUROC 0.85 (95%CI: 0.78 to 0.92)
(37)	DTA(r)	HCV (78%)	97	any	platelet count-to-spleen stiffness ratio	<30kPa >120,000 mm3	sens 0.32 spec 1.0
(38)	DTA(r)	55% HCV 89% Child-Pugh A	310	any	Baveno VI criteria	<20kPa >150,000 mm3	sens 0.87 spec 0.34 PPV 0.06, NPV 0.98
(37)	DTA(r)	HCV (78%)	97	any	Baveno VI criteria	<20kPa >150,000 mm3	sens 0.13 spec 1.0

Abbreviations: DTA – diagnostic test accuracy (retrospective or prospective); C-SR - Cochrane systematic review; SR - systematic review; CI – confidence interval; AUROC – area under the receiver operating characteristics; sens – sensitivity; spec – specificity; OV - oesophageal varices; PSR - platelet count/spleen diameter ratio; APRI - AST to platelet ratio,

Intelligence gathering

One expert queried the application of recommendation 1.2.7: 'after a diagnosis of cirrhosis, offer upper gastrointestinal endoscopy to detect oesophageal varices' and 1.2.8 'For people in whom no oesophageal varices have been detected, offer surveillance using upper gastrointestinal endoscopy every 3 years'. It was noted that endoscopy is increasingly reserved for those with high liver stiffness and low platelet count rather than all patients with newly diagnosed cirrhosis. Experts also pointed to the Baveno VI criteria for screening of varices and Expanding consensus in portal hypertension - Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension which recommends against screening upper gastrointestinal endoscopy in patients with compensated cirrhosis who have a liver stiffness <20 kPa and a platelet count >150 000/mm3 because of a low prevalence of varices in this population.

The EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis (2018) recommend endoscopy to detect the presence, size of varices, though the population specified is with decompensated cirrhosis. The British Society of Gastroenterology (BSG) UK Guidelines for the Management of Variceal Haemorrhage in Cirrhotic Patients) recommend all patients with cirrhosis should undergo endoscopy at the time of diagnosis and then at 2 to 3 year intervals.

Impact statement

We did not identify new evidence which related to recommendation 1.2.8 on endoscopic surveillance frequency: 'offer surveillance using upper gastrointestinal endoscopy every 3

years'. Therefore, no change is anticipated to the recommendation in respect of the surveillance frequency of people with confirmed cirrhosis and without varices.

However, experts identified that not all patients with compensated cirrhosis should automatically undergo invasive upper gastrointestinal endoscopy for detection of varices (as currently outlined in recommendations 1.2.7 and 1.2.8). We therefore sought to identify evidence on the accuracy of non-invasive tests for detection of varices (with endoscopy as a reference standard) in patients with confirmed cirrhosis.

Whilst the results were varied, the evidence we identified in this area suggests that tests that employ platelet count-to-spleen length (or stiffness) ratio, could be used to stratify the risk of oesophageal varices. For example, pooled results from the Cochrane systematic review cited above supported this conclusion: further analysis identified that, based on a prevalence of 53%, using platelet count-to-spleen length ratio (>909 (n/mm3)/mm) the presence of oesophageal varices of any size can be ruled out. However, the benefit of no endoscopy would need to be balanced against potentially 7% of adults with varices of any size being missed – as reported by the Cochrane review.

Whilst the potential savings and reduction in unpleasant endoscopy may be an attractive option, based on evidence - such as that stemming from the use of the Baveno criteria - there exists some uncertainty in the ability of non-invasive tests to rule out oesophageal varices. There also remains uncertainty given lack of available evidence on the long-term follow-up outcomes of related strategies. The practice of using non-invasive tests was acknowledged at the time of guideline development, but committee considered that it was not an effective method to rule out oesophageal varices and did not agree that this should be current UK practice.

As no substantive evidence was identified indicating that an update is needed to examine alternatives to endoscopy but it was suggested that endoscopy might not be needed in all patients, we asked stakeholders whether alternatives are being used in practice and that it is safe. Therefore, we are asking stakeholders 2 questions during the consultation for this surveillance review:

- Monitoring (oesophageal varices): How often (and why) are non-invasive (platelet count, spleen length, and platelet count-to-spleen length ratio) tests used in the detection varices in people with cirrhosis in the UK as an alternative to endoscopy?
- Monitoring (oesophageal varices): Is evidence available on the long-term outcomes (mortality and bleeding events) of non-invasive (platelet count, spleen length, and platelet count-to-spleen length ratio) tests versus endoscopy in the detection of varices in people with cirrhosis?

Based on stakeholder feedback (see appendix B), there was general consensus that non-invasive approaches are not adopted in this way and that the guideline position that endoscopy should be used remains sound.

New evidence is unlikely to impact on the guideline.

Managing complications

Surveillance proposal

This section of the guideline should be updated. The proposed update should focus on:

- Primary prophylaxis of variceal haemorrhage;
- Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites.

Intelligence gathering

Experts highlighted numerous publications of evidence that were relevant to this section of the guideline and areas where the guideline committee did not make recommendations during development of the guideline. Many of these studies did not meet the inclusion criteria as specified in the review protocols for the guideline; for information about the clinical review protocols see appendix C of the full guideline. A number were eligible and are included in the evidence summaries of this section.

Prophylaxis of variceal haemorrhage

2020 surveillance summary

We found 6 studies(39–44) which looked at primary prevention of variceal bleeding for medium or large varices in people with liver cirrhosis: 2 Cochrane systematic reviews, 3 systematic reviews, of which one used network meta-analysis (NMA), and one RCT.

These studies assessed non-selective beta-blockers (NSBBs) and oesophageal variceal ligation (EVL), compared with both each other and with placebo or no intervention as per guideline review questions (see Tables 11, 12, 13 for details); as well as combination therapy or other interventions (see Table 14 for details). Note that, for studies which incorporated NMA using indirect as well as direct comparisons, each comparison is presented as a single row in the table – with results for both direct and indirect NMA comparisons where data were available.

One systematic review(42) (which included 32 RCTs) used NMA to cover a range of comparisons including NSBBs versus placebo, EVL versus placebo, NSBBs versus EVL, and other therapies including in combination. As the abstract presented highlights from these results, some results in the tables below were obtained from the full paper. Due to its additional properties, carvedilol was classed separately from other NSBBs in making comparisons, in both this and other studies.

Overall, the current surveillance does not provide clear evidence of relative effectiveness of EVL or NSBBs (including carvedilol) for reducing variceal bleeding or mortality. No significant

difference was found between them in studies comparing EVL with NSBBs, whether directly, or indirectly using NMA.

Table 11: Non-specific beta-blockers (NSBBs) compared with placebo/no intervention to prevent first-time variceal bleeding (primary prevention) in people with liver cirrhosis

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(42)	SR/ NMA	(4 RCTs direct comparison, 28 indirect)	≥12	NSBB (not carvedilol)	Placebo	Variceal bleeding	No sig difference	Direct OR: 0.41 (0.14 to 1.23) NMA OR: 0.64 (0.38 to 1.07)
(42)	SR/ NMA	(5 RCTs direct comparison, 27 indirect)	≥12	NSBB (not carvedilol)	Placebo	Mortality	No sig difference	Direct OR: 0.80 (0.46 to 1.40) NMA OR: 0.70 (0.49 to 1.00)
(42)	SR/ NMA	(0 RCTs direct comparison, 32 indirect)	≥12	NSBB (carvedilol)	Placebo	Variceal bleeding	Improved with intervention	NMA OR: 0.21 (0.08-0.56)
(42)	SR/ NMA	(0 RCTs direct comparison, 32 indirect)	≥12	NSBB (carvedilol)	Placebo	Mortality	No sig difference	NMA OR: 0.89 (0.42-1.89)

Abbreviations: C-SR – Cochrane systematic review; SR - systematic review; NMA – network meta-analysis; RR – relative risk; OR – odds ratio; CI – confidence interval; NR – not reported. NSBB – non-specific beta-blockers

Table 12: Esophageal variceal ligation compared with placebo/no intervention to prevent first-time variceal bleeding (primary prevention) in people with liver cirrhosis

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(43)	C-SR	(6 studies) 637	NR	EVL	No intervention	Upper gastrointestinal bleeding	Improved with intervention	RR 0.44 (95% CI 0.28 to 0.72) I2 = 61%; NNTTB = 5 persons
(42)	SR/ NMA	(4 RCTs direct comparison, 28 indirect)	≥12	EVL	Placebo	Variceal bleeding	Improved with intervention	Direct OR: 0.36 (0.14 to 0.92) NMA OR: 0.33 (0.19 to 0.55)
(43)	C-SR	(6 studies) 637	NR	EVL	No intervention	All-cause mortality	Improved with intervention	RR 0.55 (95% CI 0.43 to 0.70) I2 = 0%; NNTTB = 6 persons

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(42)	SR/ NMA	(4 RCTs direct comparison, 28 indirect)	≥12	EVL	Placebo	Mortality	Improved with intervention (direct)/ No sig difference (NMA)	Direct OR: 0.48 (0.28 to 0.80) NMA OR: 0.76 (0.51 to 1.14)

Abbreviations: C-SR – Cochrane systematic review; SR - systematic review; NMA – network meta-analysis; RR – relative risk; OR – odds ratio; CI – confidence interval; NR – not reported; EVL - esophageal variceal ligation.

Table 13: NSBBs compared with EVL to prevent first-time variceal bleeding (primary prevention) in people with liver cirrhosis

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(41)	SR	(4 RCTs)	NR	NSBB (carvedilol)	EVL	Variceal bleeding	No sig difference	RR 0.74 (95% CI, 0.37 to 1.49)
(39)	SR	(4 RCTs)	NR	NSBB (carvedilol)	EVL	Variceal bleeding	No sig difference	RR: 0.74 (95%CI, 0.37 to 1.49)
(40)	RCT	200	6	NSBB (carvedilol: 12.5 mg daily)	EVL	Variceal bleed (reduction)	Improvement with intervention	RR: 2.7 (P<0.05) [No CIs reported]
(42)	SR/ NMA	(2 RCTs direct comparison, 30 indirect)	≥12	EVL	NSBB (carvedilol)	Variceal bleeding	No sig difference	Direct OR: 1.50 (0.49 to 4.60) NMA OR: 1.56 (0.67 to 3.64)
(41)	SR	(2 RCTs)	NR	NSBB (carvedilol)	EVL	All-cause mortality	No sig difference	RR 1.06 (95%CI 0.75 to 1.50)
(39)	SR	(4 RCTs)	NR	NSBB (carvedilol)	EVL	All-cause mortality	No sig difference	RR: 1.10 (95%CI, 0.76 to 1.58)
(42)	SR/ NMA	(2 RCTs direct comparison, 30 indirect)	≥12	EVL	NSBB (carvedilol)	Mortality	No sig difference	Direct OR: 0.86 (0.48 to 1.54) NMA OR: 0.86 (0.45 to 1.61)
(39)	SR	(4 studies)	NR	NSBB (carvedilol)	EVL	Bleeding-related mortality	No sig difference	RR: 1.02 (95%CI: 0.34 to 3.10)
(42)	SR/ NMA	(12 studies direct comparison, 20 indirect) 945	≥12	EVL	NSBB (not inc. carvedilol)	Variceal bleeding	Improvement with EVL	Direct OR: 0.52 (0.35 to 0.78) NMA OR: 0.51 (0.34 to 0.76)

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(42)	SR/ NMA	(12 studies direct comparison, 20 indirect) 915	≥12	EVL	NSBB (not inc. carvedilol)	Mortality	No sig difference	Direct OR: 1.35 (0.98 to 1.86) NMA OR: 1.09 (0.80 to 1.49)

Abbreviations: C-SR – Cochrane systematic review; SR - systematic review; NMA – network meta-analysis; RR – relative risk; OR – odds ratio; CI – confidence interval; NR – not reported; NSBB – non-specific beta-blockers; EVL - esophogeal variceal ligation.

Table 14: Other interventions, including combination therapies, to prevent first-time variceal bleeding (primary prevention) in people with liver cirrhosis

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(42)	SR/ NMA	(0 RCTs direct comparison, 32 indirect)	≥12	NSBB (not inc. carvedilol) + EVL	Placebo	Variceal bleeding	Improved with intervention	NMA OR: 0.34 (0.14 to 0.86)
(42)	SR/ NMA	(0 RCTs direct comparison, 32 indirect)	≥12	NSBB (not inc. carvedilol) + EVL	Placebo	Mortality	No sig difference	NMA OR: 0.49 (0.23 to 1.02)
(42)	SR/ NMA	(0 RCTs direct comparison, 32 indirect)	≥12	NSBB (not inc. carvedilol) + ISMN	Placebo	Mortality	Improved with intervention	NMA OR: 0.44 (0.21 to 0.93)
(41)	SR	(3 RCTs)	NR	NSBB (carvedilol)	NSBB (propanolol)	Variceal bleeding	No sig difference	RR: 0.76 (0.27 to 2.14)
(44)	C-SR	(3 RCTs)	NR	NSBB (carvedilol)	NSBB (propanolol)	Upper gastrointestinal bleeding	No sig difference	RR: 1.47 (0.71 to 3.06)
(44)	C-SR	(2 RCTs)	NR	NSBB (carvedilol)	NSBB (propranolol or nadolol)	Mortality	Not estimable	Not estimable
(44)	C-SR	(3 RCTs)	NR	NSBB (carvedilol)	NSBB (propanolol)	Serious adverse events	No sig difference	RR: 1.5 (0.6 to 3.75)
(41)	SR	(1 RCT) 48	NR	NSBB (carvedilol)	NSBB + ISMN	All-cause mortality	No sig difference	RR 1.07 (95%CI 0.38 to 3.03)

Abbreviations: C-SR – Cochrane systematic review; SR - systematic review; NMA – network meta-analysis; RR – relative risk; OR – odds ratio; CI – confidence interval; NR – not reported; NSBB – non-specific beta-blockers; EVL - esophogeal variceal ligation; ISMN – isosorbide mononitrate..

Intelligence gathering

One topic expert highlighted that recommendation 1.3.1, 'offer endoscopic variceal band ligation for the primary prevention of bleeding for people with cirrhosis who have medium to large oesophageal varices', is contentious, with health professionals deferring to other guidelines in this area. Notably, other guidelines recommend band ligation or NSBB as primary prophylaxis for variceal bleeding in patients with medium or large varices (see also UK Guidelines for the Management of Variceal Haemorrhage in Cirrhotic Patients).

Impact Statement

The current guideline recommends EVL as primary prophylaxis for preventing bleeding from medium/large varices.

Whilst NSBBs are not recommended as a prophylactic treatment for medium/large varices in the current guideline, during development the Guideline Development Group acknowledged (see 'Other considerations' in full guideline) that beta-blockers may have a role where band ligation is unavailable or contraindicated. For comparison and recommendation purposes, the current guideline considered NSBBs as a category, rather than looking at individual beta-blockers.

The current guideline was informed by moderate quality evidence suggesting that EVL may reduce variceal bleeding compared with NSBBs, and by very low-quality evidence suggesting no difference in mortality. An economic model was developed, applying results for clinical effectiveness from the clinical meta-analysis for the guideline to cost data from a single cost-effectiveness study. This suggested a modelled ICER for EVL vs NSBBs well within the accepted £20,000/QALY threshold, forming the basis of current guideline recommendations.

Topic experts suggested during the current surveillance that it is contentious to recommend EVL over NSBBs, and that other guidelines from around the world recommend both interventions, including the current BSG UK Guideline for the Management of Variceal Haemorrhage in Cirrhotic Patients.

Whereas the current guideline considered NSBBs as a single class of treatment, new evidence from the current surveillance found slightly different results for carvedilol - a newer-generation NSBB with additional arteriolar vasodilating action - and propranolol, an older NSBB.

In the current surveillance, a systematic review with network meta-analysis(42) found no significant difference between NSBBs (including carvedilol) and placebo for decreasing mortality; carvedilol decreased variceal bleeding.

Two systematic reviews(42,43) found that, compared with placebo or no intervention, EVL decreases variceal bleeding. Both studies also found that EVL decreases mortality in studies comparing EVL directly with placebo or no intervention; however, the NMA(42) found no difference in mortality when also including indirect comparisons in NMA.

Four studies reported on NSBBs (including carvedilol) compared with EVL – including 3 systematic reviews and 1 RCT. No difference was found between NSBBs and EVL for reducing variceal bleeding in the review studies, nor for mortality, nor for bleeding-related mortality in the single study which reported this outcome.

Other studies found some reduction in variceal bleeding and/or mortality for various combination therapies compared with placebo; for example, one systematic review(42) found through NMA that NSBBs (not carvedilol) combined with ISMNs may reduce mortality compared with placebo.

Overall, the evidence from current surveillance suggests that both NSBBs and EVL are more effective than placebo/no intervention in reducing first-time variceal bleeding. EVL may also reduce all-cause mortality, whilst NSBBs may not – the point estimate shows advantage compared with placebo, but this is not statistically significant. No clear advantage was apparent for EVL compared with NSBBs, for both variceal bleeding and all-cause mortality. In addition, consideration may be warranted of the role of combination therapies, with new evidence from current surveillance indicating some promise compared with single agents.

There is clearer evidence for EVL reducing mortality compared with placebo/no intervention than there is for NSBBs. However, in direct comparisons of the 2 interventions there appears to be little evidence of improved effectiveness of EVL compared with NSBBs for reducing either variceal bleeding or mortality. New evidence from the current surveillance may impact the cost-effectiveness calculations which led to the current guideline recommending EVL, and this may impact on recommendations.

New evidence may impact on current recommendations.

Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

2020 surveillance summary

We found one study(45) which looked at prevention of first-time infection (primary prevention) following variceal bleeding in people with liver cirrhosis. This involved assessment of the antibiotic ceftriaxone for a 3-day versus a 7-day regimen, for patients with acute oesophageal variceal bleeding receiving EVL (see Table 15).

The study found no difference in outcomes between a 3- and 7-day treatment regimen.

Table 15: Interventions to prevent first-time infection (primary prevention) following variceal bleeding in people with liver cirrhosis

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(45)	RCT	71	1	IV ceftriaxone 500 mg every 12 hours for 3 days	Same regimen for 7 days	Rebleeding rate within 14 days (1o endpoint)	No sig difference	3 patients in each group developed rebleeding within 14 days, 8% vs. 9%, p>0.99 [RR=0.87 (point estimate)] [No CIs reported]
(45)	RCT	71	1	IV ceftriaxone 500 mg every 12 hours for 3 days	Same regimen for 7 days	Survival rate within 28 days	No sig difference	100 vs. 97% (p=0.465) [RR=1.03 (point estimate)] [No CIs reported]
(45)	RCT	71	1	IV ceftriaxone 500 mg every 12 hours for 3 days	Same regimen for 7 days	Amount of transfusion during admission	No sig difference	2.71 +/- 2.84 units vs. 3.18 +/- 4.07 (p=0.839) [Ratio of units used = 0.85 (3 days' treatment vs 7 days)] [No CIs reported]

Abbreviations: RCT – randomised controlled trial; RR – relative risk; CI – confidence interval; NR – not reported.

Intelligence gathering

A topic expert suggested 3 studies in this area, including a forthcoming Cochrane review on Antibiotic prophylaxis for people with cirrhosis and variceal bleeding; a large retrospective observational study comparing mortality with and without antibiotics for patients with cirrhosis and upper gastrointestinal bleeding (n=6,451 patients with cirrhosis)(46); and an RCT(45) which is included in this surveillance review. With a longer follow-up time and larger number of patients, the large observational study was able to observe mortality as well as intermediate outcomes, finding that timely administration of antibiotics was significantly associated with a 30% reduction in 30-day mortality rate.

An MHRA Drug Safety Update highlighted risks of using fluoroquinolone antibiotics. These concerns may be relevant when considering the evidence for this area of the guideline, although fluoroquinolones are not specifically recommended for primary prophylaxis of infection following variceal bleeding.

Relating to this, a topic expert identified that antibiotic prescribing of fluroquinolones should be reviewed with consideration of monitoring and surveillance of patients. In this context they also suggested that a comparison is made between NG50 and recommendations in European Association for the Study of the Liver (EASL) Clinical Practice Guidelines for the management of patients with decompensated cirrhosis (2018). The EASL guidelines recommend ceftriaxone as the first choice in patients with decompensated cirrhosis, those already on quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacterial infections. Oral quinolones (norfloxacin) should be used in other patients.

It should be noted also that norfloxacin is not currently available in the UK.

Impact Statement

Little additional new evidence was identified in this surveillance review. An observational study(46) showed that antibiotic prophylaxis for patients with cirrhosis hospitalised following upper gastrointestinal bleeding may reduce overall 30-day mortality. Limited evidence from one small RCT suggested a 3-day regimen may be as effective as a 7-day regimen for improving rebleeding rate, survival after 28 days, and amount of transfusion during admission; this finding needs to be confirmed by larger studies.

The current guideline recommends prophylactic intravenous antibiotics for people with cirrhosis and upper gastrointestinal bleeding, without recommending any particular class of antibiotics. Prescriptions should be reviewed in line with Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. Evidence informing the current guideline suggested that IV ceftriaxone is probably more effective than fluoroquinolones for reducing bacterial infection; a single study suggested it may however possibly also increase mortality. An MHRA Drug Safety Update raises questions over use of fluoroquinolone antibiotics, which may be relevant when considering the evidence for this area of the current guideline, although fluoroquinolones are not specifically recommended in the guideline for this purpose. No relevant evidence was identified. Safety is also discussed in the next section which addresses recommendations where fluoroquinolones are recommended.

Overall, no new evidence was found which is likely to change the current guideline recommendations.

New evidence is unlikely to change guideline recommendations.

Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

2020 surveillance summary

We identified 1 RCT which addressed the review question: what is the clinical and cost-effectiveness of TIPS compared with LVP with albumin in the management of diuretic resistant ascites due to cirrhosis? The relevant outcomes are reported in Table 16 below.

Table 16 – TIPS & LVP for ascites

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(47)	RCT	62 (29/33)	12	TIPS (covered)	LVP+A	survival without a liver transplant	Improved with intervention	93% vs 52% (p=0.003)
(47)	RCT	62 (29/33)	12	TIPS (covered)	LVP+A	days hospitalisation	Improved with intervention	17 vs 35 (p=0.04)

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(47)	RCT	62 (29/33)	12	TIPS (covered)	LVP+A	free of HE	No significant difference	65% vs 65%

Abbreviations: RCT – randomised control trial; LVP+A - large-volume paracentesis with albumin.

Intelligence gathering

One expert queried whether the use of indwelling drains/pumps for treatment of diuretic resistant ascites should be covered by the guideline.

One expert noted that the BSG is developing a new guideline which covers TIPS placement and should be considered for comparison. This guideline published in October 2019: Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS) in the management of portal hypertension.

Impact statement

Recommendation 1.3.4 states, 'consider a transjugular intrahepatic portosystemic shunt for people with cirrhosis who have refractory ascites'. Whilst the new evidence from 1 study is limited it broadly supports the current recommendation 1.3.4; the findings suggest that polytetrafluoroethylene (PTFE)-covered TIPS is used as the first-line intervention, when compared with LVP with albumin. Furthermore, the BSG guideline that published in October 2019, Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS) in the management of portal hypertension, complements and is in-line with recommendation 1.3.4 of NG50 with respect to TIPS for ascites.

One expert queried whether the use of indwelling drains/pumps for treatment of diuretic resistant ascites should be covered by the guideline. This topic is included in the NICE pathway for cirrhosis which includes a cross-reference to Subcutaneous automated low-flow pump implantation for refractory ascites caused by cirrhosis (2018) NICE interventional procedures guidance 631. People using the NICE pathway can navigate to the guidance and relevant information on evidence-based recommendations on subcutaneous automated low-flow pump implantation for refractory ascites in adults.

New evidence is unlikely to change guideline recommendations.

Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

2020 surveillance summary

Through the search for evidence we found 7 studies(48–53) which looked at prevention of first-time SBP (primary prevention) in people with liver cirrhosis and ascites: 3 RCTs and 4 systematic reviews, 3 of which used NMA. These studies included assessment of various antibiotics including fluoroquinolones (particularly ciprofloxacin and norfloxacin), rifaximin, and co-trimoxazole, compared with both each other and with placebo or no intervention (see Table 17 for details). Whilst results for norfloxacin are reported here for completeness, it should be noted that norfloxacin is no longer available in the UK.

We also considered a recently published Cochrane systematic review (CSR)(54), suggested by topic experts and published after the search cut-off for this surveillance review. The review used NMA to combine trial data for both primary and secondary prophylaxis of SBP, including for norfloxacin and ciprofloxacin, rifaximin and co-trimoxazole. Results are not included in Table 17, since the quantitative data may not be directly comparable with data on primary prophylaxis of SBP from the other included studies; a narrative summary is included below.

Table 17: Interventions to prevent first-time spontaneous bacterial peritonitis (SBP) (primary prevention) in people with liver cirrhosis and ascites

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(48)	SR/ NMA	(3 RCTs direct comparison, 13 indirect) 1,984 (in NMA)	NR	Rifaximin	Norfloxacin	SBP (reduction)	Improved with intervention	NMA OR: 2.04 (1.11 to 3.70)
(48)	SR/ NMA	(2 RCTs direct comparison, 12 indirect)	NR	Rifaximin	Norfloxacin	Mortality (reduction)	Improved with intervention	NMA OR: 1.85 (1.09 to 3.13)
(48)	SR/ NMA	(0 RCTs direct comparison, 16 indirect) 1,984 (in NMA)	NR	Rifaximin	Ciprofloxacin	SBP (reduction)	No sig difference	NMA OR: 1.25 (0.36 to 4.17)

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(48)	SR/ NMA	(0 RCTs direct comparison, 14 indirect) 1,984 (in NMA)	NR	Rifaximin	Ciprofloxacin	Mortality (reduction)	No sig difference	NMA OR: 1.85 (0.78 to 4.35)
(48)	SR/ NMA			Co-trimoxazole	Placebo	SBP (reduction)	No sig difference	NMA OR: 2.94 (0.90–10.0)
(48)	SR/ NMA			Co-trimoxazole	Placebo	Mortality (reduction)	Improved with intervention	NMA OR: 2.56 (1.18–5.89)
(48)	SR/ NMA			Co-trimoxazole	Norfloxacin	SBP (reduction)	No sig difference	NMA OR: 1.06 (0.36 to 3.23)
(48)	SR/ NMA			Co-trimoxazole	Norfloxacin	Mortality (reduction)	No sig difference	NMA OR: 1.59 (0.75 to 3.33)
(48)	SR/ NMA			Co-trimoxazole	Ciprofloxacin	SBP (reduction)	No sig difference	NMA OR: 1.53 (0.15 to 2.94)
(48)	SR/ NMA			Co-trimoxazole	Ciprofloxacin	Mortality (reduction)	No sig difference	NMA OR: 1.56 (0.58 to 4.12)
(48)	SR/ NMA			Co-trimoxazole	Rifaximin	SBP (reduction)	No sig difference	NMA OR: 0.53 (0.15 to 1.82)
(48)	SR/ NMA			Co-trimoxazole	Rifaximin	Mortality (reduction)	No sig difference	NMA OR: 0.85 (0.34 to 2.13)
(51)	SR	(3 studies: 2 in sensitivity analysis) 173	NR	Rifaximin	Systemic antibiotics (unspecified)	SBP	No sig difference	OR: 0.59 (0.32 to 1.09); P=0.10 With sensitivity analysis: OR: 0.56 (0.30 to 1.05); P=0.07
(51)	SR	(4 studies)	NR	Rifaximin	No antibiotics	SBP	Improved with intervention	OR: 0.53 (0.28 to 0.99); P=0.05 With sensitivity analysis: OR: 0.23 (0.10 to 0.52); P<0.00
(52)	SR/ NMA	(10 studies) (in NMA)	NR	Rifaximin	Placebo	SBP	Improved with intervention	RR: 0.15 (0.05 to 0.42)
(53)	RCT	334	NR	alternating norfloxacin and rifaximin	norfloxacin or rifaximin alone	SBP (reduction)	Improved with intervention	74.7 vs. 56.4% vs. 68.3% p<0.048

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(50)	RCT	291	6	Norfloxacin	Placebo	6-month mortality (hazard ratio)	Improved with intervention	HR: 0.35 (0.13 to 0.93)
(52)	SR/ NMA	(10 studies) (in NMA)	NR	Norfloxacin	Placebo	SBP	Improved with intervention	RR: 0.23 (0.09 to 0.56); P=0.001
(52)	SR/ NMA	(10 studies) (in NMA)	NR	Norfloxacin	Placebo	Mortality	Improved with intervention	RR: 0.68 (0.47 to 0.99); P = 0.04
(52)	SR/ NMA	(10 studies) (in NMA)	NR	Ciprofloxacin	Placebo	SBP	Improved with intervention	RR: 0.23 (0.07 to 0.79); P=0.02
(49)	RCT	124	12	ciprofloxacin (weekly 400 mg)	norfloxacin (daily 400 mg)	SBP	No sig difference	SBP: 4/55 vs 3/57 (7.3% vs. 5.3%, P = 0.712).
(49)	RCT	124	12	ciprofloxacin (weekly 400 mg)	norfloxacin (daily 400 mg)	Transplant-free survival at 1 year	Comparable between groups	72.7% vs. 73.7%, P=0.970

Abbreviations: RCT – randomised controlled trial; C-SR – Cochrane systematic review; SR - systematic review; NMA – network meta-analysis; RR – relative risk; OR – odds ratio; CI – confidence interval; NR – not reported. SBP - spontaneous bacterial peritonitis

Regarding the additional CSR(54), the authors reported no statistically significant difference in the guideline-defined critical outcomes of reduced mortality and SBP occurrence for any of the above antibiotics compared with both no intervention and each other. Furthermore, they reported that results from a subgroup analysis of 8 RCTs, using primary prophylaxis only, did not differ from the results for primary and secondary prophylaxis combined – however, quantitative data on this was not provided. In contrast with most identified evidence, the CSR reported NMA data for antibiotic adverse effects also, finding no difference in the majority of cases.

No data on the third critical outcome of health-related quality of life was found in any of the evidence.

Intelligence gathering

In March 2019, the MHRA issued restrictions and precautions for the use of fluoroquinolone antibiotics because of rare reports of disabling and potentially long-lasting or irreversible side effects (see Drug Safety Update for details). As part of this surveillance review experts were asked whether offering a fluoroquinolone is appropriate, whether alternative antibiotics are recommended and whether evidence is available that is relevant to the guideline.

A topic expert suggested a number of studies in this area, which are included as part of this surveillance review where eligible. The topic expert highlighted one of these studies, an

RCT(50) as providing specific evidence on fluoroquinolone safety. This study compared norfloxacin with placebo for patients with advanced cirrhosis, focusing primarily on mortality. For non-fatal adverse events other than liver-related complications, at both 6 and 12 months, no difference was observed between the norfloxacin and placebo groups. Furthermore, norfloxacin significantly decreased the incidence of any and Gram-negative bacterial infections without increasing infections caused by *Clostridium difficile* or multi-resistant bacteria. However, as noted above, norfloxacin is no longer available in the UK.

One expert identified that antibiotic prescribing of fluroquinolones should be reviewed with consideration of monitoring and surveillance of patients and suggested that a comparison is made between NG50 and recommendations in European Association for the Study of the Liver (EASL) Clinical Practice Guidelines for the management of patients with decompensated cirrhosis (2018). The EASL guidelines recommend that ceftriaxone is the first choice in patients with decompensated cirrhosis, those already on quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacterial infections; use oral quinolones (norfloxacin) in other patients.). Another expert highlighted that SBP is a life-threatening condition and noted that prophylaxis with a fluoroquinolone (norfloxacin) is recommended in the EASL guidelines. The expert also noted that use remains widespread but it is unclear whether this comment referred to the UK, and/or to all fluoroquinolones and whether the situation may have changed since the MHRA alert on fluoroquinolones and also the removal of norfloxacin from the UK market.

An expert mentioned that the adverse effects of fluoroquinolones are well recognised. Previously published papers mentioned liver injury (Fluoroquinolone therapy and idiosyncratic acute liver injury: a population-based study) and *Clostridium difficile* (Clinical and economic burden of Clostridium difficile infection in Europe: a systematic review of healthcare-facility-acquired infection). In addition, the expert noted that fluoroquinolones are useful but close observation for side effects such as muscle aches, tendonitis is needed in both inpatients and after discharge. They suggested that a recommendation could be made for appropriate monitoring of patients prescribed fluoroquinolones.

Impact Statement

The current guideline recommends offering prophylactic oral ciprofloxacin or norfloxacin until ascites has resolved. Norfloxacin is no longer available in the UK and the recommendation wording will be amended to remove norfloxacin.

In developing the current guideline, evidence at the time showed probable benefits for fluoroquinolone antibiotics compared with placebo for reducing both SBP and mortality. However, in 2019 the MHRA issued a Drug Safety Update alerting risks of using fluoroquinolones and this is highlighted on the guideline landing page.

Seven studies were included in the current surveillance, which all compared fluoroquinolone antibiotics with each other, and/or with placebo, and/or with other antibiotics. A topic expert highlighted one of these studies, an RCT(50), as providing evidence for safety of fluoroquinolones. This study compared norfloxacin with placebo for patients with advanced

cirrhosis, focusing primarily on mortality. For non-fatal adverse events other than liver-related complications, at both 6 and 12 months, no difference was observed between the norfloxacin and placebo groups.

Most of the evidence from current surveillance suggests that fluoroquinolones are more effective than placebo in reducing both SBP incidence and all-cause mortality. Rifaximin also appears to reduce SBP occurrence compared with placebo, although any benefit in reducing mortality is unclear. Co-trimoxazole appears to reduce mortality, though the benefit in reducing SBP occurrence is less clear. A systematic review using network meta-analysis(55) (NMA) suggests that rifaximin may be more effective than norfloxacin and have similar effectiveness to ciprofloxacin in reducing both SBP and mortality. Other studies of rifaximin found no difference in effectiveness compared with fluoroquinolones. Another systematic review/NMA(48) suggests no difference in effectiveness for co-trimoxazole compared with either norfloxacin or ciprofloxacin, for either SBP occurrence or mortality.

A recently published CSR with NMA found slightly different results, with antibiotics not demonstrating significant improvement for either SBP incidence or mortality, compared with placebo or each other. However, analysis for this CSR was performed differently in combining primary and secondary SBP prophylaxis, and qualitatively reporting results for a subgroup analysis of primary prophylaxis only.

Topic experts suggested a mixture of possible risks and benefits of using fluoroquinolones, given also that SBP is a life-threatening condition. They suggested that surveillance of patients prescribed fluoroquinolones may be appropriate.

New evidence was identified which shows co-trimoxazole and rifaximin, when compared with the fluoroquinolone antibiotics, may be at least equivalent for reducing both SBP and mortality – though uncertainty remains and rifaximin is not licensed in this indication. Taken together with the potential for serious side effects of fluoroquinolones and withdrawal of norfloxacin from the UK, there is likely to be an impact on recommendations.

New evidence identified that may change current recommendations.

Areas not currently covered in the guideline

In surveillance, evidence was identified for areas not covered by the guideline. This new evidence has been considered for possible addition as a new section of the guideline.

Volume replacers in hepatorenal syndrome

2020 surveillance summary

No studies relevant to this section of the guideline were identified.

Intelligence gathering

A topic expert recommended 5 studies in this area, including a suite of 4 Cochrane Reviews assessing various drug therapies for treating hepatorenal syndrome (HRS).

Impact statement

Insufficient evidence was available during development of the current guideline for any recommendations to be made in this area.

No new evidence was included in the current surveillance. All studies identified via the topic expert suggestions and database search were of vasoactive drugs or other treatments for HRS; none specifically compared different volume replacers as per the review question for the guideline.

The question of the most clinical and cost-effective volume replacer will therefore remain as a research recommendation following the current surveillance.

New evidence is unlikely to impact on the guideline.

Management of an episode of acute hepatic encephalopathy

2020 surveillance summary

Twelve studies relevant to this section of the guideline were identified. The key findings are identified in Table 18 below.

Table 18: Interventions to treat hepatic encephalopathy (HE)

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(56)	C-SR	(24 RCTs) 1,487	NR	Lactulose and lactitol	Placebo/no intervention	HE	Improved with intervention	RR: 0.58 (0.50 to 0.69)
(56)	C-SR	(24 RCTs) 1,487	NR	Lactulose and lactitol	Placebo/no intervention	Mortality	Improved with intervention	RR: 0.59 (0.40 to 0.87)

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(57)	SR	(31 RCTs)	NR	Lactulose and lactitol	Placebo/no intervention	HE	Improved with intervention	RR: 0.63 (0.53 to 0.74); NNT = 4
(57)	SR	(31 RCTs)	NR	Lactulose and lactitol	Placebo/no intervention	Mortality	Improved with intervention	RR: 0.36 (0.14 to 0.94); NNT = 20
(58)	C-SR	(2 RCTs)	NR	AST-120	Lactulose	Mortality	No sig difference	RR: 1.05 (0.59 to 1.85)
(58)	C-SR	(2 RCTs)	NR	AST-120	Lactulose	HE	No sig difference	RR: 1.05 (0.59 to 1.85)
(58)	C-SR	(3 RCTs)	NR	Polyethylene glycol (PEG)	Lactulose	Mortality	No sig difference	RR: 0.50 (0.09 to 2.64)
(58)	C-SR	(3 RCTs)	NR	Polyethylene glycol (PEG)	Lactulose	HE	Improved with intervention	RR: 0.19 (0.08 to 0.44)
(59)	RCT	100	NR	Polyethylene glycol (PEG)	Lactulose	HE clinical improvement	Improvement with intervention	94% vs 72% (p<0.05)
(59)	RCT	100	NR	Polyethylene glycol (PEG)	Lactulose	HE resolution time / hospital stay length	Improvement with intervention	P<0.001
(60)	RCT	40	NR	PEG + lactulose	Lactulose	HESA score	Improvement with intervention	p=0.04
(60)	RCT	40	NR	PEG + lactulose	Lactulose	Hospital stay length	Improvement with intervention	p=0.03
(56)	C-SR	(16 studies) 827	NR	BCAA (oral/IV)	Various: placebo/no intervention, diets, lactulose, neomycin	HE	Improved with intervention	RR: 0.73 (0.61 to 0.88)
(56)	C-SR	(15 studies) 760	NR	BCAA (oral/IV)	Various: placebo/no intervention, diets, lactulose, neomycin	Mortality	No sig difference	RR: 0.88 (0.69 to 1.11)

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Placebo/no intervention	HE	Improved with intervention/ No sig difference	RR: 0.70 (0.59 to 0.83) (all trials); RR: 0.96 (0.85 to 1.07) (low risk of bias)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Placebo/no intervention	Mortality	Improved with intervention/ No sig difference	RR: 0.42 (0.24 to 0.72) (all trials); RR: 0.47 (0.06 to 3.58) (low risk of bias)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Placebo/no intervention	Serious adverse events	Improved with intervention/ No sig difference	RR: 0.63 (0.45 to 0.90) (all trials); RR: 0.83 (0.15 to 4.65) (low risk of bias)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Lactulose	HE	No sig difference	RR: 1.13 (0.81 to 1.57)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Lactulose	Mortality	No sig difference	RR: 0.68 (0.11 to 4.17)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Lactulose	Serious adverse events	No sig difference	RR: 0.69 (0.22 to 2.11)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Probiotics	HE	Improved with intervention	RR: 0.71 (0.56 to 0.90)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Probiotics	Mortality	No sig difference	RR: 1.01 (0.11 to 9.51)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Probiotics	Serious adverse events	No sig difference	RR: 1.07 (0.23 to 4.88)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Rifaximin	HE	No sig difference	RR: 1.06 (0.57 to 1.96)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Rifaximin	Mortality	No sig difference	RR: 0.33 (0.04 to 3.03)
(61)	C-SR	NR	NR	L-ornithine L-aspartate (LOLA)	Rifaximin	Serious adverse events	No sig difference	RR: 0.32 (0.01 to 7.42)

Study	Type	n	Duration (months)	Intervention	Comparator	Outcome	Result	Statistic
(62)	RCT	193	NR	L-ornithine L-aspartate (LOLA)	Placebo	Mean recovery time (days)	Improvement with intervention	Mean 1.92+/-0.93 vs 2.50+/-1.03 (p=0.002)
(63)	RCT	35	NR	LOLA + lactulose	Lactulose (+ placebo)	Mental status improvement (at 7 days)	No sig difference	90% vs 84.6% (p=1.0)
(64)	C-SR	(12 RCTs) 842	NR	Flumazenil	Placebo	HE	Improved with intervention	RR: 0.75 (0.71 to 0.80)
(64)	C-SR	(12 RCTs) 842	NR	Flumazenil	Placebo	Mortality	No sig difference	RR: 0.75 (0.48 to 1.16)
(58)	C-SR	(3 RCTs)	NR	Sodium benzoate	Non-absorbable disaccharide	Mortality	No sig difference	RR: 1.26 (0.49 to 3.28)
(58)	C-SR	(3 RCTs)	NR	Sodium benzoate	Non-absorbable disaccharide	HE	No sig difference	RR: 1.22 (0.51 to 2.93)
(58)	C-SR	NR	NR	Glycerol phenylbutyrate	Placebo	Mortality	No sig difference	RR: 0.65 (0.11 to 3.81)
(58)	C-SR	NR	NR	Glycerol phenylbutyrate	Placebo	HE	Improved with intervention	RR: 0.57 (0.36 to 0.90)
(58)	C-SR	NR	NR	Ornithine phenylacetate	Placebo	Mortality	No sig difference	RR: 0.73 (0.35 to 1.51)
(58)	C-SR	NR	NR	Ornithine phenylacetate	Placebo	HE	No sig difference	RR: 2.71 (0.12 to 62.70)
(55)	RCT	80	NR	Ornithine aspartate + rifaximin	1 component only	Total effective rate	Improved with intervention	p<0.05
(55)	RCT	80	NR	Ornithine aspartate + rifaximin	1 component only	Improvement rate	Improved with intervention	p<0.05
(65)	RCT	120	NR	Rifaximin	Metronidazole	HE clinical improvement	No sig difference	75% vs 76.7% (p=0.412)
(65)	RCT	120	NR	Rifaximin	Metronidazole	Hospital stay	No sig difference	Mean 3.9+/-1.7 vs 4.2+/-2.1 (p=0.435)

Abbreviations: RCT – randomised controlled trial; C-SR – Cochrane systematic review; SR - systematic review; NMA – network meta-analysis; RR – relative risk; OR – odds ratio; CI – confidence interval; NR – not reported.

Intelligence gathering

A topic expert suggested examining a suite of 7 Cochrane reviews, 1 systematic review and a guideline: Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). All included studies are detailed in Table 18.

Impact statement

Evidence available at the time of development that informed the current guideline was inconclusive; thus, the guideline was unable to make any recommendation on managing an episode of acute HE. The committee considered that use of non-absorbable disaccharides (NAD), i.e. lactulose in the UK, was standard practice as part of treatment for overt HE; however, minimal evidence was found for NAD versus placebo or no intervention. Neither did evidence informing the guideline show clear improvement for any alternative interventions over NAD.

Twelve studies included in the current surveillance review assessed: NAD versus placebo/no intervention; and other treatments for acute HE, mainly versus NAD or placebo/no intervention - with one study using probiotics and one using rifaximin as the comparator.

The new evidence suggested that NAD is more effective than placebo/no intervention, for both improving HE and reducing mortality, as are several other interventions. BCAA may also be more effective than a range of comparators, including placebo/no intervention, for improving HE. There was some evidence suggesting that polyethylene glycol (PEG) is more effective compared with lactulose for improving HE, though not mortality. It should be noted that not all these interventions are currently available in the UK.

The current surveillance review has identified new evidence, including Cochrane reviews and other evidence highlighted by topic experts, which improves the evidence base for management of acute HE, both for NAD and alternative treatments. Evidence from current surveillance may indicate that NAD (i.e. lactulose in the UK) is effective in managing overt HE compared with placebo/no intervention. Limited evidence may also indicate increased effectiveness for polyethylene glycol (PEG), and/or branched-chain amino acids (BCAA) compared with NAD.

Whilst new evidence to support lactulose treatment of overt HE episodes was included in this surveillance review, it was noted that lactulose is standard NHS practice (see, e.g. McPherson and Thomson, 2019: Management of hepatic encephalopathy: beyond the acute episode [British Society of Gastroenterology]), Other products in the studies are not available in the UK. There would be little benefit of undertaking a formal evidence review in this area and there is no impact on the guideline.

New evidence is unlikely to impact on the guideline.

Albumin administrations & plasma expanders

2020 surveillance summary

Albumin administrations for people with cirrhosis with uncomplicated ascites

An NIHR Signal was published in 2018, which described an Italian multi-centre, open-label randomised trial from the same year (the ANSWER trial)(66); this study is discussed in the following NIHR signal Albumin administrations can prolong survival for some people with liver disease. This RCT sought to study the effects of long-term albumin infusions in patients with uncomplicated ascites and decompensated cirrhosis (n=440) over 11 months. The key findings are identified in Table 19 below.

Table 19 – Albumin administration

Study	Intervention	Comparator	Outcome	Result	Statistic
(66)	albumin infusions	Usual care	18-month mortality	Favours intervention	HR 0.62, 95% CI 0.40 to 0.95
(66)	albumin infusions	Usual care	number of therapeutic paracenteses	Favours intervention	HR 0.43, 95% CI 0.29 to 0.62
(66)	albumin infusions	Usual care	Hospital days	Favours intervention	45% reduction in intervention vs usual care: 19.39 days (95% CI 18.71 to 20.09) 10.70 days (95% CI 10.27 to 11.15)

Abbreviations: HR - Hazard ratio; RCT – randomised control trial.

In addition, the following findings were reported:

- Albumin also reduced rates of other complications including bacterial infection, encephalopathy, and kidney failure.
- People in the usual care group showed greater decline in quality of life than people receiving albumin, as measured by standard questionnaires at 3, 6 and to 12 months. There was no difference between groups at 18 months.

Plasma expanders for people with cirrhosis and large ascites treated with abdominal paracentesis (AP)

We identified 1 Cochrane systematic review(67) which explored the benefits and harms of any plasma volume expanders for paracentesis in people with cirrhosis and large ascites. Key findings from the review are presented in Table 20 below.

Table 20 – plasma expanders

Study	n	Duration (mean follow-up)	Intervention	Comparator	Outcome	Result	Statistic
(67)	248 (4 RCTs)	64 days	AP with plasma expansion	no plasma expansion	mortality	No significant difference	RR 0.52, 95% CI 0.06 to 4.83
(67)	181 (4 RCTs)	64 days	AP with plasma expansion	no plasma expansion	renal impairment	No significant difference	RR 1.61, 95% CI 0.79 to 3.27
(67)	1014 (14 RCTs)	208 days	AP with experimental plasma expanders	AP with albumin	mortality	No significant difference	RR 1.03, 95% CI 0.82 to 1.30
(67)	1007 (17 RCTs)	174 days	AP with experimental plasma expanders	AP with albumin	renal impairment	No significant difference	RR 1.17, 95% CI 0.71 to 1.91

Abbreviations: AP - abdominal paracentesis; RR – relative risk; CI – confidence interval.

Intelligence gathering

No intelligence was received for this area.

Impact statement

Albumin administrations for people with cirrhosis with uncomplicated ascites

The NIHR Signal report and corresponding RCT(66) suggest that people with cirrhosis and uncomplicated ascites might live longer if they received regular intravenous albumin; albumin infusions also reduced the need for paracentesis and was associated with a reduction in total hospital days. Currently, NG50 makes no recommendation on the use of albumin infusions in patients with uncomplicated ascites and decompensated cirrhosis.

There were several inclusion criteria for the study, including diagnosis of liver cirrhosis with uncomplicated ascites, ongoing diuretic treatment with an antialdosteronic drug and being stable for 4 days before the trial. Given the large number of patient inclusion and exclusion criteria for this trial, there is limited generalisability from the study findings to the wider population. Further confirmatory research is needed on albumin administration, including identification of patient groups that might benefit most, to trigger an impact on the guideline.

Plasma expanders for people with cirrhosis and large ascites treated with abdominal paracentesis

The Cochrane systematic review(67) which considered plasma volume expanders in connection to paracentesis in people with cirrhosis could not clarify any benefit of plasma expansion versus no plasma expansion, and differences between one plasma expander versus

another plasma expander. The available evidence was from small short-term trials with very low certainty. Further evidence with a clear evidence of effect is required to have an impact on the guideline.

New evidence is unlikely to impact on the guideline.

Research recommendations

Assessing the risk of cirrhosis

Development of a risk tool to identify people at risk of cirrhosis.

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Treating small oesophageal varices

Do non-selective beta-blockers (NSBBs) improve survival and prevent first variceal bleeds in people with cirrhosis that is associated with small oesophageal varices?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified. All the studies on NSBBs included in this review relate to patients with medium/large rather than small varices. Therefore, the research recommendation will be retained for the next surveillance review.

Antibiotic resistance in treating spontaneous bacterial peritonitis

How frequently does antibiotic resistance occur, and how significant are antibiotic treatment-related complications when antibiotics are used for the primary prevention of SBP in people at high risk of having, or developing, cirrhosis?

Summary of findings

Some evidence from a single RCT relevant to the research recommendation was found and no ongoing studies were identified. The research recommendation will be retained for the next surveillance review.

Transjugular intrahepatic portosystemic shunt

What is the quality of life in people who have had a transjugular intrahepatic portosystemic shunt (TIPS)?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified. Therefore, the research recommendation will be retained for the next surveillance review.

Acute hepatic encephalopathy

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?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified. Therefore, the research recommendation will be retained for the next surveillance review.

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