Cirrhosis in over 16s: assessment and management

Consultation on draft guideline - Stakeholder comments table
[16/05/2023 to 12/06/2023]

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British Association for the Study of the Liver (BASL) and British Society of Gastroentero logy (BSG)	Guideline	General	General	The draft NICE guidance is confusing and without strong justification for the new statements on varices. We think it's important that NICE takes into account the views of BSG/BASL, to avoid another guidance document that doesn't reflect the realities of clinical practice or the evidence base.	Thank you. We have carefully considered your comments and responded to each of them below.
British Association for the Study of the Liver (BASL) and British Society of Gastroentero logy (BSG)	Guideline	General	General	We did a lot of consultation on this for the guidance document, and it seemed the overall consensus was that is was a bit early to start advocating NSBB for CSPH. We think it is strange that they recommend something which they say needs more evidence and is a research priority - people will struggle to get funding for trials and demonstrate equipoise for something that is already NICE guidance.	Thank you. The guideline does not advocate NSBB for CSPH, but suggests that clinicians may consider it as an option. This is in line with recommendations in the Baveno VII guideline (5.14). The committee were unable to make a strong recommendation about this because the evidence base is still small and there is some uncertainty. Because of this the committee made a research recommendation. We will review these recommendations when the results from the BOPPP trial are available after recruitment has ended and 3 years follow up. There may be other benefits for use of NSBBs in patients with advanced cirrhosis and the research recommendation will increase the likelihood of funding for trials in this area since NICE research recommendations are a priority for many funders.
British Association	Guideline	General	General	It is very important that CSPH is clearly defined otherwise there will be	Thank you. Defining CSPH is beyond the remit of this update. The scope for the update

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for the Study of the Liver (BASL) and British Society of Gastroentero logy (BSG)				misinterpretation with blanket use of NSBB in any patient with cirrhosis. We must make it clear that there is insufficient evidence to treat patients with NSBB to prevent decompensation using non-invasive criteria alone without endoscopy (this would be the research agenda). Dr Dhiraj Tripathi collaborated in this editorial just published in Liver International: https://onlinelibrary.wiley.com/doi/full/10.1111/liv.15582. I think it summarises the key evidence and evidence gaps. We think current draft NICE guidance will open the flood gates to use of NSBB…but not so fast!!	explains that the remit of the guideline was to consider the primary prevention of variceal bleeding, the primary prevention of spontaneous bacterial peritonitis and the effectiveness of NSBB to prevent decompensation. In Evidence Review A, the committee note that "CSPH can alternatively be diagnosed on the basis of clinical features (e.g. ascites, varices) as well as non-invasive methods including liver stiffness (transient elastography, or Fibroscan), serum biomarkers and other imaging." They noted that in the studies Villanueva (2022) IPD meta-analysis, of the four studies included, only 1 directly used a measure of HVPG >10mmHg to define CSPH, the other studies used a diagnosis of cirrhosis and the presence of small varices (Evidence Review C). The committee agreed to update the recommendation to give these examples. The recommendations about the use of NSBB are consistent with Dr Tripathi's note of caution when using drugs reducing cardiac-output and drugs inducing systemic vasodilation in people with cirrhosis. It was for this reason that the committee recommended starting on a very low dose and titrating upward depending on

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					the persons ability to tolerate the medicine. The committee have reorganised the information in the recommendations to make this clearer by making a separate section about prescribing NSBB to people with cirrhosis.
British Association for the Study of the Liver (BASL) and British Society of Gastroentero logy (BSG)	Guideline	General	General	We are a bit puzzled by some of the recommendations, in particular relating to prevention of decompensation and small varices (the presence of which is consistent with CSPH - even more so than HVPG). It is likely there will be an impact on BOPPP due to loss of equipoise. I think the BSG OP guidance is more clearer.	Thank you. We have clarified in the recommendation that the presence of varices is consistent with CSPH. The committee was aware of, and very supportive of the BOPPP trial and took care that they did not disadvantage it with their recommendations.
British Association for the Study of the Liver (BASL) and British Society of Gastroentero logy (BSG)	Guideline	General	General	NICE make recommendations but then in the explanations say there isn't the evidence yet and that they are a research priority. They seem to recommend using the Baveno VII criteria for beta blockers in CSPH for example (without mentioning Baveno), but don't reference the Baveno VI recommendations and say everyone should with cirrhosis should have an endoscopy- but if they are suggesting everyone should have a beta blocker if they have CSPH why do they need an endoscopy? Firstly, there is no mention of Baveno 6 guidelines-ie varices that require treatment are	Thank you. The committee were unable to make a strong recommendation about this because the evidence base is still small and there is some uncertainty. Because of this the committee made a research recommendation. The criteria for recommending beta-blockers are based on the studies that underpin the recommendations. The committee were reassured that the conclusion they made based on the evidence they considered matched the Baveno VII recommendations but agreed the underpinning evidence for both was likely to be the same.

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				highly unlikely to be identified if the fibroscan<20kPa, and platelets>150. So to recommend endoscopy in everyone who has a diagnosis of cirrhosis is very much against international guidelines-unless the reasons is to recruit for BOPP (which I think is a good reason, but not stated) Secondly, the assumption that everyone should be endoscoped because banding can be performed at the same time I think fails to appreciate the endoscopic process. Most patients being screened (in my experience) will be having the endoscopy under local. If banding is to then occur, it is likely that sedation will be required (indeed I would argue that it is mandated) in which case a relative needs to be available to take the patient home etc. ie, realistically, there will be many occasions when banding will not be performed. In the era of antibiotic resistance, I am not convinced about the role of antibiotics in the primary prophylaxis of SBP-but this should hopefully be answered by ongoing clinical trials. I guess the guidelines don't actually suggest this but I think the wording is woolly. It also seems illogical to make a recommendation, and then say that the recommendation should be a key	The NICE guideline recommends that everyone who is diagnosed with cirrhosis should have an upper GI endoscopy to detect varices (recommendation 1.2.7). This recommendation has been in the guideline since 2016. Given that, the committee agreed it was reasonable to highlight that if the circumstances were right, this was also an opportunity to band varices. The rationale and impact section explains that they were aware that this would require some forethought and that it would not always be possible, not least because often endoscopy is carried out by healthcare professionals who are not able to undertake EVL. The committee discussed your comment and agreed that the 2016 recommendation should be modified to clarify that diagnostic endoscopy should not be performed if the person with cirrhosis was going to be given NSBB since it would be pointless to do so. With regard to antibiotic prophylaxis, the committee discussed the evidence and agreed that current data does not support a significant effect of these medicines in preventing SBP, however, as explained in the committee discussion of the evidence section of the evidence review on preventing SBP (evidence

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				recommendation for research-and this is a refrain that is repeated. Re primary prevention of decompensation-I don't agree with the assessment of the evidence. As HVPG is not routinely available in the UK, how is clinically significant portal hypertension identified/defined. Furthermore, as mentioned above this area is also one recommended as a research priority. In the section on Other Complications-whenever TIPS is being considered for patients with diuretic refractory ascites, the first part of that line has to be "in the first instance, establish whether the patient is a candidate for transplantation." I think these guidelines have tried to offer a didactic approach for the clinician-and yet fail to. eg SBP prophylaxis-don't-but then, possibly do (based on evidence when antibiotic resistance was not a thing). Identify CSPH, and start beta-blockers-but probably in the context of a trial. There is nothing wrong with saying that the evidence is not quite there to make a hard	review B), the credible intervals were too wide in the network meta-analysis to give the committee enough confidence to recommend not using antibiotics. They were concerned that this had the potential to do harm. The previous version of this guideline, which was published in 2016 recommended only providing antibiotic prophylaxis for SBP to people with an ascitic protein of <15g/l. The committee noted that the antibiotics recommended in the 2016 guideline were no longer the antibiotics of choice for preventing SBP. One of them had been withdrawn from use and the other was the subject of an MHRA safety warning. As a result, the committee amended the recommendation to take account of other measures of liver disease severity (MELD and Child-Pugh) and to clarify that antibiotics should not be prescribed to people with cirrhosis that is not severe (which was already the unspoken intent of the previous recommendation). The uncertainty of the evidence led the committee to make a research recommendation to drive research of a higher quality than what is currently available so that when the guideline is updated, a future committee will be able to make a stronger recommendation about whether antibiotics are

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				recommendation-but may well be in the next 3-4 years. We have tried to address the carvedilol prescribing issue but to no avail. It may be that the route we have taken is the wrong one. I am struggling to see how we will change it- again this is the one area where the NICE statement could have been helpful. The risk of beta blockers in advanced cirrhosis is almost certainly a class effect (remember the papers in use of beta blockers in patients with ascites) and whilst Carvedilol may cause a bit more hypotension- that is mitigated by dose reduction. So if we are to give constructive feedback, it would be a plea for the NICE guidelines to effectively endorse the use of carvedilol in patients with cirrhosis, recognising the need to measure BP and dose adjust. NICE has always been about evidence and cost/benefit and there is a real risk of over prescribing in the absence of clear evidence.	a useful prophylactic measure for people with severe liver disease. We are aware that the ASEPTIC clinical trial is shortly due to complete recruitment and will provide further data to enable an update of these recommendations in due course. The recommendations cross refer to the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use which set out very clearly NICEs position on good antimicrobial stewardship. Re primary prevention of decompensation, the committee noted that the RCT evidence came from a study where people underwent HVPG measurement and that this is not a standard of care in the UK. However, of the four studies included in the IPD meta-analysis, 3 did not use HVPG to determine CSPH (Evidence Review C). They agreed that it was possible to identify CSPH using non-invasive measures. In Evidence Review A, the committee note that "CSPH can alternatively be diagnosed on the basis of clinical features (e.g. ascites, varices) as well as non-invasive methods including liver stiffness (transient elastography, or Fibroscan), serum biomarkers and other imaging."

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					As a result of this consultation, the committee have added HVPG >10mmHg and presence of oesophageal varices to the recommendation as examples of CSPH since this is what was used in the studies that provided the evidence. The section on Other Complications is not part of this update and for that reason the text was greyed out in the consultation document. Please see the scope for the update which explains the areas of the guideline that are being updated. With regards to only using carvedilol to prevent decompensation in the context of a trial, this is not what the committee recommend. The recommendation is that clinicians consider providing carvedilol to slow or prevent decompensation in people with known or suspected CSPH (see links earlier in this response for how that might be ascertained). With response to the carvedilol prescribing issue, it is not possible for NICE to endorse the use of carvedilol in people with severe liver disease since this is a direct contraindication in the SPC for the drug. The regulation of medicinal compounds is the role of the MHRA

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					and not NICE and therefore we are required to note off label uses of drugs in our recommendations. However, the committee were mindful of the concerns you raised and have reworded the information about the contraindication to minimise its impact.
British Association for the Study of the Liver (BASL) and British Society of Gastroentero logy (BSG)	Guideline	General	General	Also the statement on carvedilol being contraindicated in clinically significant hepatic impairment is new and will potentially result in GPs refusing to prescribe the drug. The definition of clinically significant hepatic impairment is vague and some could interpret this as anyone with varices (which it strictly is as any grade of varices is consistent with CSPH). Worse case scenario is a tsunami of "Decline to Prescribe (carvedilol) " notifications from GPs and all carvedilol prescriptions for primary prevention being the responsibility of secondary/tertiary care i.e. all us clinicians on this email chain. The recommendation to consider carvedilol in prevention of decompensation in CSPH makes no sense when the same document informs the reader that carvedilol is contraindicated in clinically significant hepatic impairment. Or am I missing something? Also I do not believe there is sufficient evidence for blanket recommendation of propranolol. PREDESCI	Thank you. The statement on carvedilol being contraindicated in clinically significant hepatic impairment is part of the UK license for the drug and is neither new, nor is it within NICEs remit to change. Please see the 'contraindications' section of any carvedilol preparation SPC. We have raised this with colleagues at MHRA. The contraindication listed on emc is for clinically significant hepatic dysfunction. The committee discussed this and agreed that, since there is clear evidence of benefit in people with oesophageal varices and for the prevention of decompensation, these could not be considered to be significant hepatic dysfunction. They were aware that some evidence suggested there were risks of prescribing NSBBs to people with ascites, so agreed that this was an example of significant hepatic dysfunction. The committee acknowledged that some of the evidence came from studies where people underwent HVPG

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				randomised only propranolol responders according to HVPG criteria - so definitely not aligning with UK practice. There is more evidence for carvedilol from recent meta-analysis but I believe we need more. So I would personally take out 1.3.9-11 and just stick with research recommendation 3. Both BOPPP and CALIBRE can provide data but they do not exclude decompensated patients and were not designed to answer this question at inception. Certainly the evidence on role of NSBB in preventing decompensation based on NITs without endoscopy needs to be generated. This study will the real game changer. I am concerned the guidance in its present form could lead to change in current practice which would harm our patients. Particular worry is discontinuation of carvedilol in primary care and over prescription of NSBB in patients who may not benefit.	and that this is not a standard of care in the UK, however some did not (see response above and Evidence Review C). They agreed that it was possible to identify CSPH using non-invasive measures. In Evidence Review A, the committee note that "CSPH can alternatively be diagnosed on the basis of clinical features (e.g. ascites, varices) as well as non-invasive methods including liver stiffness (transient elastography, or Fibroscan), serum biomarkers and other imaging." NICE are monitoring both the BOPP and CALBRE trials and have been in contact with the trial Principal Investigators. When the results from those trials are published, NICE will assess their impact on the guideline and may update the guideline again. The committee noted your concerns about the statement of the contraindication in the guideline and agreed that they wanted to minimise the possibility of this unintended consequence. As a result they agreed to add a section to the guideline that contains all the details of prescribing NSBB to people with cirrhosis.
British Association	Guideline	001	004	Rec 1.2.7: There is no mention of using non-invasive markers to stratify risk of portal	Thank you. Rec 1.2.7 is in a greyed-out part of the guideline and is not part of this update. The

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for the Study of the Liver (BASL) and British Society of Gastroentero logy (BSG)				hypertension. This goes against mainstream European guidelines which have been well validated in this area: patients meeting Baveno VI criteria (LSM<20 Platelets <150) have a low risk of high risk varices.	scope for the update explains that the remit of the guideline was to consider the primary prevention of variceal bleeding, the primary prevention of spontaneous bacterial peritonitis and the effectiveness of NSBB to prevent decompensation. We have passed your comment on to our surveillance team for further investigation.
British Association for the Study of the Liver (BASL) and British Society of Gastroentero logy (BSG)	Guideline	001	006	Rec 1.2.8: This is not nuanced enough, and consideration should be given to presence/absence of small varices, aetiological cure, and aetiology.	Thank you. Rec 1.2.8 is in a greyed-out part of the guideline and is not part of this update. The scope for the update explains that the remit of the guideline was to consider the primary prevention of variceal bleeding, the primary prevention of spontaneous bacterial peritonitis and the effectiveness of NSBB to prevent decompensation.
British Association for the Study of the Liver (BASL) and British Society of Gastroentero logy (BSG)	Guideline	004	011	Rec 1.3.9: Will the guideline define clinically significant portal hypertension according to liver stiffness measurement?	Thank you. Defining CSPH is beyond the remit of this update. The committee discussed your comment and agreed that it was important to give a steer on what constituted CSPH, since there is no widely agreed definition for non-invasive measures they used the entry criteria to the studies that were used in the evidence review on preventing decompensation (Evidence Review C). The studies in that review used either directly measure HPVG >10mmHg or a diagnosis of cirrhosis plus the

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					presence of small varices as entry criteria to their studies. The rationale and impact section notes that CSPH 'can be diagnosed on the basis of clinical features (for example, ascites or small varices) as well as through non-invasive methods, including tests to measure liver stiffness, or serum biomarkers' but since the committee did not examine the evidence about this they were unable to define thresholds.
NHS England	Guideline	General	General	The consultation is mainly about assessment and management of oesophageal varices as wider recommendations related to the assessment and management of cirrhosis remain unchanged.	Thank you. The update focuses on 3 areas of care for people with cirrhosis: the prevention of oesophageal variceal bleeding, the prevention of spontaneous bacterial peritonitis and the prevention of decompensation.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*