NICE National Institute for Health and Care Excellence

Appendix B: Stakeholder consultation comments table

2018 surveillance of Alcohol-use disorders: diagnosis and management of physical complications (2010)

Consultation dates: 22 November to 5 December 2018

Do you agree with the proposal to partially update the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
British Society of Gastroenterology Comments endorsed by Royal College of Physicians	Yes	No comments provided	Thank you for your response.
British Association for the Study of the Liver (BASL)	Yes	**EF:** General Comments: **Wernicke's Encephalopathy**: I have concerns about the proposal to alter the wording of the Wernicke's Encephalopathy section without there being any new evidence. I agree that clarification about the doses of treatment would be helpful in practice but whatever is proposed should be qualified with a statement	Thank you for your response. **Wernicke's encephalopathy:** The changes to Wernicke's encephalopathy will be to add clarity to the recommendation wording. Feedback received indicates that the current wording of 'Thiamine should be given in doses toward the upper end of the 'British national formulary' range' was unclear and not helpful in practice. But your concern will be noted to ensure that as the update is planned from the outset there is caution in changes

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		along the lines that the evidence for a specific dosing regimen is unclear. I would urge the reviewers to make a clear distinction between the treatment of overt/ incipient Wernicke's as opposed to the prevention of Wernicke's in 'at risk' individuals. Although based on no new evidence I have included a local guidance for Wernicke's Encephalopathy based upon the limited pharmacokinetic studies and previously described consensus. **Alcohol Withdrawal:** I also have concerns that symptom-triggered treatments are not considered appropriate. Whilst reservations about CIWA-Ar have been raised with regards to liver disease patients (Hecksel et al, 2008), fixed dose treatments for patients with advanced alcohol-related liver disease risk encephalopathy. I also echo the concern that clomethiazole is still suggested in this context: it is rarely used in clinical practice. **Pharmacotherapy for ARLD**: The paper cited by Forrest et al, 2018 indicates that the discriminant function is inadequately prognostic and should probably not be used. The EASL guidelines suggest the Glasgow Alcoholic Hepatitis Score; the AGA suggests the MELD, though the evidence for a threshold for therapy using the MELD is without evidence. **SM:** General comments about the partial update	made to recommendation 1.2.1.1 around doses. The aim of this change is to add clarity, and clear up any discrepancy with the BNF and the NICE guideline. **Alcohol withdrawal:** The evidence base for a symptom-triggered regimen still appears supportive of recommendation 1.1.3.4 and we are not suggesting an update to this recommendation. However, we did receive topic expert feedback that, in practice, a symptom-triggered regimen may not be optimal. New evidence from 3 RCTs on symptom-triggered lorazepam indicated it is as effective as fixed dose lorazepam but with significantly shorter length of treatment and lower doses of lorazepam. This is in line with current recommendation 1.1.3.4 and we are not proposing to update this recommendation. Thank you for your comment on clomethiazole. We address this issue below. **Pharmacotherapy for ARLD:** When reviewing recommendation 1.3.3, we considered the paper by Forrest et al 2018 highlighting that discriminant score may be inadequately prognostic, and sought further clinical expert advice on this issue, to help us understand the impact of the new evidence and relation to clinical practice. The view from experts was that this paper alone was not sufficient to change the recommendation at this time point and we should await further evidence before any updates are considered. We did ask for further evidence on this subject during the stakeholder consultation, but no new evidence was identified. We will revisit this topic at the next surveillance review.

		Treatment for acute alcohol withdrawal Slightly surprised that Clomethiazole still appears and whether this will be considered again as part of the revision Slightly surprised that "Topic experts also highlighted that symptom-triggered alcohol detox regimens may not be optimal, resulting in adverse complications" p12. I have not heard many voice those concerns and the evidence would certainly support them **Assessment and diagnosis of alcohol-related liver disease** It appears contradictory that "new evidence is unlikely to change guideline recommendations" while NG50 (Cirrhosis in adults) is quite explicit on recommendations about the use of Transient Elastography in heavy drinkers. CG100 would therefore be at odds with NG50. CG100 recommends consideration of histological assessment, whereas NG50 is quite clear on heavy drinkers undergoing TE. In addition, the BSG guidelines "Guidelines on the management of abnormal liver blood tests" Newsome et al Gut 2017, has a section on ARLD which is of relevance, here.	**Treatment for acute alcohol withdrawal** Thank you for your comment on clomethiazole. As we are proposing an update of recommendation 1.1.3.1 'treatment for alcohol withdrawal', the recommendation will be updated by a committee based on the best available evidence. We will pass on your comment to the developers, that clomethiazole is rarely used in clinical practice. Thank you for your comment on symptom-triggered regimen. We address this issue above. **Assessment and diagnosis of alcohol-related liver disease** New evidence for transient elastography will be considered at the next surveillance review of cirrhosis in over 16s: assessment and management (NICE guideline NG50). It was not considered for CG100 to avoid overlaps between NG50 and CG100. A link will be added to highlight that information is available on the diagnosis, management and treatment of cirrhosis in cirrhosis in over 16s: assessment and management (NICE guideline NG50). Thank you for highlighting the BSG guidelines and information on treatment of Wernicke-Korsakoff syndrome (WKS). WKS is covered by alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence (NICE guideline CG115). We are currently reviewing this guideline and will consider this information.

		Prophylaxis and Treatment of Wernicke-Korsakoff Syndrome document	
Royal College of Paediatrics and Child Health		We have not received any responses for this consultation.	Thank you for your response.

Do you agree with the 3 proposals to withdraw the following recommendations from section 1.4 Alcohol-related pancreatitis of alcohol-use disorders: diagnosis and management of physical complications (NICE guideline CG100) and replace with recommendations from the more recent guideline on pancreatitis (NICE guideline NG104)?

- **Proposal 1: withdraw recommendation 1.4.2.2 from CG100 and incorporate pancreatitis guideline recommendation 1.3.8**
- **Proposal 2: withdraw recommendation 1.4.3.1 from CG100 and incorporate pancreatitis guideline recommendation 1.2.3**
- **Proposal 3: withdraw recommendation 1.4.4.1 from CG100 and incorporate pancreatitis guideline recommendations 1.2.5 to 1.2.7**

Stakeholder	Overall response	Comments	NICE response
British Society of Gastroenterology Comments endorsed by Royal College of Physicians	Yes	All three proposals	Thank you for your response and support for the proposal.

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British Association for the Study of the Liver (BASL)	Yes but recommend minor revision on proposal 2	SV: Do not offer prophylactic antimicrobials to people with acute pancreatitis. Revise to: Do not offer prophylactic antimicrobials to people with mild acute pancreatitis. SM: The NICE Guideline on pancreatitis (NG104) is comprehensive and new since the CG 100 was written. I would agree with the proposals to bring the CG 100 recommendations in line with the NG 104 guideline recommendation. Furthermore, given the extent of NG 104, I wonder whether it is now necessary to have a section within CG100 on alcohol-related pancreatitis or whether this should defer fully to the newer NG 104	SV Thank you for your response. Revision to recommendations within pancreatitis (NICE guideline NG104) is beyond the scope of the current review. However, the pancreatitis guideline said 'do not' regardless of severity based on more recent evidence than CG100. The pancreatitis guideline committee's argument was that even with no clear evidence of benefit, the potential harms outweighed the potential benefits and saying 'do not' is in keeping with current views on antimicrobial stewardship. SM Thank you for your response and support for the proposal. We have only suggested removing recommendations from alcohol-use disorders: diagnosis and management of physical complications (NICE guideline CG100) that we believe were so clearly covered by pancreatitis (NICE guideline NG104) as to be redundant. We did not suggest removing the entire section as we were conscious that NG104 did not cover enzyme therapy in the same way as CG100, and that some other recommendations were felt to be not as clearly covered by NG104.
Royal College of Paediatrics and Child Health	Not answered	No comments provided	Thank you for your response.

Are there any ongoing trials or systematic reviews due to publish within the next 2 years that NICE should be aware of for future surveillance of this topic? In particular, studies that relate to section 1.3 alcohol-related liver disease (NICE guideline CG100) and concern: • **diagnostics for cirrhosis/fibrosis,** • **pharmacotherapy for alcohol-related liver disease** • **prognostic tools for predicting patients likely to benefit from prednisolone (e.g. discriminant function)?**			
Stakeholder	**Overall response**	**Comments**	**NICE response**
British Society of Gastroenterology Comments endorsed by Royal College of Physicians	Yes probably	No comments provided	Thank you for your response.
British Association for the Study of the Liver (BASL)		**Diagnostics for cirrhosis/fibrosis** Peng Y, Li Y, He Y, Wei Q, Xie Q, Zhang L, Xia Y, et al. The role of neutrophil to lymphocyte ratio for the assessment of liver fibrosis and cirrhosis: a systematic review. Expert Rev Gastroenterol Hepatol. 2018 ;12:503-513 **Pharmacotherapy for alcohol related liver disease**	Thank you for your detailed and helpful response. **Diagnostics for cirrhosis/fibrosis** We have assessed this study and feel it better fits with cirrhosis in over 16s: assessment and management (NICE guideline NG50), which covers diagnostics for cirrhosis in greater detail and would be the natural place to be updating in the future for diagnostics related to cirrhosis.

		Two Trials presented as Abstracts at AASLD November 2018: Philippe Mathurin Jean-Francois Dufour, Natalie H. Bzowej, Mitchell L. Shiffman, Sarah Arterburn, Tuan Nguyen, et al. Selonsertib in Combination with Prednisolone for the Treatment of Severe Alcoholic Hepatitis: A Phase 2 Randomized Controlled Trial. AASLD 2018 Gyongyi Szabo, Mack C. Mitchell, Craig J McClain, Srinivasan Dasarathy, Arthur J. McCullough, Laura Nagy, Aimee Kroll- Desrosiers, Svetlana Radaeva and Bruce Barton. LB-1: IL-1 Receptor Antagonist in Combination with Pentoxifylline and Zinc for Severe Alcoholic Hepatitis: A Multicenter Randomized Double-Bind Placebo-Controlled Clinical Trial. AASLD 2018 Registered Trials of Potential Interest: A Novel Pharmacotherapy for Alcoholism and Alcohol Liver disease (metadoxine) NCT01504295 Meta-Analysis of Drug Therapy in Patients With Severe Alcoholic Hepatitis NCT02796469 **Prognostic tools for predicting patients likely to benefit from prednisolone**	**Pharmacotherapy for alcohol related liver disease** Thank you for highlighting these 2 conference abstracts. We do not include conference abstracts in a surveillance reviews. Thank you for highlighting the two registered trials. A Novel Pharmacotherapy for Alcoholism and Alcohol Liver disease (metadoxine) NCT01504295 This trial has less than 50 patients and completed in 2015 so would not qualify for ongoing surveillance. Meta-Analysis of Drug Therapy in Patients With Severe Alcoholic Hepatitis NCT02796469 This study completed in 2016 so would not qualify for ongoing surveillance. **Prognostic tools for predicting patients likely to benefit from prednisolone** Thank you for highlighting these studies. Shasthry SM, Rastogi A, Bihari C, Vijayaraghavan R, Arora V, Sharma MK, Sarin S. Histological activity score on baseline liver biopsy can predict non-response to steroids in patients with severe alcoholic hepatitis. Virchows Arch. 2018;472:667-675 This would not meet inclusion in our surveillance review due to it not being an RCT or systematic review. Sukriti S, Maras JS, Bihari C, Das S, Vyas AK, Sharma S, et al. Microvesicles in hepatic and peripheral vein can predict nonresponse to corticosteroid therapy in severe alcoholic hepatitis Aliment Pharmacol Ther. 2018; 47:1151-1161

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		Shasthry SM, Rastogi A, Bihari C, Vijayaraghavan R, Arora V, Sharma MK, Sarin S. Histological activity score on baseline liver biopsy can predict non-response to steroids in patients with severe alcoholic hepatitis. Virchows Arch. 2018;472:667-675 Sukriti S, Maras JS, Bihari C, Das S, Vyas AK, Sharma S, et al. Microvesicles in hepatic and peripheral vein can predict nonresponse to corticosteroid therapy in severe alcoholic hepatitis Aliment Pharmacol Ther. 2018; 47:1151-1161 Garcia-Saenz-de-Sicilia M, Duvoor C, Altamirano J, Chavez-Araujo R, Prado V, de Lourdes Candolo-Martinelli A, et al A. A day-4 Lille Model predicts response to corticosteroids and morality in severe alcoholic hepatitis. Am J Gastroenterol. 2017;112:306-315. Ewan H Forrest, Natasha Storey, Rohit Sinha et al. The Neutrophil-To-Lymphocyte Ratio In Alcoholic Hepatitis: Influence On Corticosteroid Treatment: in submission	This would not meet inclusion in our surveillance review due to it not being an RCT or systematic review. Garcia-Saenz-de-Sicilia M, Duvoor C, Altamirano J, Chavez-Araujo R, Prado V, de Lourdes Candolo-Martinelli A, et al A. A day-4 Lille Model predicts response to corticosteroids and morality in severe alcoholic hepatitis. Am J Gastroenterol. 2017;112:306-315. This would not meet inclusion in our surveillance review due to it not being an RCT or systematic review. Ewan H Forrest, Natasha Storey, Rohit Sinha et al. The Neutrophil-To-Lymphocyte Ratio In Alcoholic Hepatitis: Influence On Corticosteroid Treatment: in submission This would not meet inclusion in our surveillance review due to it not being an RCT or systematic review.
Royal College of Paediatrics and Child Health	Not answered	No comments provided	Thank you.

Do you have any comments on areas excluded from the scope of the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**

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British Society of Gastroenterology Comments endorsed by Royal College of Physicians		1. [Conflict of interest declared – noted by NICE but removed for confidentiality reasons.] 2. The current update is essentially an update of a limited guideline. If there is to be a further update in the future, I advise that there is consideration of what physical complications in other systems should be considered, apart from the liver, pancreas and brain. 3. The update on the treatment of alcohol-related liver disease (ARLD) is very good and the main addition to the 2010 guideline. 4. The 2018 update emphasises the need to avoid stigma, which is laudable. It also strives to use the expression "Alcohol-related" rather than "Alcoholic". There are instances where this is missed and the word "Alcoholic" is used. This needs to be changed. 5. We sent questionnaires to 21 topic experts and received 7 responses. This response is disappointing. It would help to assess the authority of the Guideline if the members of the guidance committee were given. 6. 1.2. Wernicke's Encephalopathy (WE). The expression "Alcohol-related brain damage" (ARBD) should also be used in this section. WE is a severe, specific condition, as is WKS. Many people have ARBD, which is less severe and more difficult to diagnose, especially when they have acute withdrawal. Given this consideration, I would advise parenteral thiamine to all patients with alcohol problems, who are admitted acutely. The change to oral thiamine can be made after assessment over 24 hours or longer. 7. I THINK THAT THE FOCUS ON WE, RATHER THAN ARBD, WILL BE HARMFUL AND LEAD TO MISSED ARBD, WITH SEVERE PHYSICAL, MENTAL AND SOCIAL CONSEQUENCES.	Thank you for your response and detailed comments. Comments 1-2 We appreciate that the scope of alcohol-related physical complications is much broader than NICE guideline CG100 recommendations cover. The scope of the guideline was limited to the conditions felt to be most important and that did not currently have NICE guidance available at the time. NICE has guidelines on a number of conditions that could be associated with alcohol use, such as: cirrhosis in over 16s: assessment and management (NICE guideline NG50); pancreatitis (NICE guideline NG104); atrial fibrillation: management (NICE guideline CG180); colorectal cancer: diagnosis and management (NICE guideline CG131); and cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NICE guideline NG36). Comment 3 Thank you for your support of the previous guideline update. Comment 4 Thank you for highlighting that we may still have stigma terminology within our surveillance review. NICE is committed to reducing stigma terminology and we will rectify this. Comment 5 During surveillance reviews full topic expert feedback is often not achieved, but NICE does use additional clinical experts when needed, as well as stakeholder consultation to ensure a wide range of experts can comment. Comments 6-8

		8. PATIENTS WITH ARBD AND WE CAN IMPROVE WITH ORAL THIAMINE AND ABSTINENCE OVER 6-12 MONTHS. IT IS IMPORTAANT TO STRESS THE NEED FOR LONG TERM THAIMINE AND ABSTINENCE IN THIS GROUP. 9. Parenteral Thiamine. The evidence-base for the dose is limited. In 2000, I gave evidence to the RCPL Working Party on Alcohol and gave our hospital guidelines, as there was no evidence-base. These guidelines were included in the RCPL 2001 Working Party paper. They are now used by the pharmaceutical company, which manufactures pabrinex and clinicians use them. I doubt whether a clinical trial would be useful. 10. It would help to spell out what blood tests to perform in patients admitted. In particular, blood magnesium and calcium are often omitted, sometimes with severe consequences, such as fatal cardiac arrhythmias. 11. Richard Aspinall from the BSG made the following 3 points, which I would agree with. 1.1.1.1 "For people in acute alcohol withdrawal with, or who are assessed to be at high risk of developing, alcohol withdrawal seizures or delirium tremens, offer admission to hospital for medically assisted alcohol withdrawal." – I think this should be changed to *consider* admission to hospital, given outpatient/daycase "detoxification" is safe and effective depending on circumstances and if the necessary nursing support is available. 1.3.3.1 – I would suggest changing this recommendation which advocates using Discrimination Function >32 to select for steroids. DF is not enough in predicting steroid	Thank you for this comment. Currently alcohol-use disorders: diagnosis and management of physical complications (NICE guideline CG100) only includes Wernicke's encephalopathy (WE). The committee did consider whether thiamine should be recommended in low risk groups at risk of WE, but did not feel the evidence was strong enough to recommend widespread use of thiamine in this group because of a lack of evidence. Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence (NICE guideline CG115) includes a section on WKS (recommendations 1.3.8.5-1.3.8.6). We will, however, note this concern around wording for WE or ARBD, and the need for longer-term thiamine and alcohol abstinence. Comment 9 Thank you for this comment. We will note this issue of no clear dose consensus to ensure it is captured during the refresh. Comment 10 Thank you for this comment on blood tests. We will note this for guideline update. Comment 11 Thank you for this comment on recommendation 1.1.1.1. We are unable to change guideline wording to consider as this would change the strength of the recommendation which was based on the evidence base and committee judgement. The GDG agreed, by expert consensus, that individuals may also need admission due to the severity or predicted severity of the syndrome. More

		response –from the post-hoc STOPAH data, GAHS, ABIC and MELD were all better predictors of response, with ABIC and GAHS better at predicting survival benefit (Forrest EH et al, J Hepatol 2018). 1.3.4.1 – I would say nutritional support should be offered to all patients with acute alcohol-related hepatitis (AAH), not just "if needed". As per the EASL guidance, several studies have highlighted that protein energy malnutrition is present in almost every patient with severe AAH and is associated with poor prognosis.	specifically, if a person presents following or in a withdrawal seizure or delirium tremens they should be admitted for medical care. Thank you for the comment on recommendation 1.3.3.1. We have included the Forrest et al 2018 study in our surveillance review but received clinical feedback that this is not strong enough to change clinical practice at this time and further evidence is needed. Thank you for the comment on recommendation 1.3.4.1. We are unable to change guideline wording to remove 'if needed' as this would change the meaning of the recommendation which was based on the evidence base and committee judgement. Evidence that enteral nutrition consistently improved outcomes as monotherapy or in combination with other therapies in severe alcohol-related hepatitis was not available.
British Association for the Study of the Liver (BASL)	No	No comments provided	Thank you for your response.
Royal College of Paediatrics and Child Health	Not answered	No comments provided	Thank you for your response.

Do you have any comments on equalities issues?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
British Society of Gastroenterology	Yes	The guidance should include health inequalities and provide data, such as on mortality of the poorest and richest quintiles, especially for ARLD. This emphasises the need for	Thank you for your comment. Health inequalities were considered during guideline development, and this included recognition of a person's social position. NICE guidelines do not include

Comments endorsed by Royal College of Physicians		rapid vitamin and nutritional supplementation, and for it to be continued post-discharge from hospital.	epidemiological data, although potential equality issues and the broader context are considered during guideline development. The committee also acknowledged that social situations could lead to neglect and poor diet, for example. The guideline does offer cross-references to Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition (NICE guideline CG32), which provides more detail on nutritional support, including in the community.
British Association for the Study of the Liver (BASL)	No	No comments provided	Thank you for your response.
Royal College of Paediatrics and Child Health	Not answered	No comments provided	Thank you for your response.