NICE National Institute for Health and Care Excellence

Alcohol Use Disorders (standing committee update)

Consultation on draft guideline - Stakeholder comments table

20/12/16 to 24/01/17

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

ID	Type	Organisation name	Document	Page No	Line No	Comments	Developer's response
1.	SH	British Association for the Study of the Liver (BASL)	Full	general	general	The choice of ''offer'' is correct. The data are not conclusive and the overall effect on mortality is only seen in those without bleeding or infection – and this was not studied in a randomised controlled fashion. Furthermore a number of hepatologists across the country remain to be convinced that corticosteroids add sufficient benefit to justify their use clinically and would be unhappy with a stronger recommendation.	Thank you for your comment. The recommendation is worded to reflect certainty in the evidence relating to outcomes that were considered by the committee to be most important for clinical decision-making. While the strength of the recommendation has not changed from the original guideline, the committee were keen to make it a more focused recommendation, reflecting the fact that the majority of evidence now comes from the recent STOPAH trial and is more equivocal in terms of benefit. The committee therefore included several pre-conditions (as bullet points) to the 'offer' recommendation. These restrict the eligible treatment population to those for whom a short-term survival benefit is demonstrated in RCTs (that is, patients with no active infection, GI bleeding or renal impairment). The third pre-condition requires that clinicians discuss both the potential benefits and harms with eligible patients before starting corticosteroid treatment.
2.	SH	British Association	Full	10	30	There are very few new studies included. But it is noteworthy that the study by Thursz et al. is by far the	Thank you. We agree with your comment that although there are few new studies,

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		for the Study of the Liver (BASL)				largest; it is also from the current era reflecting current practice and an entirely UK based study and thus much more relevant than most of the others included in the meta-analysis for the NICE guidelines. The mortality conclusions are not strongly in favour of corticosteroids in those free from bleeding or infection and further studies are said to be underway. The effect of gender and ethnicity remains to be addressed.	the STOPAH trial (Thursz et al. 2015) represents a significant addition to the existing evidence base. This is noted in the Linking Evidence to Recommendations table (section 2.6 of the Addendum): "The recently published multicentre STOPAH trail (Thursz 2015) includes twice the number of participants as all other included studies combined….The committee noted that STOPAH was one of only two included studies directly applicable to a UK patient population…. It was also agreed that the population for whom the recommendation is made should match that of the STOPAH trial, as this was the study that contributed the most robust and directly applicable evidence of relative benefits and harms." The committee noted during decision-making that women with severe alcoholic hepatitis may have worse outcomes than men for a given degree of severity. This was taken into account when reviewing the evidence from studies conducted in all-male populations, which was downgraded for 'indirectness' in relation to the mixed-gender population of interest. The committee are aware that the STOPAH trial included a multivariate analysis of treatment group on mortality, adjusting for baseline factors that were

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							statistically significant in univariate analyses. Gender was not included in that analysis, suggesting it was not an independent predictor of outcome. We acknowledged that it remains unclear whether treatment outcomes for severe alcoholic hepatitis differ between ethnic groups. The committee noted that the majority of evidence supporting the recommendation comes from the STOPAH trial in which 96% of patients were classed as Caucasian. This is highlighted as a potential equalities issue for this guideline update. We will notify the NICE Surveillance team to identify any published findings from the on-going trials to which you refer, and these will be added to the evidence base in any future updates of this guideline.
3.	SH	British Association for the Study of the Liver (BASL)	Full	21	19	The meta analysis also revealed no effect on overall or liver related mortality. Although there is comment on increased mortality the sub-set with infection it needs to be noted that the vigour with which infection has been sought in these many studies will vary substantially.	Thank you for your comment. The meta-analysis undertaken for this review found that all-cause mortality *and* liver-related mortality are reduced within the first month by steroid treatment, but only in patients with severe AH (DF≥32) and no active infection or GI bleeding at treatment commencement. The evidence relating to liver-related mortality was from fewer studies (as some studies did not report cause of death) and may be compromised because studies used different criteria for categorising some of the fatal complications of AH as 'liver-' or

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							'non-liver related' (for example, GI bleeding or sepsis). Evidence was not available to undertake a subgroup analysis of mortality among patients with and without active infection at baseline. Few trials permitted inclusion of patients with infection; those that did do not report mortality separately for patients with and without infection. This is noted in the 'Quality of Evidence' section of the Linking Evidence to Recommendations table (section 2.6 of the Addendum). The review did, however, find that treatment with steroids increased rates of serious infection within 90 days in all levels of severity of AH. It is not known what proportion of these infections were treatment-related, and what proportion of patients died as a result of the infection. We acknowledge the point you make about infection monitoring in the Linking Evidence to Recommendations table, as follows: "However it was acknowledged that in a highly monitored research study population, identification of infections is likely to be higher than in the general population, particularly when patients have been discharged from inpatient care. Levels of follow-up (which varies widely between centres) will be key to the

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							prompt identification and treatment of infections and their longer-term sequelae."
4.	SH	British Association for the Study of the Liver (BASL)	Full	21	21 - 29	The long term effect of reducing early abstinence and a reduction in alcohol intake in the long term need to be considered in all studies in this field. These may prove essential in converting any early benefit from corticosteroids into a long term effect on mortality	Thank you for your comment. The effect of subsequent alcohol consumption / abstinence on long-term outcomes in survivors was not a subgroup analysis specified in the review protocol for this update. The committee are aware that the STOPAH trial included a logistic regression analysis to assess the effect of alcohol consumption status at day 90 on 1 year mortality. Those data confirm that modest drinking (within pre-2016 government guidelines) was associated with a twofold increase, and a return to previous drinking levels with a threefold increase in 1 year mortality compared with abstinence at day 90. However the analysis did not examine whether there were treatment group differences and was limited by reliance on self-reported drinking behaviour and large amounts of missing data. The committee does acknowledge the importance of post-discharge abstinence and referral to appropriate professional support several times in the Linking Evidence to Recommendations table (section 2.6 of the Addendum) as follows: **Relative value of different outcomes**

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							"Surviving an episode of severe AH is less likely to determine patients' longer-term physical, social and psychological wellbeing than maintaining abstinence from alcohol, which is the only way of preventing further injury to the liver" **Other considerations** "…patients whose condition improves sufficiently may be discharged home, whereupon non-liver related factors (most notably, subsequent drinking behaviour) will have the biggest impact on longer-term outcomes." **Equalities issues** "4. Poor social support, complex physical or psychological comorbidities, and social problems were identified as potential equalities issues as these factors may impact on individuals' longer-term outcomes following discharge from hospital. Clinicians should refer to NICE CG115 (Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence) regarding referral to specialist alcohol services for assessment and the implementation of appropriate support interventions to promote abstinence and prevent relapse."
5.	SH	British Association for the Study	Full	27	17	There should be strong research recommendation for future studies. Bacterial infection can be sought more rapidly and frequently with a fast turn around using molecular	Thank you for your comment. We acknowledge that the association of corticosteroid treatment with an

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		of the Liver (BASL)				techniques to seek 16s in blood in addition to more conventional techniques. At the very least blood could be studied retrospectively. It is critical to know if infection is an opportunistic consequence of corticosteroid therapy and thus inevitable.	increased risk of serious infection in this population is important new evidence which may offset its therapeutic benefit. However it may be difficult in practice to determine the aetiology of these infections. The recommendation stresses that relative risks and harms of should be discussed with patients before starting treatment. A topic expert noted that the STOPAH trial investigators have recently published a paper confirming that prednisolone was associated with an increased risk of infection developing after treatment (though not during). Furthermore, their analysis confirmed that development of infection was associated with increased 90-day mortality in patients with severe AH treated with prednisolone. The authors suggest that monitoring levels of circulating bacterial DNA before treatment could identify patients at high risk of infection if given prednisolone http://www.gastrojournal.org/article/S0016-5085(16)35533-0/pdf
6.	SH	British Society of Gastroenterology	Recommendation 1 1. Offer corticosteroid treatment to people with severe alcohol-	General	General	BSG welcomes the opportunity to respond to this important consultation. Our comment would be as such · Previous studies in this arena occurred during a period 40 years when there was marked improvement in the overall management and understanding of both liver disease and sick patients in general. As such it difficult to	Thank you for your comments. We agree that older studies included in the evidence review are of limited applicability to current practice, but that the large, UK-based STOPAH trial provides sufficient quantity and quality of evidence on which to base an 'offer' recommendation, with the pre-conditions specified in the accompanying bullet

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			related hepatitis and a discriminant function of 32 or more, only after: • effectively treating any active infection or gastrointestinal bleeding that may be present; • controlling any renal impairment; • discussing the potential benefits and risks with the person and their family or carer, explaining that corticosteroid treatment:			draw overall firm conclusion from them But the 'offer' of CS is appropriate given the results of STOPAH and the scale and quality of the trial. · We believe that more work needs to be done around prognostication to guide management of these patients. In particular the DF is a relatively blunt tool that was only used due to its entry criteria in previous AAH studies. Therefore allow the possibility of an alternative scoring to be used. · The use of the word 'offer' is appropriate it stresses the marginal gain and also the risk and qualifies the need for a conversation with patients and carers to explain pros and cons . We are pleased to see in the main text the acknowledgement re impaired cognition not only from Alcohol withdrawal / HE but an implication re cognitive dysfunction due to alcohol brain damage. · We think there should also be emphasis on the experience of staff who look after and assess and treat these patients i.e. The patient COMPLEXITY should be matched by staff COMPETENCY so that patients are not needlessly exposed to a higher risk strategy (reference NCEPOD report) · It may be worth emphasising again that longer term outcome is more strongly related to abstinence and the need to ensure referral and subsequent management by competent alcohol team offering a full array of therapeutic options	points. The committee discussed alternative prognostication scoring methods to the DF, including the Glasgow Alcoholic Hepatitis Score (GAHS), Lille score and model for end-stage liver disease (MELD). It was noted that each measure was developed for a somewhat different purpose: the GAHS to identify patients with AH at greatest risk of mortality; the Lille score to identify non-responders to steroid treatment, and MELD to quantify end-stage liver disease in order to prioritise patients for liver transplantation. While these measures will all identify a 'severe' subset of patients, only Maddrey's DF was specifically developed to identify patients with severe AH who might benefit from corticosteroid therapy. The review protocol did specify a subgroup analysis looking at outcomes for patients with 'severe' alcoholic hepatitis, however defined in studies. However, as you are aware, published trials to date have only used DF≥32 (and/or hepatic encephalopathy) as a threshold for defining 'severe' AH, so we are unable to advise use of alternative measures in the recommendation at this time. We will notify the NICE Surveillance team to identify future randomised-controlled trials that may use other validated

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			o has been shown to improve survival in the short term (1 month) o has not been shown to improve survival over a longer term (3 months to 1 year) has been shown to increase the risk of serious infections within the first 3 months of starting treatment. [2017]				prognostic indicators as a threshold for treatment, in order to inform subsequent updates of this guideline. We did not review evidence relating to staff competency in this clinical area. The full guideline (NICE CG100) includes a number of recommendations emphasising that healthcare professionals should have the appropriate skills in assessing and managing patients with physical complications of alcohol use disorders, including recommendation 1.3.1.2: "Refer people to a specialist experienced in the management of alcohol-related liver disease to confirm a clinical diagnosis of alcohol-related liver disease". Regarding abstinence, the committee debated whether to add the following statement (in italics below) to one of the bullet-points in the recommendation – namely, that corticosteroid treatment… • …has not been shown to improve survival over a longer term (3 months to 1 year), *so it is important that the person does not start drinking alcohol again*" However, it was agreed that evidence for the statement in italics was not reviewed as part of this update, so it could not be

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							included in the recommendation. None of the included studies examined the effect of abstinence (or provision of professional support) on longer-term outcomes by treatment group. The committee are aware that the STOPAH trial included a logistic regression analysis to assess the effect of alcohol consumption status at day 90 on 1 year mortality. Those data confirm that modest drinking (within pre-2016 government guidelines) was associated with a twofold increase, and a return to previous drinking levels with a threefold increase in 1 year mortality compared with abstinence at day 90. However the analysis did not examine whether there were treatment group differences and was limited by reliance on self-reported drinking behaviour and large amounts of missing data. The committee does, however, acknowledge the importance of post-discharge abstinence and referral to appropriate professional support several times in the Linking Evidence to Recommendations table (section 2.6 of the Addendum) as follows: **Relative value of different outcomes** "Surviving an episode of severe AH is less likely to determine patients' longer-term physical, social and psychological wellbeing than maintaining abstinence from alcohol, which is the only way of

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							preventing further injury to the liver" **Other considerations** "…patients whose condition improves sufficiently may be discharged home, whereupon non-liver related factors (most notably, subsequent drinking behaviour) will have the biggest impact on longer-term outcomes." **Equalities issues** "4. Poor social support, complex physical or psychological comorbidities, and social problems were identified as potential equalities issues as these factors may impact on individuals' longer-term outcomes following discharge from hospital. Clinicians should refer to NICE CG115 (Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence) regarding referral to specialist alcohol services for assessment and the implementation of appropriate support interventions to promote abstinence and prevent relapse."
7.	SH	British Society of Gastroenterology		11	General	On page 11 of the summary, the definition of decompensated liver disease is a bit unusual, they say - "Liver disease complicated by the development of jaundice, ascites, bruising or abnormal bleeding and/or hepatic encephalopathy". Most of us would define it as "...complicated by jaundice, ascites, variceal bleeding or hepatic encephalopathy".	Thank you for your comment. An amendment to the glossary wording for 'decompensated liver disease' has been made in both the NICE summary version and the guideline addendum, in line with your advice.
8.	SH	British		General	General	Regarding corticosteroids for acute alcoholic hepatitis, I	Thank you for your comments. The

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		Society of Gastroenterology				would perhaps add 2 comments: In patients with a DF>32, consider using the Glasgow Alcoholic Hepatitis Score to identify patients more likely to benefit from corticosteroids [ref Forrest EH et al, Gut 2007]. In patients who receive corticosteroids, consider using the Lille Score at Day 7 to identify patients unlikely to benefit from further steroid therapy [ref Louvet A et al, Hepatology 2007].	committee discussed the Glasgow Alcoholic Hepatitis Score (GAHS) and noted that it was developed to identify patients with AH at greatest risk of mortality, while Maddrey's Discriminant Function (DF) was specifically developed to identify patients with severe AH who might benefit from corticosteroid therapy. While the observational study you cite suggests that a GAHS≥9 may have superior utility to DF≥32 in identifying patients most likely to benefit from treatment with corticosteroids, none of the randomised controlled trials included in the review reported outcomes for patients using the GAHS threshold as an indicator of 'severe' AH. As the majority of studies (including the STOPAH trial) all used DF≥32, we can only refer to this prognostic threshold in the recommendation. The following is noted in the 'Quality of Evidence section of the Linking Evidence to Recommendations table (section 2.6 of the Addendum: "Topic experts confirmed that…the DF threshold score of ≥32 remains a valid tool for identifying people with severe AH who are likely to benefit from treatment with corticosteroids. It is used widely in the clinical setting because it is well validated, has proved useful over time and is relatively simple to calculate compared with some of the more recently developed tools such as the Glasgow

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							Alcoholic Hepatitis Score." Similarly, the committee was aware of the Lille score for monitoring response to steroid therapy. This is discussed in the 'Other Considerations' section of the Linking Evidence to Recommendations table: "The committee discussed the Lille score, which was developed to identify patients not responding to corticosteroids by day 7 of treatment. Topic experts confirmed that there is current variation in UK clinical practice regarding use of the Lille score for monitoring response to treatment. Lack of response to steroids after the first week of therapy, indicated by a Lille score ≥0.45, has been proposed as a factor determining subsequent mortality (Louvet et al. 2007). However a logistic regression analysis undertaken as part of the STOPAH trial (Thursz et al. 2015) found that the Lille score, measured in a subsample of participants treated with corticosteroids, did not have adequate performance (at a threshold for the area under the ROC curve of 0.75) for predicting mortality at any of the three time points studied. Response to corticosteroid treatment at day 7 was not an outcome specified in the review protocol for this update, and none of the included studies reported outcomes separately for treatment responders and non-responders. It was

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							therefore agreed that monitoring response to steroid treatment should not be included in the recommendation as the relevant evidence had not been reviewed in this guideline update." We will notify the NICE Surveillance team to identify any future randomised-controlled trials that use alternative validated prognostic indicators to the DF as a threshold for treatment, in order to inform subsequent updates of this guideline.
9.	SH	Foundation for Liver Research	Stakeholder consultation comments form	1	Researh recommendations 1 to 5 inc	Agree that all should stand	Thank you for your comment.
10.	SH	Royal College of Physicians	General	General	General	Endorsed the comments submitted by the British Society of Gastroenterology	Thank you.
11.	SH	NHS England	Full	General	General	To ensure that the specific issues related to veterans are highlighted in paragraph 2.1	Thank you for your comment. This review was undertaken as an update to NICE CG100: Alcohol-use disorders: diagnosis and management of physical complications. The focus was specifically on the safety and efficacy of corticosteroid treatment for people admitted to hospital with severe alcoholic hepatitis. Paragraph 2.1 of the Addendum is a general introduction to the subject of alcoholic hepatitis and is not intended to focus on specific vulnerable groups.

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							One study included in the review recruited male patients from six 6 Veterans Administration Medical Centres in the USA (Mendenhall 1984). However the review protocol did not specify analyses of outcomes for any particular population subgroups. Given the age and setting of the Mendenhall study, its applicability to a current UK military veteran population is unclear. The committee did consider a range of equalities issues when formulating the new recommendation, including the impact of factors such as poor social support, complex physical or psychological comorbidities, and social problems. These are noted in the Linking Evidence to Recommendations table (section 2.6 of the Addendum) with the following advice: "Clinicians should refer to NICE CG115 (Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence) regarding referral to specialist alcohol services for assessment and the implementation of appropriate support interventions to promote abstinence and prevent relapse."
12.	SH	NHS England	Full	General	General	There should be universal completion of the audit to check against use and then liaising with medical colleagues for a checklist on what to do next.	Thank you for your comment. The focus of this update to NICE CG100 was corticosteroid treatment for people

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							admitted to hospital with severe alcoholic hepatitis. People with this condition will have longstanding alcohol misuse issues. The Alcohol Use Disorders Identification Test (AUDIT) is a screening questionnaire for use in community settings to identify people who may have alcohol-use disorders. It is recommended in the NICE public health guideline on prevention of alcohol-use disorders PH24 and was therefore outside the remit of the current update. We will pass your comment to the NICE Surveillance team to inform decisions about future updates of the relevant NICE guidelines covering screening and prevention of alcohol-use disorders.
13.	SH	NHS England	Full	General	General	Detection question - what investigations might be routinely performed in those attending mental health clinics with either obvious alcohol use disorders or those whose alcohol use disorder has not yet come to clinical attention. This will be of significant concern to veteran services, with the increased risk of alcohol use disorders, and the increased tendency for veterans to not present for treatment amongst the alcohol use disorders group.	Thank you for your comment. The focus of this update to NICE CG100 was on the safety and efficacy of corticosteroid treatment for people admitted to hospital with severe alcoholic hepatitis. Your query is therefore not within the remit of the current update. We will pass your comment to the NICE Surveillance team to inform decisions about future updates of the relevant NICE guidelines covering screening and prevention of alcohol-use disorders.
14.	SH	NHS England	Full	General	General	There is a need to link the final guidance to work being done with Home Office and guidance for Caseworkers around alcoholism and impact of withdrawal in IRCs.	Thank you for your comment. The focus of this update to NICE CG100 was on the safety and efficacy of corticosteroid

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							treatment for people admitted to hospital with severe alcoholic hepatitis. It is not clear which part of the Addendum your comment relates to.

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