Alcohol-use disorders: physical complications
Evidence Update March 2012

A summary of selected new evidence relevant to NICE clinical guideline 100 'Diagnosis and management of alcohol-related physical complications' (2010)

Evidence Update 10

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might reinforce or generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE guidance development centres. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/alcohol). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:

 [1]**Alcohol-use disorders: diagnosis and clinical management of alcohol-related physical complications. NICE clinical guideline 100 (2010). Available from www.nice.org.uk/guidance/CG100**

Just over 1500 pieces of evidence were identified and assessed, of which 17 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Other relevant accredited guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other accredited guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

 [1]Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. Available from www.nice.org.uk/guidance/CG115

Quality standards

- Alcohol dependence and harmful alcohol use. NICE quality standard. Available from www.nice.org.uk/guidance/qualitystandards/alcoholdependence/home.jsp

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance is denoted by the Accreditation Mark 

Key messages

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages for this Evidence Update. It also indicates the EUAG's opinion on whether new evidence identified by the Evidence Update reinforces or has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance which may be affected, please see the full commentaries.

	Effect on guidance	
Key message	**Potential change**	**No change**
Acute alcohol withdrawal		
Benzodiazepines		
• Benzodiazepines seem to be more effective than placebo in reduction of seizures due to alcohol withdrawal.		✓
Anticonvulsants		
• Carbamazepine may have some benefit in alcohol withdrawal as measured by Clinical Institute Withdrawal Assessment – Alcohol revised score, but generally anticonvulsants show no benefit against placebo or other drugs for any other outcome.		✓
Other drugs		
• Evidence of the effect of gammahydroxybutyrate in alcohol withdrawal is insufficient and concerns exist about its potential for dependence and misuse.		✓
• Baclofen may have some clinical use in alcohol withdrawal, but evidence is limited.		✓
Dosing regimens for alcohol withdrawal		
• Using symptom-triggered benzodiazepines in an outpatient setting may be effective in reducing alcohol withdrawal symptoms, but concerns remain about the potential for drug misuse in largely unsupervised settings.		✓
Alcohol-related liver disease		
Early liver transplantation		
• Limited evidence suggests that liver transplantation at an earlier stage of disease does not appear to result in reduced mortality but may be associated with an increased risk of cancers, compared with standard care.		✓
Pentoxifylline for alcoholic hepatitis		
• Limited evidence suggests that pentoxifylline may be effective in reducing mortality in people with alcoholic hepatitis compared with prednisolone. A UK trial is underway, which may provide more evidence in this area.		✓

Key message	Effect on guidance	
	Potential change	No change
Alcohol-related pancreatitis		
Promoting abstinence from alcohol		
• Regularly repeated interventions to promote abstinence from alcohol may lead to reductions in recurrence of acute alcohol-related pancreatitis.	✓	
Pancreatic surgery versus endoscopic therapy for chronic alcohol-related pancreatitis		
• Evidence suggests that surgery for chronic alcohol-related pancreatitis continues to provide better pain relief than endoscopic treatment in the long term.		✓
• Coeliac axis block appears to give pain relief in people with chronic pancreatitis.		✓
Prophylactic antibiotics for acute alcohol-related pancreatitis		
• Evidence does not support use of prophylactic antibiotics in people with severe acute or necrotising pancreatitis.		✓
Nutritional support for acute alcohol related pancreatitis		
• Enteral nutrition seems to be associated with better outcomes than parenteral nutrition in people with acute alcohol-related pancreatitis.		✓
Determining severity of pancreatitis		
• Concurrent organ failure and infected pancreatic necrosis seem to be associated with higher mortality than either condition alone.		✓

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided.

1.1 Acute alcohol withdrawal

Benzodiazepines

A Cochrane review (**Amato et al. 2010**) of 64 studies of benzodiazepines in 4309 participants undergoing alcohol withdrawal found that for reduction in seizures, benzodiazepines were more effective than placebo (relative risk [RR] = 0.16, 95% confidence interval [CI] 0.04 to 0.69).

Benzodiazepines did not show a significant benefit compared with other drugs (anticonvulsants, antipsychotics and 'miscellanea') in terms of: seizures, delirium control, severe life-threatening side effects, drop-outs, drop-outs due to side effects, and patient's global assessment scores. No benzodiazepine showed significantly greater benefit than any other benzodiazepine, and combination treatment with a benzodiazepine plus another type of drug compared with a non-benzodiazepine drug alone showed no benefit. However, the authors stated that drawing definite conclusions about the safety and efficacy of benzodiazepines was not possible because of the heterogeneity of the trials, both in interventions and the assessment of outcomes.

This updated Cochrane review supports current recommendations in NICE CG100 for the use of benzodiazepines for acute alcohol withdrawal. Most of the data in Amato et al. 2010 have remained the same since Ntais et al.'s 2005 paper, which was included in developing the NICE guidance.

Anticonvulsants

Minozzi et al. (2010) conducted a Cochrane review of 56 studies of anticonvulsants for alcohol withdrawal in a total of 4076 patients. Overall, anticonvulsants were not significantly better than placebo for the outcomes alcohol withdrawal seizures, adverse events, drop-outs or drop-outs due to adverse events. Carbamazepine was significantly more effective than benzodiazepines in reducing the Clinical Institute Withdrawal Assessment – Alcohol revised (CIWA-Ar) score at the end of treatment (mean difference = −1.04, 95% CI −1.89 to −0.20, p = 0.015), but no other outcome showed significant benefit of anticonvulsants versus any other drug. Finally, no significant differences were seen in comparisons between anticonvulsants.

These results support NICE CG100, which recommends carbamazepine but no other anticonvulsant for alcohol withdrawal.

Other drugs

A Cochrane review of gammahydroxybutyrate (GHB) in alcohol withdrawal (**Leone et al. 2011**) looked at 13 RCTs in a total of 648 participants and concluded that evidence is insufficient to be confident of a difference between GHB and placebo or whether GHB is more or less effective than other drugs. It also highlighted the concerns about dependence and risk of misuse or abuse of GHB. These findings support the recommendations in NICE CG115, which states 'do not use GHB for the treatment of alcohol misuse'.

Another Cochrane review by **Liu and Wang (2011)** examining baclofen for alcohol withdrawal identified only one study (n = 37) that met the inclusion criteria. This study showed that baclofen and diazepam both significantly reduced CIWA–Ar scores (no statistical data given),

with no significant differences between treatments, although baclofen took longer to work. The limited evidence available for baclofen in alcohol withdrawal is unlikely to have an impact on a future review of NICE CG100.

Key references

Amato L, Minozzi S, Vecchi S et al. (2010) Benzodiazepines for alcohol withdrawal. Cochrane Database of Systematic Reviews: CD005063
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD005063.pub3/full

Leone MA, Vigna-Taglianti F, Avanzi G et al. (2011) Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses (review). Cochrane Database of Systematic Reviews: CD006266.
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD006266.pub2/full

Liu J and Wang L (2011) Baclofen for alcohol withdrawal. Cochrane Database of Systematic Reviews: CD008502.
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD008502.pub2/full

Minozzi S, Amato L, Vecchi S et al. (2010) Anticonvulsants for alcohol withdrawal. Cochrane Database of Systematic Reviews: CD005064.
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD005064.pub3/full

Supporting reference

Ntais C, Kyzas P, Pakos E et al. (2005) Benzodiazepines for alcohol withdrawal. Cochrane Database of Systematic Reviews: CD005063
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD005063/full

Dosing regimens for alcohol withdrawal

An out-patient symptom-triggered regimen of chlordiazepoxide (a benzodiazepine) was compared with a fixed-dose regimen in an RCT (**Ellholm et al. 2011**) in 165 patients with alcohol dependence undergoing supervised alcohol withdrawal. All participants were offered concurrent disulfiram or acamprosate, and attended the outpatient clinic daily. Breath alcohol levels were monitored and patients recorded their symptoms on the Short Alcohol Withdrawal Scale (SAWS) daily.

People receiving fixed-dose chlordiazepoxide took one of two regimens: those scoring 12 or more on the SAWS started at 200 mg/day tapering to 25 mg/day and those scoring less than 12 started on 80 mg/day tapering to 10 mg/day. Patients were offered an extra dose if necessary. In the symptom-triggered group, people with a SAWS score of 12 or more were prescribed a maximum daily dose of 300 mg for 10 days and those scoring less than 12 had a maximum daily dose of 120 mg.

The time to reduction in SAWS score to 12 or lower, or 6 or lower, did not differ between groups ($p = 0.924$ and $p = 0.091$ respectively). Men took longer than women to reach a SAWS score of 12 or lower ($p = 0.043$), and people drinking more than 20 drinks a day took longer to reach a SAWS score of 12 or lower and 6 or lower ($p = 0.017$ and $p = 0.034$ respectively). After a year, 46 of 78 people in the symptom-triggered group and 45 of 75 people in the fixed-dose group had relapsed.

The authors found no significant difference between the median total dose of chlordiazepoxide in the symptom triggered group (725 mg, range 50–2800 mg) and the fixed-dose group (875 mg, range 100–1900 mg). However, citing the median total dose for the fixed-dose groups was not informative because two distinct dosing regimens were used, and the wide range indicates some lack of adherence to the treatment schedule, which was not addressed in the report.

The highest total dose taken in the symptom-triggered group was greater than the highest total dose taken in the fixed-dose group, which may be an indication of misuse in the symptom-triggered group, or that patients were taking doses regularly rather than in response

to symptoms. No information was given about how, or how often, participants in the symptom-triggered group assessed their symptoms before taking a drug dose. Additionally, the authors did not report any method of assessing the correlation between symptom severity and doses taken, to address the potential for misuse of chlordiazepoxide.

In NICE CG100, a symptom-triggered regimen is recommended for people in acute alcohol withdrawal who are in hospital or another setting with facilities for 24-hour assessment and monitoring. This guideline additionally recommended further research to determine the safety and efficacy of symptom-triggered or front-loading regimens compared with fixed-dose treatment in 'acute hospital settings'. The Guideline Development Group explained in the full version of NICE CG100 that they had concerns about extrapolating positive results of trials in specialist alcohol treatment centres to general hospital settings. A recommendation to use only fixed-dose regimens for community-based withdrawal was included in NICE CG115.

The evidence from Ellholm et al. (2011), therefore, is not likely to affect recommendations in NICE CG100 or CG115.

Key reference

Ellholm B, Larsen K, Hornnes N et al. (2011) Alcohol withdrawal syndrome: symptom-triggered versus fixed-schedule treatment in an outpatient setting. Alcohol and Alcoholism 46: 318–23
Abstract: www.alcalc.oxfordjournals.org/content/early/2011/03/17/alcalc.agr020

1.2 Wernicke's encephalopathy

No new key evidence was found for this section.

1.3 Alcohol-related liver disease

Early liver transplantation

Vanlemmens et al. (2009) performed an RCT in 120 people with Child–Pugh stage B alcoholic liver cirrhosis to investigate the effect on 5-year survival of immediate listing for liver transplantation versus standard care (that is, delay of transplantation until progression to stage C disease). Although not a requirement for inclusion in the trial, at study entry, 93% of participants were abstinent from alcohol (85% for more than 3 months). Exclusion criteria included positive tests for hepatitis B or C, HIV, other organ failure, hepatocellular carcinoma, non-liver cancer, or histologically proven alcoholic hepatitis. Any patients in the standard care group who developed Child–Pugh stage C cirrhosis during the trial could be considered for liver transplantation as part of standard care.

Each group included 60 randomised participants, and the median duration of follow-up was 42 months (95% CI 32 to 48 months). In the immediate listing group, 41 participants underwent transplantation a median of 4.3 months (95% CI 2.6 to 5.8 months) after inclusion. Of the 19 people in the immediate listing group who did not undergo transplantation, seven died awaiting transplantation, five developed a contraindication to transplantation after randomisation, and seven improved. 15 participants in the standard-care group also underwent liver transplantation at a mean of 12.2 months (95% CI 7.3 to 18.9 months) because of worsening liver function. The authors stated that most patients who were randomly assigned to immediate listing for transplantation received a transplant after a short waiting period, however they did not provide information about how long patients in the standard care waited for transplantation after listing.

At the end of follow-up, 41.7 % of people in the immediate listing group and 30% of those in the standard-care group had died ($p = 0.183$). The prevalence of neoplasia was higher in the immediate listing group than in the standard care group (31.7% vs 5.0% respectively, $p < 0.001$).

The authors recognised that the sample size of their study could have resulted in a type II error, but did not provide a power calculation. Also acknowledged was the difficulty recruiting to the study because many transplant teams were reluctant to leave treatment decisions to randomisation.

A case-control study (Mathurin et al. 2011) in 26 patients with medically unresponsive severe alcoholic hepatitis looked at differences in survival between those selected for early liver transplantation and 26 matched controls who did not receive early transplantation. In France, where this study was conducted, usual practice requires 6 months' abstinence from alcohol. In this study, patients made a commitment to lifelong abstinence but had not been abstinent for the usual 6 months. In the transplantation group, 2-year survival was 71% (± 9%) compared with 23% (± 8%) in controls ($p < 0.001$). No patient resumed drinking alcohol during the initial 6-month follow-up, but three resumed drinking after that point. Less than 2% of patients admitted for an episode of severe alcoholic hepatitis were selected for transplantation and the participating centres used 2.9% of available grafts for this indication. Further research into this indication for transplantation is needed.

NICE CG100 recommends referral of patients for consideration of liver transplantation if they have decompensated liver disease after best management and 3 months' abstinence and are otherwise suitable candidates. Despite its limitations, the study by Vanlemmens et al. (2009) does not suggest benefit of early transplantation, which may also be associated with detrimental outcome, lending support to this recommendation.

Key reference

Vanlemmens C, Di Martino V, Milan C et al. (2009) Immediate listing for liver transplantation versus standard care for Child–Pugh stage B alcoholic cirrhosis. Annals of Internal Medicine 150: 153–61
Full text: www.annals.org/content/150/3/153.full.pdf+html

Supporting reference

Mathurin P, Moreno C, Damuel D et al. (2011) Early liver transplantation for severe alcoholic hepatitis. New England Journal of Medicine 365: 1790–800
Full text: www.nejm.org/doi/full/10.1056/NEJMoa1105703#t=article

Pentoxifylline for alcoholic hepatitis

Pentoxifylline was the subject of a Cochrane review (**Whitfield et al. 2009**) of five trials in 336 participants. Overall, pentoxifylline reduced mortality compared with control (RR = 0.64, 95% CI 0.46 to 0.89); however, four of the five trials showed a high risk of bias, and trial sequential analysis (which adjusts for multiple testing on accumulating data) did not support this result. Similarly, pentoxifylline reduced mortality due to hepatorenal syndrome in meta-analysis (RR = 0.40, 95% CI 0.22 to 0.71), but not in trial sequential analysis. The authors concluded that the evidence was not strong enough to determine whether pentoxifylline has a positive, negative, or neutral effect in alcoholic hepatitis.

A double-blind, double-dummy trial of pentoxifylline compared with prednisolone (**De et al. 2009**), randomly assigned 74 people with severe alcoholic hepatitis and a history of drinking more than 50 g of alcohol per day to one of two groups. The first group received pentoxifylline 400 mg three times a day and once-daily placebo for 4 weeks. The second group received prednisolone 40 mg once daily and placebo three times daily for 4 weeks. After 4 weeks, the groups were unblinded; people in the active pentoxifylline group continued treatment at the same dose for another 8 weeks and then stopped, those in the active prednisolone group had their dose tapered by 5 mg a week over 7 weeks and then stopped.

Two people in the prednisolone group withdrew from the study and were not included in the analyses, leaving 34 patients in each group. After 3 months of therapy, mortality was significantly higher in the prednisolone group (12 of 34) than in the pentoxifylline group (5 of 34, $p = 0.04$). By 1 year's follow-up, five people in the pentoxifylline group had developed recurrent encephalopathy, compared with none in the prednisolone group. Conversely, six

people in the prednisolone group developed, and died from, hepatorenal syndrome compared with none in the pentoxifylline group.

The authors recognised limitations of their study in that no histological data from biopsy, or assessment of immunological or inflammatory markers, were available. However, the report did not clearly state a primary endpoint, it contained a small number of patients and no power calculation was given. People with the most severe disease (such as recent history of sepsis, infection, gastrointestinal bleeding or renal impairment) were excluded, so these data might not be applicable to routine clinical practice in the UK.

An RCT of steroids or pentoxifylline in alcoholic hepatitis (STOPAH) is underway in the UK to compare prednisolone and pentoxifylline both alone and in combination with placebo. It started recruitment in January 2011 and expects to recruit 1200 participants.

NICE CG100 recommends corticosteroid treatment for severe acute alcoholic hepatitis. The evidence from the RCT by De et al. (2009) and the Cochrane review by Whitfield et al. (2009) is limited, and results will not be available from the STOPAH trial for a number of years, therefore current guidance is unlikely to be affected.

Key references

De BK, Gangopadhyay S, Dutta D et al. (2009) Pentoxifylline versus prednisolone for severe alcoholic hepatitis. World Journal of Gastroenterology 15: 1613–9
Full text: www.ncbi.nlm.nih.gov/pmc/articles/PMC2669113/?tool=pubmed

Whitfield K, Rambaldi A, Wetterslev J et al. (2009) Pentoxifylline for alcoholic hepatitis (review). Cochrane Database of Systematic Reviews: CD007339
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD007339.pub2/full

Supporting reference

UK Clinical Trials Gateway. Steroids or pentoxifylline in alcoholic hepatitis
www.ukctg.nihr.ac.uk/trialdetails/ISRCTN88782125

1.4 Alcohol-related pancreatitis

Promoting abstinence from alcohol

An intervention to reduce alcohol consumption in people admitted to hospital for a first occurrence of alcohol-related acute pancreatitis was investigated in an RCT by **Nordback et al. (2009)**. The intervention consisted of a 30-minute conversation covering three topics: information about the toxic effects of alcohol on the pancreas; the need to change drinking habits and the patient's responsibility for this change; and social problems faced by participants (such as unemployment and economic and marital difficulties).

People admitted to a single centre in Finland (n = 120) were randomly assigned to receive either standard care (an initial intervention only, at discharge), or to receive an initial intervention followed by similar, repeated interventions every 6 months.

The study was powered to detect a two-thirds reduction in readmission for recurrent alcohol-related acute pancreatitis, with a target enrolment of 110 patients. The expected readmission rate was based on previous data suggesting that a third of people would usually be readmitted with another episode of acute pancreatitis within 2 years. The repeated intervention was therefore expected to reduce readmissions to 11%.

Overall, 15% of participants were readmitted in 2 years. This amounted to 5 of 59 (8.5%) in the intervention group and 13 of 61 (21.3%) in the control group (p = 0.042). The number of people needed to treat with the intervention to prevent one case of recurrent acute pancreatitis over 2 years was 8. The numbers of deaths and drop-outs during the study did not differ significantly between groups. Only about a third of people in the intervention group and a quarter of those in the standard care group met criteria for severe pancreatitis.

NICE CG100 does not include any recommendations about promoting abstinence from alcohol specifically for people with alcohol-related pancreatitis. Interventions to promote abstinence from alcohol in people with alcohol-related pancreatitis may be a consideration for future reviews of NICE CG100.

Key reference

Nordback I, Pelli H, Lappalainen-Lehto R, et al. (2009) The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology 136: 848–55.
Abstract: www.gastrojournal.org/article/S0016-5085(08)02075-1/abstract

Pancreatic surgery versus endoscopic therapy for chronic alcohol-related pancreatitis

Cahen et al (2011) reported 5-year follow-up of an RCT in which 39 people with symptomatic obstuctive chronic pancreatitis underwent either endoscopic or surgical drainage (pancreaticojejunostomy) of the pancreatic duct. The trial was stopped in 2004 because an interim analysis showed a significant benefit of surgical over endoscopic treatment: at that point the median follow-up was 24 months.

This report of long-term outcomes showed that the surgical group had significantly higher pain relief compared with endoscopy (80% vs 38% respectively [difference = −43%, 95% CI −66 to −8%], p = 0.042). Pain relief was defined as complete for Izbicki pain scores ≤ 10 and partial for scores > 10 after a decrease of 50%. However, the pain scores seen in the surgical group were not significantly different from the endoscopy (22 vs 39 respectively [difference = 17, 95% CI −5 to 39], p = 0.12). Of the group undergoing initial surgery, no patients developed recurrent pancreatic duct obstruction. Conversely, nine people in the endoscopic treatment group had recurrent blockage (seven had two recurrences and two had three recurrences), three of which were resolved by further endoscopy and six required surgery. A further three patients were converted to surgery after their initial endoscopic treatment failed. Overall, nine people in the endoscopy group eventually underwent surgery.

The results of this trial lend support to NICE CG100, which recommends offering surgery in preference to endoscopic therapy to people with pain from large-duct (obstructive) chronic alcohol-related pancreatitis.

A meta-analysis by **Puli et al. (2009)** looked at pain relief after endoscopic-ultrasound directed coeliac axis block in people with chronic pancreatitis or pancreatic cancer (each disease analysed separately). For chronic pancreatitis, nine studies in 376 people were included, five of nine used a visual analogue scale, two used an unspecified pain scale, one used the Likert scale, and one categorised pain relief as complete, partial, or no pain relief. The overall proportion of patients with pain relief was 59.45% (95% CI 54.51 to 64.30). This evidence supports the recommendation in NICE CG100 to offer coeliac axis block to people with poorly controlled pain from non-obstructive small duct chronic alcohol-related pancreatitis, but does not add any information to guide the choice of this treatment over splanchnicectomy or surgery, which are also recommended in NICE CG100 for this population of patients.

Key references

Cahen DL, Gouma DJ, Laramée P et al. (2011) Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology 141: 1690–5
Abstract: www.gastrojournal.org/article/S0016-5085(11)01107-3/abstract

Puli SR, Reddy JBK, Beehtold ML et al. (2009) EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Digestive diseases and sciences 54: 2330–7
Abstract: www.springerlink.com/content/g7634n36u8l2l176/

Prophylactic antibiotics for acute alcohol-related pancreatitis

Villatoro et al. (2010) conducted a Cochrane review of prophylactic antibiotics in patients with severe acute pancreatitis and computed tomography (CT)-confirmed necrosis. Seven studies with a total of 404 patients were included. No significant benefit of antibiotic prophylaxis was seen for mortality (RR = 0. 60, 95% CI 0.34 to 1.05, p = 0.07), infected pancreatic necrosis (RR = 0.85, 95% CI 0.57 to 1.26, p = 0.42), non-pancreatic infection (RR = 0.62, 95% CI 0.36 to 1.06, p = 0.08), overall infection (RR 0.69, 95% CI 0.44 to 1.09, p = 0.12), fungal infections (RR = 1.06, 95% CI 0.41 to 2.70, p = 0.91), or need for operative treatment (RR = 0.90, 95% CI 0.62 to 1.31, p = 0.58). Similar results were seen when beta-lactams and quinolones were analysed separately.

In three studies in a total of 78 people, imipenem showed significant benefit for infected pancreatic necrosis (RR = 0.34, 95% CI 0.13 to 0.84, p = 0.02) and overall infections (RR = 0.49, 95% CI 0.28 to 0.87, p = 0.01), but no significant difference was seen for mortality, non-pancreatic infection, fungal infection, or operative treatment. However, none of the included studies were adequately powered.

Yao et al. (2010) reported a meta-analysis of antibiotic prophylaxis in acute necrotising pancreatitis that included the studies in the Cochrane review by Villatoro et al. (2010) plus two additional RCTs published in 2009. The results of this review were broadly similar to those of the Cochrane review, with the exception that infected pancreatic necrosis was significantly reduced in the antibiotic group (RR = 0.73, 95% CI 0.54 to 0.98, p = 0.04).

However when this result was further analysed by study design, the results remained significant for single centre (RR = 0.69, 95% CI 0.48 to 1.0, p = 0.05) and single-blind studies (RR = 0.58, 95% CI 0.40 to 0.83, p = 0.0003) but not for multicentre (RR = 0.78, 95% CI 0.47 to 1.29, p = 0.33) and double-blind studies (RR = 1.14, 95% CI 0.68 to 1.93, p = 0.61).

NICE CG100 recommends that prophylactic antibiotics should not be given to people with mild acute pancreatitis. For severe acute pancreatitis, in the full version of NICE CG100 the Guideline Development Group considered evidence that suggested 'other antibiotics' (not carbapenem) reduced mortality, including five of the seven studies from the Cochrane review by Villatoro et al. (2010). Because of variability in the trials, the Guideline Development Group 'did not believe there was enough evidence to support a recommendation for offering antibiotics…' The evidence from Villatoro et al (2010) and Yao et al. (2010) is unlikely to affect this view.

Key references

Villatoro ER, Mulla M, Larvin M (2010) Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews: CD002941
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD002941.pub3/full

Yao L, Huang X, Li Y et al. (2010) Prophylactic antibiotics reduce pancreatic necrosis in acute necrotizing pancreatitis: a meta-analysis of randomised trials. Digestive Surgery 27: 442–9
Full text:
www.content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowFulltext&ArtikelNr=318780&Ausgabe=254717&ProduktNr=223996

Nutritional support for acute alcohol-related pancreatitis

An updated Cochrane review of enteral versus parenteral nutrition by **Al-Omran et al (2010)** looked at eight trials comparing nasojejunal enteral nutrition with total parenteral nutrition in a total of 348 participants with acute pancreatitis. The previous Cochrane review included only two trials in 70 people. Mortality was the only outcome reported in all included studies. Enteral nutrition significantly reduced mortality compared with parenteral nutrition (RR = 0.50, 95% CI 0.28 to 0.91). Significant benefits of enteral nutrition were also seen for other outcomes

including occurrence of multiple organ failure (RR = 0.55, 95% CI 0.37 to 0.81), and also in a subgroup analysis of people with severe acute pancreatitis (RR = 0.18, 95% CI 0.06 to 0.58).

Five of the papers in the Cochrane review by Al-Omran et al (2010) were also included in a systematic review and meta-analysis by **Petrov and Whelan (2010)**, which investigated diarrhoea, abdominal bloating, or hyperglycaemia as complications of nutrition support. In intention-to-treat analyses, when compared with enteral nutrition, parenteral nutrition reduced the odds of having diarrhoea by 79% ($p < 0.001$) but increased 2.6 fold the odds of hyperglycaemia needing insulin administration ($p = 0.02$). No significant difference was seen in abdominal bloating ($p = 0.32$). The authors acknowledged that enteral nutrition has been shown to have benefits in mortality and pancreatic infectious complications (a view supported by the results from Al-Omran et al. 2010), and so should be preferred to parenteral nutrition.

Wu et al. (2010) conducted a single-centre RCT of total enteral versus total parenteral nutrition in 107 people with severe acute pancreatitis. Although the authors stated that the trial 'was designed to evaluate the effectiveness of total enteral nutrition as the preventive regimen for pancreatic necrotic infection in severe acute pancreatitis', no primary endpoint was clearly defined. All patients in this trial received concomitant prophylactic antibiotics.

A significantly higher proportion of people on total parenteral nutrition had organ failure than those on total enteral nutrition (81% vs 21% respectively, $p < 0.05$). Similar results were seen for surgical intervention (80% vs 22%, $p < 0.05$); pancreatic septic necrosis (72% vs 23%, $p < 0.05$); and mortality (43% vs 11%, $p < 0.05$).

Although the open-label nature of this trial could lead to bias, conducting an ethical double blind trial of these interventions would be difficult. The authors did not report the method of randomisation, a power calculation, or the length of follow-up, all of which increase the risk of bias in the results.

Most of the studies included in the reviews by Al-Omran et al. (2010) and Petrov and Whelan (2010) were included in the meta-analysis conducted as part of developing NICE CG100. The evidence base has not changed much, with only two additional studies included in the new reviews, and the results of the studies consistently agree with NICE CG100, which recommends enteral feeding in preference to parenteral feeding if possible.

Key references

Al-Omran M, AlBalawi ZH, Tashkandi MF et al. (2010) Enteral versus parenteral nutrition for acute pancreatitis (review). Cochrane Database of Systematic Reviews: CD002837
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD002837.pub2/full

Petrov MA, Whelan K (2010) Comparison of complications attributable to enteral and parenteral nutrition in predicted severe acute pancreatitis: a systematic review and meta-analysis. British Journal of Nutrition 103: 1287–95
Full text:
www.journals.cambridge.org/action/displayFulltext?type=6&fid=7698060&jid=BJN&volumeId=103&issueId=09&aid=7698056&bodyId=&membershipNumber=&societyETOCSession=&fulltextType=RV&fileId=S0007114510000887

Wu XM Ji KQ, Wang HY et al. (2010). Total enteral nutrition in prevention of pancreatic necrotic infection in severe acute pancreatitis. Pancreas 39: 248–51.
Abstract:
www.journals.lww.com/pancreasjournal/pages/articleviewer.aspx?year=2010&issue=03000&article=00022&type=abstract

Determining severity of pancreatitis

In a systematic review and meta-analysis, **Petrov et al. (2010)** investigated the effect of organ failure or infected pancreatic necrosis on mortality in people with acute pancreatitis. A total of 14 studies in 1478 patients were included. Organ failure was seen in 40% (600 of

1478) of participants, and infected pancreatic necrosis occurred in 21% (314 of 1478). Overall mortality was 13%, and about a third of people who either had organ failure or infected pancreatic necrosis died. People who had both organ failure and infected pancreatic necrosis had a higher risk of mortality than those who had only organ failure (RR = 1.94, 95% CI 1.32–2.85, p = 0.0007) and those who only had infected pancreatic necrosis (RR = 2.65, 95% CI 1.30–5.40, p = 0.0007).

The authors acknowledged the possibility of confounding due to the necessary observational nature of the studies. Additionally they considered that the definitions of organ failure, indications for surgery, and whether organ failure was dynamic or persistent may not have been consistently reported across studies.

These results are unlikely to affect NICE CG100 because severe effects of pancreatitis were not investigated for the guideline, and the evidence from this trial does not directly influence clinical interventions for organ failure or infected pancreatic necrosis.

Key reference

Petrov MS, Shanbag S, Chakraborty M, et al. (2010) Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 139: 813–20
Full text: www.gastrojournal.org/article/S0016-5085(10)00864-4/fulltext

New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

Alcohol-related pancreatitis

Prophylactic antibiotics for acute alcohol-related pancreatitis

- The effect of nutrition on the effect of antibiotic prophylaxis in acute necrotizing pancreatitis
  http://www.library.nhs.uk/DUETs/viewResource.aspx?resid=412078

Nutritional support for alcohol related pancreatitis

- Efficacy and safety of fibre-enriched formulations in acute pancreatitis compared to fibre-free formulas
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=412077

Further evidence uncertainties for alcohol-use disorders can be found at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr

DUETs has been established in the UK to publish uncertainties about the effects of treatment that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Alcohol use disorders: diagnosis and clinical management of alcohol related physical complications (CG100). Available from: www.nice.org.uk/guidance/CG100

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 June 2009 (the end of the search period of NICE clinical guideline 100) to 28 November 2011:

- MEDLINE
- EMBASE
- CINAHL
- Cochrane Library (Cochrane Database of Systematic Reviews, CENTRAL, HTA, NHS EED)

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. Seventeen focused search strategies were used in the original guideline to answer specific clinical questions. This Evidence Update aims to identify the most recent evidence for any intervention, therefore only the population/condition search strategy from the original guideline was included. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews (www.sign.ac.uk/methodology/filters.html).

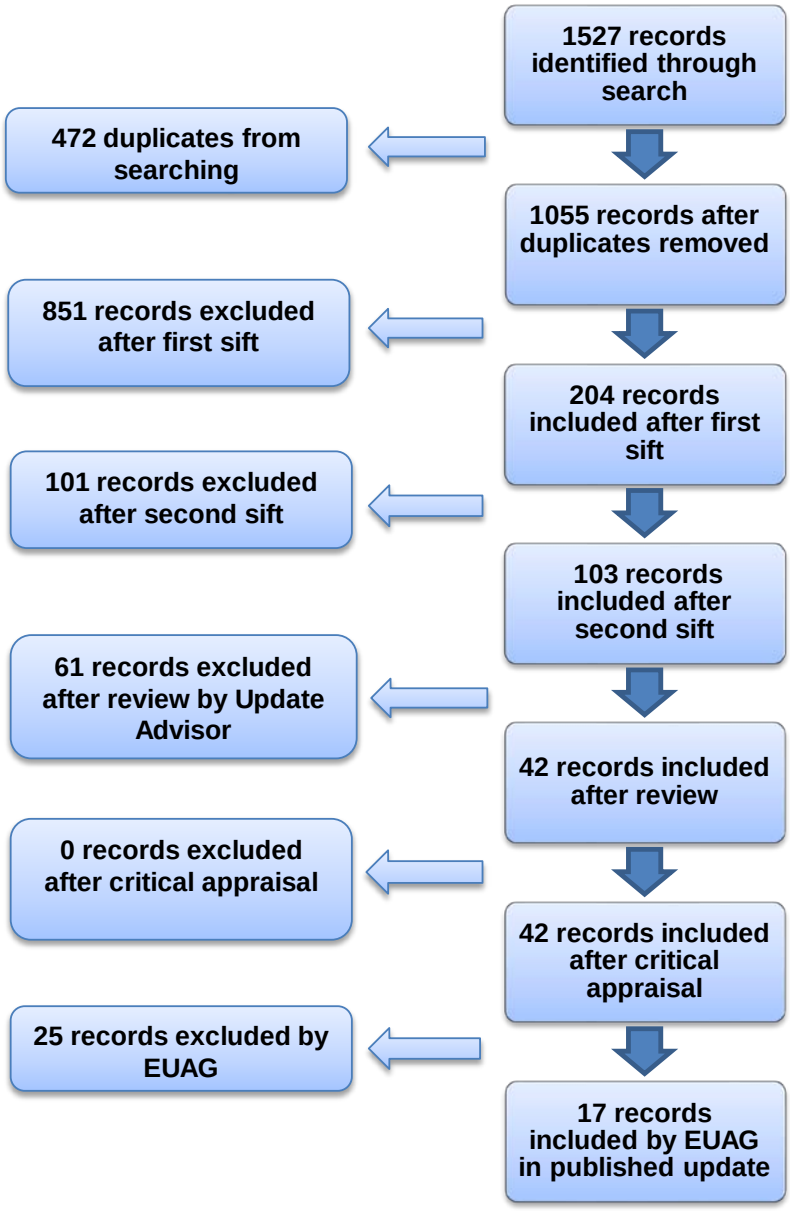
Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser (the chair of the EUAG), and the full search strategies, are available on request from contactus@evidence.nhs.uk

Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp Alcohol-Related Disorders/
2	exp Alcohol Drinking/
3	exp Alcoholic Beverages/
4	(drunkenness or ((binge or hazardous or harmful) adj2 drink$)).ti,ab.
5	(alcohol-related or drink-related or drink-induced or alcohol-induced).ti,ab.
6	(alcohol adj2 (misuse or abuse or dependent or dependence)).ti,ab.
7	alcohol$.ti,ab.
8	Ethanol/
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp Liver Diseases, Alcoholic/
11	((alcoholic or alcohol-related or drink-related or drink-induced or alcohol-induced) adj3 (steatosis or fibrosis or steatohepatitis or cirrhos$ or cirrhotic$ or hepatitis)).ti,ab.
12	((alcoholic or alcohol-related or drink-related or drink-induced or alcohol-induced) adj3 ((fatty or injury or disease$ or damage or disorder$) adj2 (liver or hepatic))).ti,ab.
13	"alcoholic liver disease".ti,ab.
14	10 or 11 or 12 or 13
15	Liver Diseases/
16	exp Fatty Liver/
17	exp Hepatitis/
18	exp Liver Cirrhosis/
19	(steatosis or fibrosis or steatohepatitis

	or cirrhos$ or cirrhotic$ or hepatitis or hepatitides or hepatofibrosis).ti,ab.
20	((fatty or injury or disease$ or damage or disorder$ or inflamm$) adj2 liver).ti,ab.
21	exp Liver Failure/
22	((liver or hepatic) adj failure).ti,ab.
23	Hepatic Insufficiency/
24	((liver or hepatic) adj insufficiency).ti,ab.
25	ESLD.ti,ab.
26	Liver Transplantation/
27	((liver or hepatic) adj2 (allograft$ or graft$ or transplant$ or resect$)).ti,ab.
28	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	9 and 28
30	14 or 29
31	exp Pancreatitis, Alcoholic/
32	((alcoholic or drink-related or drink-induced or alcohol-related or alcohol-induced) adj3 pancreatitis).ti,ab.
33	((acute or necro$) adj2 pancreatitis).ti,ab.
34	31 or 32 or 33
35	exp Pancreatitis/
36	pancreatitis.ti,ab.
37	Pancreas Transplantation/
38	((pancreat$ or pancreas) adj2 transplant$).ti,ab.
39	35 or 36 or 37 or 38
40	9 and 39
41	34 or 40
42	Alcohol-Induced Disorders, Nervous System/
43	Alcohol Withdrawal Delirium/
44	Alcohol Withdrawal Seizures/
45	(delirium adj2 tremens).ti,ab.
46	(alcohol$ adj2 withdrawal).ti,ab.
47	(alcohol adj2 delirium).ti,ab.
48	(alcohol adj2 seizure$).ti,ab.
49	exp Wernicke Encephalopathy/
50	(wernicke$ adj2 encephalopath$).ti,ab.
51	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	(acute adj2 withdrawal).ti,ab.
53	withdrawal.ti.
54	(withdrawal adj2 (seizure$ or syndrome)).ti,ab.
55	52 or 53 or 54
56	9 and 55
57	51 or 56
58	30 or 41 or 57

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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