National Institute for Health and Care Excellence

Addendum to NICE guideline 100, Alcohol-use disorders: diagnosis and management of physical complications

NICE guideline addendum CG100.1

Methods, evidence and recommendations

April 2017

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

Contents

Clinical guidelines update

The NICE clinical guidelines update team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found via appendix B.

1 Summary section

1.1 Update information

A decision was made to update the NICE guideline on management of alcohol use disorders (CG100) following an exceptional surveillance review of corticosteroid treatment for alcohol-related hepatitis. Topic experts felt that recent publication of the NIHR-funded STOPAH trial represented significant new evidence that could have an impact on current guideline recommendations. The surveillance report is available here.

The aim of this update was to review all available evidence to address the following question:

- What is the safety and efficacy of corticosteroids for acute alcohol related hepatitis?

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.2 Recommendation

1. **Offer corticosteroid[a] treatment to people with severe alcohol-related hepatitis and a discriminant function[b] 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 members or carers (as appropriate), explaining that corticosteroid treatment:
        - has been shown to improve survival in the short term (1 month)
        - 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]**

1.3 Patient-centred care

This guideline offers best practice advice on the care of people with acute severe alcohol-related hepatitis.

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

[a] Corticosteroids are used in UK clinical practice in the management of severe alcohol-related hepatitis. At the time of publication (April 2017), prednisolone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[b] Maddrey's discriminant function (DF) was described to predict prognosis in alcohol-related hepatitis and identify patients suitable for treatment with steroids. It is 4.6 x [prothrombin time – control time (seconds)] + bilirubin in mg/dl. To calculate the DF using bilirubin in micromol/l divide the bilirubin value by 17.

1.4 Methods

This update was developed based on the process and methods described in the Developing NICE guidelines: the manual.

2 Evidence review and recommendations

2.1 Introduction

Alcohol, if taken to excess, can damage the liver. The exact way in which this occurs is not completely understood. The majority of people drinking persistently above recommended safe limits will develop fatty change within the liver but a small minority will go on to develop further damage in the form of inflammation and alcoholic hepatitis (AH). Alcoholic hepatitis is thought to be the key stage in the development of fibrosis and eventually cirrhosis. In many individuals this phase of alcohol-related liver injury is silent with no obvious clinical manifestations. However in a small percentage of people, the development of alcoholic hepatitis is characterised by the onset of jaundice and other features of liver failure on a background of active, chronic and heavy alcohol consumption. The laboratory profile indicates severe disturbance of hepatic synthetic and excretory functions, with high serum bilirubin concentrations, low serum albumin levels and a raised prothrombin time; features of inflammation such as a raised white cell count are also usual. AH usually occurs in people with underlying cirrhosis (approximately 80% at the time of presentation), but may occur in individuals without significant fibrosis.

The typical age at presentation of AH is between 40 and 50 years, with the majority occurring before age 60. Men outnumber women in a ratio of 3:1, largely reflecting the greater propensity of men to drink to excess. Subsequent drinking behaviour is the most important modifier of the natural history of alcoholic hepatitis. In patients with mild to moderate AH who have not yet developed significant fibrosis, the liver injury may resolve completely if they attain and maintain abstinence in the longer term. However the outcome in people with severe AH (both in terms of the progression of their liver injury and survival) is poor, even with abstinence. Women with severe AH tend to fare badly for reasons that are not entirely clear but which may relate to their immune response to injury.

Severe AH has a poor short-term prognosis. The severity of AH can be assessed using a variety of scores, including Maddrey's Discriminant Function (MDF or DF) and the Glasgow Alcoholic Hepatitis Score. The Discriminant Function was designed specifically to identify people with severe AH who might benefit from treatment with corticosteroids. It is the most commonly used scoring system in clinical practice and is based on a composite of prothrombin time (PT) and total bilirubin. A DF score ≥32 is associated with a high short-term mortality (about 30% to 40%). Death usually occurs due to liver failure, gastrointestinal bleeding or infection. Conversely, patients with a DF<32 have short-term survival rates of 90% to 100%.

The primary treatment for alcohol-related hepatitis is withdrawal of alcohol. Many people with AH are malnourished. In the most severely malnourished, short-term mortality approaches 80%; supportive care in the form of enteral nutrition may therefore be given to improve a person's nutritional status. Medication to reduce inflammation of the liver may also be used. Corticosteroids are the most common immunomodulatory agent given to people with severe AH, which is characterised by the acute development or worsening of typical signs and symptoms such as fever, hepatomegaly, marked impairment of liver function (e.g. jaundice, coagulopathy), and manifestations of portal hypertension (e.g. ascites, hepatic encephalopathy, variceal haemorrhage). However, while corticosteroid treatment appears effective in reducing short-term mortality, potential side effects can include susceptibility to infection, which means that clinicians are uncertain about the overall risks and benefits of their use in this situation.

2.2 Review question

What is the safety and efficacy of corticosteroids for acute alcohol-related hepatitis?

2.3 Clinical evidence review

2.3.1 Methods

Deviations from the review protocol

The methods outlined in the review protocol (see Appendix C:) were used with the following amendments:

- A random effects model was used in meta-analyses due to differences across studies in terms of population (for example, the inclusion of less severe cases in some older studies, and differences regarding inclusion or exclusion of patients with baseline active infections or gastrointestinal bleeding – both of which were proposed as subgroup analyses in the review protocol, see Appendix C). Studies also varied in terms of treatment dose and duration which may yield different effect estimates;
- No information on minimal important differences (MID) was identified in the COMET database. The following MIDs were therefore used to assess the imprecision of effect estimates in this update:
  - For mortality outcomes the line of no effect (RR 1.0) was used;
  - For all other dichotomous outcomes the GRADE default MIDs were used (RR 0.8 and 1.25);
  - For quality of life measured using the EQ-5D, an MID of 0.07 points was identified from the literature (Walters & Brazier 2005).

2.3.2 Results

A systematic search was conducted (see Appendix D:) which identified 2,037 articles. The titles and abstracts were screened and 37 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix C:). Of these, 19 were excluded as they did not meet the criteria and 18 articles (corresponding to 13 different studies) met the criteria and were included.

A review flowchart is provided in Appendix E:, and the excluded studies (with reasons for exclusion) are shown in Appendix F:.

Overall summary of evidence

The 13 included studies covered the following three treatment comparisons:

- Corticosteroid (prednisolone or methylprednisolone) versus placebo: 1 new study (Thursz 2015 – comparison A), 9 studies from the original guideline;
- Corticosteroid (prednisolone or methylprednisolone) versus 'no treatment' control (open label studies): 2 studies from the original guideline
- Prednisolone + pentoxifylline (PTX) versus PTX + placebo: 2 new studies (De 2014; Thursz 2015 – comparison B).

The study by Thursz et al. 2015 (the STOPAH trial) was a 2x2 factorial trial designed to investigate the effectiveness of steroids *or* PTX in the treatment of alcoholic hepatitis. It included two relevant pairwise comparisons matching the review protocol for this update (see Appendix C), so appears listed more than once above. The prednisolone versus placebo comparison is denoted as comparison A, and the combined prednisolone+PTX versus PTX+placebo comparison is denoted as comparison B in the summary of included studies (Table 1 below) and in the evidence table (G.13).

One open-label study (Theodossi 1982) used intravenously-administered steroid medication. This study was identified in the original guideline but subsequently excluded from analyses because the guideline development group chose to focus only on orally-administered steroids. Oral mode of administration was not an inclusion criterion specified in the review protocol for this update (Appendix C), so this study was included. Another study, which had been included in the original guideline (Lesesne 1978), was excluded from this update because the comparator did not match the review protocol. The comparator group in that study was given a higher calorie diet than the steroid-treated group. However our review protocol specified that valid comparators were placebo, or a 'no treatment' or 'usual care' control, with provision of any other ‘background’ treatment (including nutritional care) the same for both groups.

For studies where there was more than one publication for the same study cohort, only data from the most recent article was included in meta-analyses (to avoid double counting of data) unless an earlier publication reported outcomes of relevance not covered in the most recent publication.

The three different treatment comparisons listed above were initially analysed as subgroups for each outcome of interest. For all outcomes but one (namely, quality of life at 1 year follow-up) there was no evidence of a subgroup effect relating to treatment comparison. For this reason, the evidence for each outcome, except quality of life, was assessed at an aggregate level in the GRADE profiles (Appendix H:) that is, as a comparison of ‘steroid treatment’ versus ‘no steroid treatment’. For the STOPAH trial, this meant that the two steroid-treated groups (prednisolone+placebo and prednisolone+PTX) were combined, as were the two non-steroid treated groups (placebo+placebo and PTX+placebo), and these were compared in any meta-analyses (see Forest plots, Appendix I:).

Data on numbers of patients with serious adverse events (including serious infections) were extracted for analysis only where it was clear that the denominator included the whole treatment group, and not just participants who had died. Three studies reported on length of hospital stay, but these data could not be included in analyses because standard deviations or confidence intervals were not presented. Thursz (2015) reported mean inpatient resource use (number of nights) by 90 day follow-up, but it is not clear what proportion of these data relate specifically to the index hospital admission at which patients were recruited to the trial. These inpatient stay data have been extracted into evidence tables (Appendix G:) but are not included in analyses.

No studies reported outcomes separately for patients with active infections or GI bleeding at baseline, but subgroup analyses were undertaken to examine treatment effects in patients with clinical indices of severe alcoholic hepatitis that are known to affect prognosis, namely: spontaneous hepatic encephalopathy at baseline and / or Maddrey’s Discriminant Function ≥32 (or equivalent ‘severity’, as defined by study authors).

Overall, the quality of available evidence ranged from high to very low. Typical reasons for downgrading included poorly described randomisation and treatment allocation procedures, high rates of attrition or missing data, and inconsistency or imprecision in effect estimates.

For a summary of included studies see Table 1 (for the full evidence tables and full GRADE profiles please see Appendix G: and Appendix H: respectively).

Table 1: Summary of included studies

Study reference (including study design)	Study population	Intervention (dose & duration)	Comparator	Outcomes reported	Comments
Blitzer 1977 Double blind RCT USA (single centre)	N=28[a] with alcoholic hepatitis (AH) Mean age: 47.6yrs Male: 100% Encephalopathy[b]: 20%	Prednisolone 40mg 26 days (tapered after 14 days)	Placebo	• All-cause mortality - Up to 28 days - ≤90 days • Liver-related mortality - ≤90 days • Serious infections - ≤90 days	Excluded: serious infection (until eradicated). Included: gastrointestinal (GI) bleeding. <u>Subgroup data for analysis:</u> All-cause mortality (28 days) BY hepatic encephalopathy at baseline
Campra 1973 Open label RCT USA (single centre)	N=45 with severe AH Mean age: 43yrs Male: 38% Encephalopathy: 40%	Prednisone 0.5 mg/kg 42 days (reduced to 0.25 mg/kg after 21 days)	No treatment control	• All-cause mortality - ≤90 days • Liver-related mortality - ≤90 days • Serious infections - ≤90 days • Length of stay	No information re: inclusion / exclusion of patients with infection. Included: GI bleeding. <u>Subgroup data for analysis:</u> All-cause mortality (90 days) BY hepatic encephalopathy at baseline
Carithers 1989 Double-blind RCT USA (4 centres)	N =66 with severe AH characterised by DF ≥ 32 or hepatic encephalopathy Mean age: 43.5yrs Male: 62% Encephalopathy: 50%	Methylprednisolone (oral or i.v.) 32mg 42 days (tapered after 28 days)	Placebo	• All-cause mortality - Up to 28 days • Liver-related mortality - Up to 28 days • Serious infections - Up to 28 days • Serious adverse events	Excluded: active infections and GI bleeding requiring transfusion <u>Subgroup data for analysis:</u> (i) All-cause mortality (28 days) BY 'severe' (DF≥32) alcoholic hepatitis at baseline[c]

Study reference (including study design)	Study population	Intervention (dose & duration)	Comparator	Outcomes reported	Comments
					(ii) All-cause mortality (28 days) BY hepatic encephalopathy at baseline
De 2014 Double-blind RCT India (single centre)	N=60 with severe AH characterised by DF ≥ 32 Mean age: 42yrs Male: 100% Encephalopathy: 35%	Prednisolone 40mg + Pentoxifylline 1200mg 77 days (prednisolone tapered after 28 days)	Pentoxifylline 1200mg + placebo	• All-cause mortality - Up to 28 days - ≤90 days - 1 year • Liver-related mortality - Up to 28 days - ≤90 days - 1 year • Serious infections - ≤90 days - 1 year • Serious adverse events	Excluded: serious infections, GI bleeding. Double blind for initial treatment phase (28 days) then trial was opened.
Depew 1980 Double-blind RCT USA (single centre)	N=28 with severe acute AH and spontaneous encephalopathy Mean age: 49.1yrs Male: 57% Encephalopathy: 100%	Prednisolone 40 mg 42 days (tapered after 28 days)	Placebo	• All-cause mortality - ≤90 days • Liver-related mortality - ≤90 days • Serious infections - ≤90 days • Length of stay	Excluded: serious bacterial infection, GI bleeding. Length of stay data extracted into evidence table but not included in analyses.
Helman 1971 Double-blind RCT USA (single centre)	N=37 with biopsy-confirmed AH Mean age: 47.8yrs Male: 32% Encephalopathy: not reported	Prednisolone 40mg 42 days (tapered after 28 days)	Placebo	• All-cause mortality - ≤90 days • Liver-related mortality - ≤90 days	<u>Subgroup data for analysis:</u> All-cause mortality (90 days) BY 'severe' alcohol-related hepatitis at baseline

Study reference (including study design)	Study population	Intervention (dose & duration)	Comparator	Outcomes reported	Comments
Maddrey 1978 Double-blind RCT USA (single centre)	N=55 with alcoholic hepatitis (AH) Mean age: 41.1yrs Male: 64% Encephalopathy[c]: 27.3%	Prednisolone 40mg 28 to 32 days.	Placebo	• All-cause mortality - Up to 28 days - ≤90 days • Liver-related mortality - Up to 28 days - ≤90 days • Serious infections - ≤90 days • Serious adverse events	Excluded: infection or active GI bleeding. <u>Subgroup data for analysis:</u> (i) All-cause mortality (28 days) BY 'severe' alcoholic hepatitis at baseline (ii) All-cause mortality (90 days) BY 'severe' alcoholic hepatitis at baseline (iii) All-cause mortality (90 days) BY hepatic encephalopathy at baseline
Mendenhall 1984 Double-blind RCT USA (6 centres)	N=178 with moderate or severe AH Mean age: 51yrs Male: 100% Encephalopathy: 68.5%	Prednisolone 60mg 30 days (tapering by 20mg first 4 days, then by 10 mg dose for 4 days until 10mg for 7 days and 5 mg for final 7 days)	Placebo	• All-cause mortality - Up to 28 days - 1 year	Excluded: serious infection and active peptic ulcer disease. <u>Subgroup data for analysis:</u> (i) All-cause mortality (28 days) BY 'severe' (DF≥32) alcoholic hepatitis at baseline[d] (ii) All-cause mortality (28 days) BY hepatic encephalopathy at baseline[e]
Porter 1971 Double-blind RCT USA (3 centres)	N=20 with severe AH Mean age: 47.3yrs Male: 65% Encephalopathy: 75%	6-methylprednisolone 40mg (parenterally) 10 days (continued until improvement or tapered and taken orally).	Placebo	• All-cause mortality - Up to 28 days - 1 year • Serious infections - ≤90 days	Excluded: serious infection and active GI bleeding.

Study reference (including study design)	Study population	Intervention (dose & duration)	Comparator	Outcomes reported	Comments
				• Serious adverse events	
Ramond 1992 Double-blind RCT France (2 centres)	N=61 with biopsy-confirmed severe alcoholic hepatitis and DF ≥32 or hepatic encephalopathy. Mean age: 48yrs Male: 26% Encephalopathy: 31%	Prednisolone 40 mg (oral or i.v.) 28 days	Placebo	• All-cause mortality - Up to 28 days - ≤90 days - 1 year	Excluded: Bacterial infection unless eradicated in 48 hours and GI bleeding. <u>Subgroup data for analysis:</u> (i) All-cause mortality (90 days) BY DF>32 without hepatic encephalopathy at baseline (ii) All-cause mortality (90 days) BY hepatic encephalopathy at baseline
Shumaker 1978 Double-blind RCT USA (unclear no. centres)	N=27 with alcoholic hepatitis. Mean age: 45yrs Male: 44% Encephalopathy: *NR*[f]	Methylprednisolone 80mg (oral or i.v.) 28 days (tapered on flexible schedule after 4 to 7 days of initial treatment)	Placebo	• All-cause mortality - Up to 28 days • Liver-related mortality - Up to 28 days	Excluded: acute infection and active GI bleeding. <u>Subgroup data for analysis:</u> All-cause mortality (28 days) BY hepatic encephalopathy at baseline
Theodossi 1982 Open label RCT UK (single centre)	N=55[a] with severe, acute AH. Age: *NR*[d] Male: 56% Encephalopathy: 62%	Methylprednisolone 1g (i.v.) 3 days	No treatment control	• All-cause mortality - Up to 28 days • Length of stay	Included: sepsis and GI bleeding. Length of stay data extracted into evidence table but not included in analyses. <u>Subgroup data for analysis:</u> All-cause mortality (28 days) BY hepatic encephalopathy at baseline

Study reference (including study design)	Study population	Intervention (dose & duration)	Comparator	Outcomes reported	Comments
Thursz 2015 Double-blind, 2x2 factorial RCT UK (65 centres)	N=1103 with severe, acute AH and DF ≥32. Age: 48.7yrs Male: 62.7% Encephalopathy[g]: 73.3%	<u>Intervention A</u>: Prednisolone 40mg + pentoxifylline-matched placebo <u>Intervention B:</u> Prednisolone 40mg + 1200mg pentoxifylline 28 days	<u>Comparator A:</u> Prednisolone-matched placebo + pentoxifylline-matched placebo <u>Comparator B:</u> 1200mg pentoxifylline + prednisolone-matched placebo	• All-cause mortality - Up to 28 days - ≤90 days - 1 year • Liver-related mortality - 1 year • Serious infections - ≤90 days • Serious adverse events • Length of stay[h] • Quality of life	Excluded: patients with baseline sepsis, GI bleeding or renal failure who could not be stabilised with treatment within 7 days of admission.

(a) N value corresponds to number of participants included in the comparison of baseline characteristics and study analyses and not the total number randomised
(b) approximate % (read from bar charts)
(c) reported as 'encephalopathy with asterixis'
(d) reported in secondary publication - Mathurin et al. 2002
(e) reported in secondary publication – Imperiale and McCullough 1990
(f) NR – not reported
(g) includes 3 grades of encephalopathy from 'mild confusion and impaired attention' to 'comatose behaviour with responsiveness to verbal and noxious stimuli'
(h) 90 day inpatient resource-use data were reported; these were extracted into the evidence table but not included in a 'length of stay' analysis due to uncertainty about what proportion of the data relate to the index hospital admission.

2.4 Health economic evidence review

2.4.1 Methods

Evidence of cost effectiveness

The committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook a systematic review of the published economic literature.

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to alcoholic hepatitis in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 13th September 2016. The health economic search strategies are detailed in Appendix J:.

The health economist also sought out relevant studies identified by the surveillance review or committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.
- Critically appraised relevant studies using the economic evaluations checklist as specified in *Developing NICE Guidelines: the manual 2014*.
- Extracted key information about the studies' methods and results into full economic evidence tables (Appendix L:).
- Generated summaries of the evidence in economic evidence profiles.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly

applicable UK analysis was available, then other less relevant studies may not have been included.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

Economic evidence profile

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H* of *Developing NICE Guidelines: the manual 2014*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty.

Table 2 explains the information contained in the economic evidence profile.

Table 2: Explanation of fields used in the economic evidence profile

Item	Description
Study	This field is used to reference the study and provide basic details on the included interventions and country of origin.
Applicability	Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as: • Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having: • Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe.
Incremental cost	The difference between the mean cost associated with one strategy and the mean cost of a comparator strategy.
Incremental effect	The difference between the mean health effect associated with the intervention and the mean health effect associated with the comparator. This is usually represented by quality-adjusted life years (QALYs) in accordance with the NICE reference case.

Item	Description
Incremental cost effectiveness ratio (ICER)	The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and decreased health effects.
Uncertainty	A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review, and de novo modelling was not feasible or prioritised, the committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

2.4.2 Results of the economic literature review

The initial search returned a total of 391 articles, of which 390 were excluded based on title and abstract screening. The 1 remaining study was included in the economic evidence review, following full text review. Table 3 contains the economic evidence profile for this review question summarising the results of the study included in the systematic review and the economic model developed for the present update. Full economic evidence tables are contained in Appendix L:.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in Appendix K:.

Table 3: Economic evidence profile

Study	Applicability	Limitations	Other comments	Cost	Effect	Incremental cost	Incremental effect	ICER	Uncertainty
Thursz et al 2015 Prednisolone (AO) Pentoxifylline (OB) Prednisolone and pentoxifylline (AB) Placebo (OO) UK	Directly applicable	Potentially serious limitations [1]	In trial cost effectiveness analysis with 28 day time horizon Model-based cost utility analysis with 1 year and 10 year time horizons	28 days: AO: £3,618 AB: £3,827 OB: £4,194 OO: £4,869	28 days (survival): AO: 0.857 AB: 0.865 OB: 0.806 OO: 0.833	28 days: AO: - AB: £659 OB: £367 OO: £675	28 days: AO: - AB: 0.008 OB: -0.059 OO: 0.027	28 days (incremental cost per additional survivor): AO: AB: £26,125 OB: Dominated OO: Dominated	28 day horizon: Deterministic and probabilistic sensitivity analyses showed that the cost effectiveness of prednisolone is robust at 28 days. 1 year and 10 year horizons: Deterministic sensitivity analysis in which all hospitalisations after the initial 28 days were assumed to be in intensive care units resulted in a considerably higher ICER for prednisolone compared to PTX (£85,427). However, prednisolone still dominated placebo. Probabilistic sensitivity analysis showed that, at a threshold of £20,000, prednisolone has the highest probability of being the most cost effective treatment. However, there was considerable uncertainty surrounding these results.
				1 year: OB: £21,223 AO: £21,653 AB: £21,992 OO: £26,082	1 year (QALYs): OB: 0.2 AO: 0.2621 AB: 0.2604 OO: 0.2604	1 year: OB: - AO: £430 AB: £339 OO: £4,429	1 year: OB: - AO: 0.0621 AB: -0.0017 OO: 0	1 year (incremental cost per QALY): OB: - AO: £6,924 AB: Dominated OO: Dominated	
				10 years: AO: £42,899 AB: £43,275 OB: £45,517 OO: £54,052	10 years (QALYs): AO: 0.4068 AB: 0.5263 OB: 0.542 OO: 0.5418	10 years: AO: - AB: £376 OB: £2,242 OO: £8,535	10 years: AO: - AB: 0.1195 OB: 0.0157 OO: -0.0002	10 years (incremental cost per QALY): AO: - AB: £3,146 OB: £142,803 OO: Dominated	

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

[1] *The model-based approach employs a simplistic approach to Markov modelling: living patients are associated with a fixed utility score, daily cost, and daily probability of death, which does not vary according to time spent in the model.*

2.5 Evidence statements

2.5.1 Clinical evidence statements

Overall, the meta-analyses showed no evidence of a difference between steroid treatment and no steroids in people with alcoholic hepatitis of all degrees of severity in relation to all-cause or liver-related mortality at 28 days, 90 days or 1 year, but there was evidence that use of steroids was associated with a clinically important increase in the risk of serious infections by 90 days (RR 1.99, 95% CIs 1.40 to 2.82; high quality evidence from 8 RCT's with 1328 participants).

However in people with severe alcoholic hepatitis (defined as DF≥32), with no active infections or gastrointestinal bleeding, 5 RCTs with 1,303 participants found a clinically important reduction in mortality from all causes within the first 28 days associated with steroid treatment compared with no steroid treatment (RR 0.70; 95%CIs 0.55 to 0.90; high quality evidence). In 3 RCTs with 157 participants with severe alcoholic hepatitis (defined as DF≥32, or hepatic encephalopathy, or other definition), steroid treatment was associated with a clinically important reduction in liver-related mortality within 28 days (RR 0.23, 95%CIs 0.08 to 0.65, moderate quality). There is low and moderate quality evidence respectively that these treatment-related differences in all-cause mortality are not maintained in the medium-term (3 months; RR 0.83, 95%CIs 0.34 to 2.05; 3 studies and 1070 participants) or the longer-term (1 year; RR 0.92, 95%CIs 0.56 to 1.51; 3 studies and 868 particpipants).

2.5.2 Health economic evidence statements

A UK-based RCT and economic analysis (Thursz et al, 2015) found, in people with severe alcoholic hepatitis (defined as DF≥32), with no active infections or gastrointestinal bleeding, that treatment with prednisolone was cost effective at time horizons of 28 days, 1 year, and 10 years, compared to placebo. (Prednisolone dominated placebo at 28 day and 1 year horizons, and placebo was associated with an ICER well above NICE's high-end threshold of £30,000 at the 10 year horizon). However, there was considerable uncertainty surrounding results at the 1 year and 10 year horizons, largely due to the reduction in mortality produced by prednisolone not persisting beyond 28 days in the trial used to inform the economic analysis.

2.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee agreed that all-cause mortality would be the outcome valued most highly by patients. Liver-related mortality is a subset of all-cause mortality, but because steroids reduce inflammation, which in turn will improve liver function in patients with severe alcoholic hepatitis (AH), this outcome may arguably be considered a better indicator of treatment efficacy. Similarly, the number of people with serious infections is a subset of the number of people with serious adverse events (SAEs). Infection rate is a critical outcome for decision-making because steroids suppress the immune system which may precipitate opportunistic and potentially very serious emergent infections in this already immunocompromised population (for example, incidences of serious fungal infections and HIV were reported among participants in some included studies). A topic expert noted that in clinical practice it is often difficult to distinguish between initial and emergent infections. The majority of trials included in the review excluded patients who already had signs of active infection, although some (including the

	Committee discussions
	STOPAH trial - Thursz et al. 2015) permitted inclusion after the initial infection was controlled with a course of appropriate treatment. Active gastrointestinal (GI) bleeding, included in the outcome 'serious adverse events', was also a frequent exclusion criterion for entry to studies. GI bleeding is a cause for concern because the coagulopathy associated with severe AH means that a new bleed can be difficult to control and may quickly result in death. The committee discussed the difficulty of distinguishing efficacy and safety outcomes in this clinical context. Some secondary complications of severe AH may directly contribute to fatality, for example uncontrolled GI bleeding, systemic infection or spontaneous bacterial peritonitis. In practice, it can be difficult to know whether such complications are attributable directly to the condition itself or may have been exacerbated by steroid treatment. In randomised controlled trials, such causes of death may be categorised as 'liver-related mortality' and will therefore be included under several of the outcomes considered in this review (all-cause mortality, liver-related mortality, SAEs and serious infections). Health-related quality of life is an important outcome for patients. However, topic experts noted that people with severe AH are extremely unwell on admission to hospital, and their quality of life will be poor at baseline. Following discharge, quality of life will depend on a number of factors: the degree of residual illness, levels of follow-up care, as well as the social and psychological resources available to patients. 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. Length of stay is an important outcome for estimating resource use. Faster resolution of liver function in response to treatment may reduce overall length of stay. Conversely however, the possible risk of treatment-related SAEs may lead to longer inpatient stays to facilitate closer monitoring, or because of the need for additional treatment and recuperation in the event of an emergent infection or other SAE.
Quality of evidence	A topic expert noted that women with severe AH may have worse outcomes than men for a given degree of severity. This was taken into account when using GRADE to appraise evidence for 'indirectness', as three of studies included in this review were undertaken in all-male populations (Blitzer 1977, De 2014, Mendenhall 1984). The recently published multicentre STOPAH trial (Thursz 2015) includes twice the number of participants as all other included studies combined. Unadjusted data from STOPAH were used in pooled analyses. The committee noted that STOPAH was one of only two included studies directly applicable to a UK patient population. They also noted that the 13 RCTs included in this review were published over a period of more than 40 years. During that time, the quality of infection control and supportive care (including nutrition) in hospitals has improved, which may limit the generalisability of the results of older trials. A topic expert further noted that although we only included trials in which both intervention and comparator groups were offered the same supportive care (including dietary provision), evidence from Helman (1971) suggests that *actual* calorie uptake may differ significantly between treatment groups during the course of a study because steroids reduce inflammation, so improving liver function, which in turn may effect a return of appetite in treated patients.

	Committee discussions
	The committee agreed that variability between studies in population inclusion criteria and duration and dose of intervention meant it was most appropriate to use a random effects analysis to explore the mean treatment effect when pooling data for meta-analyses. Forest plots were presented that showed no significant subgroup differences between the three different treatment comparisons identified in the included studies (namely, steroid versus placebo, steroid versus 'no treatment' control and steroid combined with pentoxifylline versus pentoxifylline with placebo). The committee therefore decided the data should be combined, effectively to compare 'steroid treatment' (with or without pentoxifylline in the most recent studies by De 2014 and Thursz 2015) with any 'no steroid' comparator. These refinements to the analyses were undertaken following the committee meeting; there was no change in the overall direction and magnitude of the key results that formed the basis for the committee's decision-making. Two subgroup analyses specified in the review protocol could not be undertaken. This is because outcomes were not reported separately for people with active infections or bleeding at baseline in the minority of studies that permitted inclusion of such patients. Two further subgroup analyses were undertaken to examine treatment effects in more severely ill patients with the worst prognosis: that is, those with hepatic encephalopathy (HE) at baseline, and those with a discriminant function (DF) ≥32 (with or without HE). Topic experts confirmed that despite first being proposed in the literature almost 40 years ago, 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 Alcoholic Hepatitis Score. In early trials, severe AH was defined by the presence of spontaneous hepatic encephalopathy. This is a hallmark of severity which is still valid today. However the DF≥32 is preferred because detection of HE, particularly in its early stages, involves a degree of subjective judgement. Also HE may be present in people with decompensated cirrhosis, who may fare particularly badly if given corticosteroids. The committee felt it was important to run a further subgroup analysis, where data were available, focused specifically on patients with severe AH defined only as DF≥32. All the included studies that specified DF≥32 as an inclusion criterion also included a proportion of patients who had HE at baseline (in whom the discriminant function will almost invariably be >32). Most of these studies (including the STOPAH trial) did not enable outcomes to be separately distinguished for DF≥32 only (that is, removing patients with HE). However the committee felt that an analysis restricted to DF≥32 as the key indicator of severity would permit more direct comparison with those that formed the basis of the current recommendation in NICE CG100. It was acknowledged that this additional analysis would effectively exclude older (pre-discriminant function) studies with mixed severity populations that used HE as the marker for 'severe' AH. However it was noted that these are very small studies which are likely to have been underpowered for the outcomes of interest. In subgroup analyses presented to the committee that focused specifically on outcomes in people with HE, short-term mortality was high regardless of treatment group allocation. Inclusion of these patients in a combined analysis (that is, where 'severe' AH is defined as DF≥32 *or* HE) would therefore result in more imprecise effect estimates.

	Committee discussions
	Relevant data were available for the additional DF≥32 subgroup analysis only for the 'all-cause mortality' outcome at the 28-day and 90-day time points. There was no resultant change to the overall direction and magnitude of the effect estimates that formed the basis of the committee's initial decision-making. Short-term (28-day) or medium-term (90-day) 'all-cause mortality' was reported by all included studies. Only 3 studies reported longer-term (1-year) data. Overall the quality of the evidence for the DF≥32 population was higher for the 28-day time point, due to very serious or serious imprecision in effect estimates at 90 days and 1 year respectively. Topic experts noted that by 90 days inflammation would be expected to have reduced and an episode of alcoholic-hepatitis would be considered likely to have resolved by one year. Mortality in the post-discharge period is therefore likely to be confounded by non-liver related factors, most importantly subsequent drinking behaviour. Cause of death was not reported in all studies, so there was less evidence for liver-related mortality than all-cause mortality. The overall quality of the evidence for 28-day liver-related mortality was moderate; the effect estimate was precise but data came from only 3 small studies with serious risk of bias due to inadequate reporting of randomisation and treatment allocation procedures. As with all-cause mortality, effect estimates at 90 days and 1 year were imprecise, which may be due to confounding factors. The committee noted that the robustness of the evidence for 'liver-related mortality' may be compromised because studies used different criteria for categorising some of the fatal complications of AH as 'liver-' or 'non-liver related' (for example, GI bleeding or sepsis). Rates of serious adverse events were reported in fewer studies than were rates of serious infection alone. Studies often selectively reported non-infection SAEs (such as GI bleeds) only for fatalities; these data could not be included in analyses as they did not pertain to the whole study population. For the 'severe AH' subgroup analysis (which for SAEs included patients with DF≥32 *or* HE), evidence was of overall low quality. This was due to methodological limitations of the included studies and very serious imprecision of the effect estimate. The majority of studies reporting serious infection rate for the whole study population did so for the 90-day time point (7 studies contributed to this analysis). The committee noted that a 90-day time point is preferable to 28-day data for capturing potential late or treatment-related infections. 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 vary widely between centres) will be key to the prompt identification and treatment of infections and their longer-term sequelae. Quality of life was reported only by the STOPAH trial (Thursz et al. 2105). The committee agreed with the decision to downgrade this evidence for risk of bias in relation to the 90-day and 1 year time points due to successively high rates of non-response to the EQ5D self-completion questionnaire among survivors. This is a patient population that can be difficult to reach. Those survivors not engaging with questionnaire completion at 90 days and 1 year after discharge may be more likely to have returned to drinking alcohol, so the quality of life data from the STOPAH trial may not be

	Committee discussions
	generalisable to the wider population of people who are admitted to hospital with severe AH. No data for length of hospital stay were available for analysis due to lack of reporting of standard deviations or confidence intervals.
Trade-off between benefits and harms	There is high quality evidence that all-cause and liver-related mortality are reduced within the first month by steroid treatment in patients with severe AH (DF≥32). This survival benefit is not sustained at later time points (90 days or more), although the evidence was overall of poorer quality for longer follow-up time points. There is high quality evidence of a potential harm associated with steroid treatment in terms of an increased risk of serious infections at 90 days. In light of this robust new evidence of treatment-related harm, the committee discussed the implications of changing the status of the recommendation from the current strongly worded 'offer' to a less strongly worded 'consider offering' recommendation. However, topic experts were concerned that this would deny potentially life-saving treatment to people who are very ill on admission to hospital for whom no other treatment has been shown to have survival benefit. They argued that emergent infections may be treatable in surviving patients.
Trade-off between net health benefits and resource use	The committee considered the economic evidence for the cost effectiveness of prednisolone versus placebo for the treatment of severe alcoholic hepatitis, and agreed that there is robust evidence for the cost effectiveness of corticosteroids in the short term (28 days), and also evidence for cost effectiveness at longer time horizons (1 year and 10 years), although there is a higher degree of uncertainty surrounding these results. The committee noted that the uncertainty in results at later time horizons is principally due to convergence in mortality rates between study arms after 28 days, and therefore novel economic analysis would not provide any additional insight, as results would be characterised by a similar level of uncertainty at later time horizons. Overall, the committee concluded that treatment of severe alcoholic hepatitis with corticosteroids is likely to be cost effective compared with no treatment, as the evidence suggests that it results in a short-term reduction in mortality, and lower total costs.
Other considerations	Overall the committee was persuaded of the need to retain the current 'offer corticosteroids' recommendation for people with DF≥32 in light of high quality evidence of a short-term survival benefit (which is likely to be directly due to improved liver function) and health economic evidence of the cost-effectiveness of steroids compared with no steroid treatment in this population. The topic experts noted that while there is no standard treatment regimen, steroids would always be started on an inpatient basis and continued usually for 28 days, with or without a 2-week tapering period. During this time 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. In light of robust new evidence of an increased risk of serious infections associated with steroids in this population, the committee were keen that the recommendation should include advice to inform patients (or their family

	Committee discussions
	members or carers) about the benefits, limitations and potential side-effects of corticosteroids before starting treatment. 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. Steroids should therefore only be offered to people who are free from signs of infection, GI bleeding or severe renal impairment. However, if patients do have an active infection, GI bleeding or severe renal impairment on admission they should not be excluded from being offered a course of steroids once the pre-existing contraindication has been effectively controlled with appropriate treatment. Topic experts noted there is evidence to suggest that people successfully treated for pre-existing infections before starting steroids do not have a worse response nor a higher risk of adverse events than those in whom steroid treatment can be started without delay. 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 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. Only two included studies required histological confirmation of AH prior to inclusion in the trial. Topic experts noted that while liver biopsy is the diagnostic gold standard, a specialist (trans jugular) procedure is required (to which not all centres have access) in order to minimise the risk of uncontrolled bleeding in this vulnerable population. Consequently biopsy confirmation does not reflect 'real world' practice where treatment decisions are most usually made on an assumed diagnosis of severe AH, based on the patient's drinking history, clinical status, laboratory test results and imaging studies. The committee noted there are currently on-going trials to assess the effects of steroid treatment combined with prophylactic antibiotics in patients with severe AH. Once published, the results of these trials will be incorporated into future updates of this guideline. **Equalities issues** 1. Ethnicity may be a potential equalities issue. It is 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. 2. Cognitive impairment was identified as a potential equalities issue. People with severe AH may have varying degrees of hepatic encephalopathy on admission to hospital, ranging from mild confusion to coma. This may impact on the ability of clinicians to

	Committee discussions
	determine drinking history and symptoms. It will also be important to assess each individual's capacity to understand the relative benefits and harms prior to starting steroid treatment. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent and the code of practice that accompanies the Mental Capacity Act. In Wales, healthcare professionals should follow advice on consent from the Welsh Government. 3. 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. 4. English not being a first language was identified as a potential equalities issue. Individuals may not be able to fully describe their medical history or symptoms in English. This also has implications for discussing and understanding the relative benefits and harms of steroid treatment. Where possible, assistance of interpreters should be sought.

2.7 Recommendation

1. Offer corticosteroid[a] treatment to people with severe alcohol-related hepatitis and a discriminant function[b] 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 members or carers (as appropriate), explaining that corticosteroid treatment
  - has been shown to improve survival in the short term (1 month)
  - has not been shown to improve survival over a longer term (3 months to 1 year)

[a] Corticosteroids are used in UK clinical practice in the management of severe alcohol-related hepatitis. At the time of publication (April 2017), prednisolone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[b] Maddrey's discriminant function (DF) was described to predict prognosis in alcohol-related hepatitis and identify patients suitable for treatment with steroids. It is 4.6 x [prothrombin time – control time (seconds)] + bilirubin in mg/dl. To calculate the DF using bilirubin in micromol/l divide the bilirubin value by 17.

- has been shown to increase the risk of serious infections within the first 3 months of starting treatment. [**2017**]

2.8 Research recommendations

The committee did not make any research recommendations for this review question.

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4 Glossary and abbreviations

Please refer to the NICE glossary.

Alcohol - ethanol (ethyl alcohol) is the main psychoactive ingredient in alcoholic drinks. By extension, the term 'alcohol' can be used interchangeably with ethanol, and to describe an alcoholic drink.

Alcohol-related hepatitis – a term used interchangeably with 'alcoholic hepatitis'. The condition is characterised by the presence of inflammation and cellular damage and thought to be the key stage in the development of fibrosis and eventually cirrhosis.

Ascites - accumulation of fluid in the peritoneal cavity, leading to abnormal abdominal swelling.

Bilirubin (biochemical test) - bilirubin is a yellow compound that is formed from the normal process of blood cell breakdown, which occurs in the liver. A test can be undertaken to assess the amount of bilirubin in a person's blood. A raised concentration of bilirubin may occur if the liver cannot process the breakdown of bilirubin, due to inflammation, obstruction or excess bilirubin production.

Binge drinking: A heavy drinking session in which someone drinks at least twice the maximum recommended units of alcohol per day in one session.

Child-Pugh score: A clinical score using clinical parameters (bilirubin, INR, albumin, presence of ascites and hepatic encephalopathy) to classify severity of chronic liver disease.

Corticosteroids / glucocorticosteroids: Corticosteroids, often known as steroids, are an immunomodulatory medicine prescribed for a wide range of conditions. They are a man-made version of hormones normally produced by the adrenal glands (two small glands that sit on top of the kidneys). Corticosteroids are available in different forms, including: tablets (oral steroids), injections – which can be into blood vessels, joints or muscles, inhalers – such as mouth or nasal sprays or lotions, gels or creams (topical steroids)

Decompensated liver disease / cirrhosis - decompensation occurs when the liver is failing; it is marked by complications including jaundice, fluid retention manifesting as ascites and/or ankle swelling, variceal bleeding and/or neuropsychiatric problems generically termed hepatic encephalopathy.

Discriminant function (DF): see Maddrey score

Glasgow Alcoholic Hepatitis Score: This score is used to determine severity and can be used to predict 28 and 84 day survival. It can also be used as a tool to guide steroid treatment decision; if the score is 9 or more there is 28 day and 84 day survival benefit in treating with steroids. This score uses clinical parameters of leucocytes, urea and bilirubin concentration and prothrombin time to predict mortality in people with alcoholic hepatitis.

Hepatic encephalopathy: If the liver is not working properly, toxins can build up in the blood. These toxins can accumulate and affect the nervous system, and produce a wide spectrum of changes ranging from poor concentration and attention, an impaired ability to undertake tests of cognitive function, to changes in consciousness culminating in coma

Hepato-renal syndrome: Impaired renal function which is often precipitated by events lowering blood pressure. It is a complication of end-stage liver disease or acute liver failure. It can be precipitated by several different factors, including infections, alcoholic hepatitis and bleeding.

Lille score: Assesses the probability of survival at 6 months in patients treated with corticosteroids after 7 days of treatment; it can be used to identify non-responders who may

benefit from stopping steroid treatment. This score uses the clinical parameters of bilirubin concentration on commencement and after one week of corticosteroid treatment, creatinine, albumin and prothrombin time. Patients with a high risk of mortality are less likely to benefit from further corticosteroid treatment after 7 days.

Maddrey score / Maddrey's discriminant function (MDF or DF) score: Used to determine severity of alcoholic hepatitis and the likely benefit of corticosteroid treatment. This score uses clinical parameters of bilirubin concentration and prothrombin time and is calculated as: 4.6 x (patient's PTT (in secs) – matched control's PTT (in secs)) + serum bilirubin (mg/dl). A score of 32 or higher indicate severe alcoholic hepatitis that carries an adverse prognosis, with mortality of 20 to 30% within 1 month of presentation and 30 to 40% within 6 months after presentation. Patients with a score <32 have less severe disease and there is no added benefit of steroid treatment.

Malnutrition: Malnourishment is a state of nutrition in which a deficiency of energy, protein and/or other nutrients causes measurable adverse effects on tissue/body form, composition, function or clinical outcome.

Medically-assisted alcohol withdrawal: the withdrawal of alcohol in a dependent drinker as a planned or semi-planned procedure using medication to prevent withdrawal symptoms

MELD score: predicts 30 and 90 days survival. Can be used to assess the severity of alcohol-related hepatitis. This score uses clinical parameters of serum bilirubin concentration, serum creatinine concentration and INR to predict survival in end stage liver disease.

Prothrombin time (PTT) / INR: A blood test that assesses how long it takes a person's blood to clot. The liver produces the clotting factor necessary for blood clots to form; damage to the liver results in impaired production, hence poor clotting

Spontaneous bacterial peritonitis: bacterial infection of ascitic fluid. It is usually asymptomatic and carries a poor prognosis.

Appendices

Appendix A: Standing Committee members and NICE teams

A.1 Core members

Name	Role
Tessa Lewis (Chair)	Chair - GP, Medical Advisor in Therapeutics
John Cape	Director of Psychological Therapies Programme
Alison Eastwood	Professor (Research)
Sarah Fishburn	Lay member
Imran Jawaid	Sessional GP
Catriona McDaid	Senior Research Fellow
Nick Screaton	Radiologist
Sophie Wilne	Vice Chair, Paediatric Oncologist
Gail Fortes Mayer	Commissioner
Victoria Hetherington	Senior Nurse Practitioner, Clinical Lead

A.2 Topic expert Committee members

Name	Role
Ashwin Dhanda	NIHR Academic Clinical Lecturer in Hepatology
Marsha Morgan	Principal Research Associate & Honorary Consultant Physician
Leroy Simpson	Lay member
Adrian Jugdoyal	Hepatology Advanced Nurse Practitioner/University Lecturer
Neeraj Bhala	Consultant Physican in GI Medicine
Roz Gittins	Chief Pharmacist

A.3 NICE project team

Name	Role
Christine Carson	Guideline Lead
Mark Baker	Clinical Adviser
Steven Barnes	Technical Lead
Ross Maconachie	Health Economics Lead
Caroline Kier	Guideline Commissioning Manager
Helen Dickinson	Guideline Co-ordinator
Sandra Robinson	Meetings in Public Co-ordinator
David Tyldesley	Resource Impact Lead
Shelly Patel	Medicines Evidence and Advice Adviser
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A.4 Clinical guidelines update team

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Appendix B: Declarations of interest

The standing committee and topic experts interests have been declared and collated and are available here. (Link to be populated in time for consultation & publication)

Appendix C: Review protocol

	Details
Review Question	What is the safety and efficacy of corticosteroids for acute alcohol-related hepatitis?
Objectives	This question was referred for an exceptional update due to publication of a large NIHR trial: STOPAH. The outcomes of this trial may affect the current recommendations associated with this review question.
Type of Review	Intervention question
Language	English language only
Study Design	If a recent (2015 onwards), high quality systemic review has been published then this will be used. If no systematic review fitting these criteria exists, then individual RCT data will be included. Quasi RCTs (contemporaneous allocation) will be included for adverse events only. We are aware that the STOPAH trial adjusted their results for PT ratio or INR, bilirubin, age, WBC count, urea, creatinine and encephalopathy. We will use the unadjusted data from STOPAH as presented in the meta-analysis. Observational studies, abstracts, posters, reviews, letter/editorials, foreign language publications and unpublished studies will be excluded.
Status	Published studies (full text only) with no date limit. All studies included in the original guideline will also be considered.
Population	People (aged 10 years and over) with acute alcohol-related hepatitis.
Intervention	Any corticosteroids administered through any route and at any dose: ○ prednisolone ○ methylprednisolone ○ dexamethasone ○ hydrocortisone ○ budesonide +/- other supportive care (including N-acetylcholine, pentoxifylline, antioxidants or enteral feeding).
Comparator	• placebo, or • no treatment, or • usual care +/- other supportive care (including, but not limited to: N-acetylcholine, pentoxifylline, antioxidants or enteral feeding).
Outcomes	• All-cause mortality at: - 28 days - ≤ 90 days - 1 year • Liver-related mortality at: - 28 days - ≤ 90 days - 1 year • Number of people with serious infections at: - 28 days

	Details
	- ≤ 90 days - 1 year • Number of people with serious adverse events • Length of stay (days) • Quality of life
Other criteria for inclusion / exclusion of studies	**Inclusion** The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been incorrectly sifted out. **Exclusion** Women who are pregnant. Children younger than 10 years.
Analysis of subgroups or subsets	**Subgroups:** • People with GI bleeding at start of treatment • People with infection at start of treatment • People with spontaneous Hepatic Encephalopathy • People with severe alcohol related hepatitis (defined as Discriminant Function (Maddrey) score of ≥32, hepatic encephalopathy, or otherwise defined 'severe hepatitis') - Where a study has a mixed population, it will be included in the "severe" subgroup if over 90% of the population has a Maddrey DF score of ≥32, hepatic encephalopathy, or otherwise defined 'severe hepatitis'.
Data extraction and quality assessment	<u>Sifting</u> Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. The sifting will be undertaken using the EPPI- Reviewer priority screening function[a]. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered not to be relevant to the topic will be excluded. *i) Selection based on titles and abstracts* A full double-sift of titles and abstracts will not be conducted due to the nature of the review question (typical intervention question); a support analyst will sift a 10% sample of titles and abstracts, and % agreement will be assessed. Where the percentage is less than 100%:

[a] In an amendment to the protocol, priority screening in Eppi reviewer was not used. There was 100% sensitivity for study inclusion when the support analyst checked a random 10% sample of articles. In addition, several published systematic reviews were cross-checked (see table of excluded studies, Appendix F) and did not identify identify any further studies meeting the review protocol inclusion criteria.

	Details
	- any papers identified by the support analyst that were not identified by the lead analyst, the full text will be ordered and assessed for inclusion - if agreement is less than 95%, a further 10% sample will be sifted by the support analyst to ensure rigorous identification and selection of studies. - an additional check will be the results of the 'Priority screening' function in EPPI-Reviewer 4[b] *ii) Selection based on full papers* A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). However in cases of uncertainty the following mechanisms will be in place: - technical analyst will discuss with a support technical analyst - comparison with included studies of other systematic reviews - recourse to members of the committee <u>Data extraction</u> Information from included studies will be extracted into standardised evidence tables. <u>Critical appraisal</u> The risk of bias of each included study will be assessed using theRCT checklist proposed in the NICE manual (based on the Cochrane Risk of Bias checklist) <u>Quality assessment</u> GRADE methodology will be used to assess the quality of evidence on an outcome basis: • Risk of bias will be assessed using critical appraisal checklists • Inconsistency will be assessed using I^2: - 0-40%: no serious - 41- 70%: serious - 71- 100: very serious If there is very serious unexplained heterogeneity (71% or more), a sensitivity analysis will be undertaken on route of administration of steroids; removing i.v. administration of steroids. • Indirectness will be assessed after considering the population, intervention and outcomes of included studies, relative to the target population; • Imprecision will be assessed using whether the confidence intervals around point estimates cross the MIDs for each outcome. For mortality outcomes, the line of no difference will be used as the MID. For other outcomes, COMET and published literature will be checked for appropriate minimal important differences (MID) and if none are available Topic Experts will be asked to provide MID's. *Reliability of quality assessment:* A full double-scoring quality assessment will not be conducted due to the nature of the review question (typical intervention review) and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following:

	Details
	• Internal QA (10%) by CGUT technical adviser on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. • The committee will be sent the evidence synthesis prior to the committee meeting and the committee will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	• If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. A fixed effects model will be used if it is expected that the studies will be homogenous in terms of population and we can assume a similar effect size across studies. A random effects model will be used if this assumption is not correct. • Where available, unadjusted data will be extracted and reported in the review. If unadjusted data is not available, adjusted data will be used. It will be noted what data are used for each study. • A narrative evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
Search strategies	<u>Sources to be searched</u> • Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA. • Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. <u>Supplementary search techniques</u> • If relevant systematic reviews are identified, the reference list will be analysed for any further studies relevant to the question. <u>Limits</u> • Studies reported in English • Study design RCT filters will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • The search will be run from June 2009 to the present[a]

Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 4. The Medline (Ovid) search strategy is shown in Table 5. The same strategy was translated for the other databases listed.

Table 4: Clinical search summary

Database	Date searched	Number retrieved
MEDLINE (Ovid)	13/09/2016	586
MEDLINE In-Process (Ovid)	13/09/2016	37
Embase (Ovid)	13/09/2016	1,661
Cochrane Database of Systematic Reviews (CDSR)	13/09/2016	14
Cochrane Central Register of Controlled Trials (CENTRAL)	13/09/2016	255
Database of Abstracts of Reviews of Effect (DARE)	13/09/2016	4
Health Technology Assessment (HTA Database)	13/09/2016	0
PubMed	13/09/2016	61

Table 5: Clinical search terms (Medline search)

Line number/Search term/Number retrieved
1 Hepatitis, Alcoholic/ (1950)
2 Hepatic Encephalopathy/ (9543)
3 ((severe* or serious* or acute*) adj4 hepat*).tw. (27041)
4 ((hepat* or portal systemic or portosystemic) adj4 (encephalopath* or coma* or stupor*)).tw. (8183)
5 Hepatorenal Syndrome/ (1168)
6 (hepatorenal adj4 (syndrome* or insuffic* or disease* or fail*)).tw. (1880)
7 Hematemesis/ (2254)
8 ((upper GI or upper gastro* or varice* or varix) adj4 (bleed* or hemorrhag* or blood loss or hematochez*)).tw. (12847)
9 or/1-8 (54854)
10 exp Ethanol/ (99830)
11 exp Alcoholic Beverages/ (16686)
12 exp Alcohol-Related Disorders/ (104389)
13 exp Alcohol Drinking/ (58982)
14 Alcoholic Neuropathy/ (118)

Line number/Search term/Number retrieved
15 (alcohol* or ethanol* or beer* or wine* or spirit*).tw. (346946)
16 (dipsomania* or drunkenness).tw. (905)
17 ((binge* or hazard* or harmful* or problem* or unhealth* or unsaf* or peril* or risk* or damag* or destruct* or ruinous* or disadvantag* or detriment* or trouble*) adj4 drink*).tw. (13058)
18 or/10-17 (413075)
19 exp Hepatitis/ (147698)
20 hepat*.tw. (552369)
21 (liver* adj4 (inflam* or swell* or distend* or protrud*)).tw. (7464)
22 or/19-21 (578728)
23 18 and 22 (29325)
24 9 or 23 (79634)
25 exp Adrenal Cortex Hormones/ (367758)
26 (corticosteroid* or corticoid* or adrenocorticosteroid* or hydroxycorticosteroid* or ketosteroid*).tw. (89776)
27 (adrenal cort* adj4 (hormone* or steroid*)).tw. (1900)
28 ((cortic* or adrenocort*) adj4 (steroid* or hormone*)).tw. (21232)
29 ((adrenal or adreno) adj4 steroid*).tw. (5560)
30 (glucocorticoid* or glucorticoid* or glycocorticoid* or glucocorticoidsteroid* or glucocorticosteroid*).tw. (57597)
31 exp Prednisolone/ (47595)
32 prednisolone*.tw. (20916)
33 (Delta-Phoricol or Deltacortril or Deltastab or Pevanti or Precortisyl or Pred Forte or Predenema or Predfoam or Prednesol or Predsol or Sintisone).tw. (52)
34 (Ak-Pred or Articulose-50 or AsmalPred Plus or Delta-Cortef or Econopred or Flo-Pred or Hydeltra-TBA or Hydeltrasol or Inflamase or Key-Pred-SP or Key-Pred or Millipred or Omnipred or Orapred or Pediapred or Pred Mild or Pred-Phosphate or Pred or Predaject or Predalone or Predate or Predcor or Prednisol or Predonine or Prelone or Veripred).tw. (2664)
35 (Predmix or Solupred or Decortin H or Prednisolut or Ultracortenol).tw. (54)
36 (methylprednisolone* or medrone).tw. (12506)

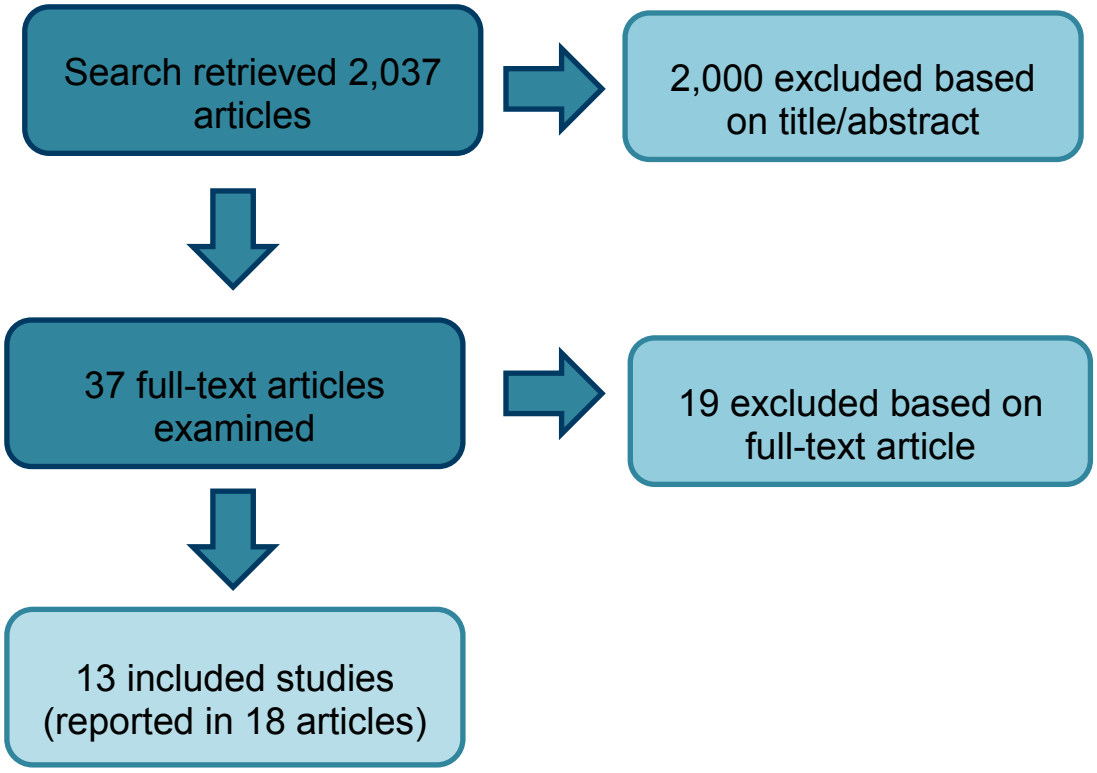
Line number/Search term/Number retrieved
37 (A-Methapred or Adlone or D-Med or depMedalone or Depo-Medrol or Depo-Predate or Depoject or Depopred or Duralone or M-Prednisol or Medralone or Medrol Acetate or Medrol or Solu-Medrol or solu-medrone or betnelan or betnesol or calcort or depomedrone or adcortyl or kenalog or Depo-medrone).tw. (585)
38 exp Dexamethasone/ (47278)
39 dexamethasone*.tw. (46000)
40 (Decadron or Dexafree or Dexsol or Dropodex or Martapan or Maxidex or Oradexon or Ozurdex).tw. (323)
41 (Aeroseb-Dex or Ak-Dex or Alba Dex or Baldex or Baycadron or Dalalone or Decaderm in Estergel or Decaject or Decaspray or Dexacort or Dexameth or Dexasone or Dexone or DexPak or Hexadrol or Solurex or Zema).tw. (32)
42 (hydrocortisone* or efcortesol or cortef or cortisol or cortisone* or epicortisol or solu-cortef).tw. (75269)
43 (Anflam or Colifoam or Corlan or Cortenema or Cortopin or Cortropin or Dermacort or Dioderm or Efcortelan Soluble or Efcortelan or Exe-Cort or Hc45 or Hydrocortistab or Hydrocortisyl or Hydrocortone or Lanacort or Locoid or Mildison or Plenadren or Timocort).tw. (66)
44 (A-Hydrocort or Acticort or Aeroseb-HC or Ala-Cort or Anucort-HC or Anuprep HC or Aquanil HC or Bactine or CaldeCort or Carmol HC or Cetacort or Colocort or Cort-Dome or CortaGel or Cortaid or Cortef or Corticaine or Corticool or Cortifair or Cortifoam or Cortizone or Cortril or Delcort or Dermacort or Dermarest or Dri-Cort or Dermasorb HC or Dermol HC or Dermolate or EarSol-HC or GRx HiCort or Hemril-HC or Hi-Cor or Hycort or Hydrocortone or HydroSkin or HydroTex or Hytone or Lacticare-HC or Massengill Medicated or Noble Formula HC or NuCort or Nutracort or Orabase HCA or Pandel or Procort or Proctocort or Recort Plus or Rectacort-HC or S-T Cort or Scalacort DK or Synacort or Tegrin-HC or Texacort or U-Cort or Westcort or Xerese).tw. (89)
45 exp Budesonide/ (3976)
46 (budesonide* or budelin or pulmicort or horacort or rhinocort).tw. (4141)
47 (Budenofalk or Cortiment or Entocort or Preferid or Uceris).tw. (49)
48 Prednisone/ (37027)
49 prednisone*.tw. (22347)
50 (Dehydrocortisone or delta-Cortisone or Prednison Hexal or Sone or Sterapred or Ultracorten or Winpred or Cortan or Cortancyl or Panafcort or Cutason or Decortin or Dacortin or Encortone or Encorton or Enkortolon or Kortancyl or Panasol or Predni Tablinen or Prednidib or Predniment or Prednison acsis or Prednison Galen or Pronisone or Rectodelt).tw. (372)
51 (Decortisyl or Econosone or Lodotra).tw. (0)
52 (Deltasone or Liquid Pred or Meticorten or Orasone or Panasol-S or Prednicen-M or Rayos or Sterapred).tw. (62)
53 exp Triamcinolone/ (8718)

Line number/Search term/Number retrieved
54 triamcinolone*.tw. (6001)
55 (Adcortyl or Kenalog or Ledercort or Lederspan or Nasacort or Volon).tw. (237)
56 (AllerNaze or Amcort or Aristocort or Aristospan or Articulose LA or Atolone or Azmacort or Cinalone 40 or Cinonide 40 or Delta-Tritex or Dermasorb TA or Flutex or Kenacort or Kenaject or Kenonel or Oralone Dental or pediaderm TA or Tac or Tri-Kort or Triacet or Triam-A or Triam or Triamcinair or Triamolone or Triamonide or Trianex or Triderm or Triesence or Trilog or Trilone or Tristoject or Trivaris or Trymex).tw. (7370)
57 exp Betamethasone/ (6696)
58 Betamethasone*.tw. (3944)
59 (Audavate or Betacap or Betesil or Betnelan or Betnesol or Betnovate RD or Betnovate or Bettamousse or Bextasol or Diprosone or Vista-Methasone).tw. (84)
60 (Alphatrex or B-S-P or Beta-Val or Betatrex or Cel-U-Jec or Celestone or Diprolene or Luxiq or Maxivate or Psorion or Selestoject or Sernivo or Teladar or Uticort or Valisone).tw. (112)
61 Beclomethasone/ (2907)
62 beclomethasone*.tw. (2567)
63 (Beclometasone or Asmabec Clickhaler or Ascocortonyl or Beclamet or Beclo Asma or Beclo AZU or Beclocort or Beclomet or Bemedrex Easyhaler or Beclorhinol or Becloturmant or Sanasthmax or Beclovent or Beconase or Becloforte or Becodisk* or Becotide or Propaderm or Sanasthmyl or Bronchocort or Junik or Qvar or Aerobec or Beclazone or Ecobec or Filair or Nasobec or Prolair or Respocort or Ventolair or Vancenase or Vanceril or Aldecin or Viarin or Apo-Beclomethasone).tw. (331)
64 (Beceze or Beclo Aqua or Beclogen or Clenil or Clipper or Hayfever Relief or Nasal Spray for Hayfever or Nasal-Bec or Pollenase Nasal or Pulvinal or Qnasl).tw. (106)
65 Pyridoxine/ (7511)
66 Pyrrolidonecarboxylic Acid/ (2663)
67 (Pyridox* or Rodex or Metadoxine).tw. (12929)
68 (pyrrolidone adj4 carboxylate).tw. (62)
69 ((Pyrrolidonecarboxylic or Pidolic or Pyroglutamic or Pidolate) adj4 (acid* or magnesium)).tw. (661)
70 Pyroglutamate.tw. (518)
71 ("5" adj4 (oxop* or ketoproline)).tw. (621)
72 Acetylcysteine/ (11454)
73 (acetylcystein* or N-Acetyl-L-cystein* or N Acetyl L cystein*).tw. (12624)

Line number/Search term/Number retrieved	
74	(Fabrol or Parvolex).tw. (10)
75	(Acetadote or Cetylev or Mucomyst or Mucosil).tw. (35)
76	or/25-75 (512955)
77	24 and 76 (2926)
78	Animals/ not Humans/ (4280821)
79	77 not 78 (2499)
80	limit 79 to english language (1855)
81	Randomized Controlled Trial.pt. (430183)
82	Controlled Clinical Trial.pt. (91662)
83	Clinical Trial.pt. (505439)
84	exp Clinical Trials as Topic/ (301913)
85	Placebos/ (33683)
86	Random Allocation/ (88793)
87	Double-Blind Method/ (139170)
88	Single-Blind Method/ (22755)
89	Cross-Over Studies/ (39555)
90	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (857004)
91	(random$ adj3 allocat$).tw. (23947)
92	placebo$.tw. (169726)
93	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (136297)
94	(crossover$ or (cross adj over$)).tw. (62947)
95	or/81-94 (1550276)
96	animals/ not humans/ (4280821)
97	95 not 96 (1443982)
98	Meta-Analysis.pt. (73055)
99	Meta-Analysis as Topic/ (15371)

Line number/Search term/Number retrieved	
100	Review.pt. (2102999)
101	exp Review Literature as Topic/ (9050)
102	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (84590)
103	(review$ or overview$).ti. (315404)
104	(systematic$ adj5 (review$ or overview$)).tw. (79655)
105	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (5606)
106	((studies or trial$) adj2 (review$ or overview$)).tw. (29921)
107	(integrat$ adj3 (research or review$ or literature)).tw. (6672)
108	(pool$ adj2 (analy$ or data)).tw. (18270)
109	(handsearch$ or (hand adj3 search$)).tw. (6868)
110	(manual$ adj3 search$).tw. (3839)
111	or/98-110 (2287581)
112	animals/ not humans/ (4280821)
113	111 not 112 (2144193)
114	97 or 113 (3310753)
115	80 and 114 (586)

Appendix E: Review flowchart



Appendix F:Excluded studies

Reference	Reason for exclusion
Anonymous . (1990). Erratum: Methylprednisolone therapy in patients with severe alcoholic hepatitis: Randomized multicenter trial (Am J Gastroenterol, Vol. 85, No. 4 (473)). American Journal of Gastroenterology, 85(6), pp.776.	Incorrect publication type: erratum to Carrithers (1989) - contains no relevant new information.
Boitnott J K, and Maddrey W C. (1981). Alcoholic liver disease: I. Interrelationships among histologic features and the histologic effects of prednisolone therapy. Hepatology, 1(6), pp.599-612.	Incorrect outcomes: secondary publication to Maddrey (1978); looks only at histological outcomes in subsample of original study population.
Carey W D. (1992). Steroids in alcoholic hepatitis: Another salvo of data. American Journal of Gastroenterology, 87(9), pp.1219-1220.	Incorrect publication type - commentary on Ramond 1992 study.
Christensen E, and Gluud C. (1995). Glucocorticoids are ineffective in alcoholic hepatitis: a meta-analysis adjusting for confounding variables. Gut, 37(1), pp.113-8.	Incorrect publication type: meta-analysis. Used for cross-checking. No additional studies identified.
Hmoud B S, Patel K, Bataller R, and Singal A K. (2016). Corticosteroids and occurrence of and mortality from infections in severe alcoholic hepatitis: a meta-analysis of randomized trials. Liver International, 36(5), pp.721-8.	Incorrect publication type: meta-analysis. Used for cross-checking. No additional relevant studies identified.
Horwitz R J. (1992). Prednisolone for severe alcoholic hepatitis. Annals of Internal Medicine, 117(SUPPL. 2), pp.36.	Incorrect publication type - commentary on Ramond 1992 study
Lesesne H R, and Fallon H J. (1973). Treatment of liver disease with corticosteroids. Medical Clinics of North America, 57(5), pp.1191-201.	Incorrect publication type: non-systematic review of clinical area.
Lesesne H R, Bozymski E M, and Fallon H J. (1978). Treatment of alcoholic hepatitis with encephalopathy. Comparison of prednisolone with caloric supplements. Gastroenterology, 74(2 Pt 1), pp.169-73.	Incorrect comparator (compares prednisolone therapy with nutritional supplementation of >1600 calories/day without prednisolone)
Mathurin P, O'Grady J, Carithers R L, Phillips M, Ramond M J, and Louvet A. (2009). Corticosteroids improve 28-day survival in patients with severe alcoholic hepatitis: individual data analysis of the last 5 randomized controlled trials. Journal of hepatology, 50(Suppl. No 1), pp.S82.	Incorrect publication type – conference poster abstract
Mathurin P, O'Grady J, Carithers R L, Phillips M, Louvet A, Mendenhall C L, Ramond M J, Naveau S, Maddrey W C, and Morgan T R. (2011). Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut, 60(2), pp.255-60.	Incorrect publication type - meta-analysis. Includes studies with comparators not matching the RP. No additionaly relevant studies identified.
Mathurin P, Louvet A, Duhamel A, Nahon P, Carbonell N, Boursier J, Anty R, Diaz E, Thabut D, Moirand R, Lebrec D, Moreno C,	Incorrect comparator - compares Prednisolone

Reference	Reason for exclusion
Talbodec N, Paupard T, Naveau S, Silvain C, Pageaux G P, Sobesky R, Canva-Delcambre V, Dharancy S, Salleron J, and Dao T. (2013). Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. JAMA, 310(10), pp.1033-41.	monotherapy with combination therapy (Prednisolone + Pentoxifylline).
Njei B, Do A, McCarty T R, and Fortune B E. (2016). Corticosteroids Versus Pentoxifylline for Severe Alcoholic Hepatitis: A Sequential Analysis of Randomized Controlled Trials. J Clinical Gastroenterology	Incorrect publication type - meta-analysis. Used for cross-checking. No additional relevant studies identified.
Rambaldi A, Saconato H H, Christensen E, Thorlund K, Wetterslev J, and Gluud C. (2008). Systematic review: glucocorticosteroids for alcoholic hepatitis--a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. Alimentary Pharmacology & Therapeutics, 27(12), pp.1167-78.	Incorrect publication type - meta-analysis. No additional relevant studies identified.
Schlichting P, Juhl E, Poulsen H, and Winkel P. (1976). Alcoholic hepatitis superimposed on cirrhosis. Clinical significance and effect of long-term prednisone treatment. Scandinavian Journal of Gastroenterology, 11(3), pp.305-12.	Incorrect population - compares cirrhosis patients with and without alchoholic hepatitis
Schlichting P, Christensen E, Fauerholdt L, Poulsen H, Juhl E, and Tygstrup N. (1982). Prednisone and chronic liver disease. II. Clinical versus morphological criteria for selection of patients for prednisone treatment. Liver, 2(2), pp.113-8.	Incorrect population - non-alcoholic females with chronic aggressive hepatitis
Schlichting P, Fauerholdt L, Christensen E, Poulsen H, Juhl E, and Tygstrup N. (1982). Prednisone treatment of chronic liver disease. I. Chronic aggressive hepatitis as a therapeutic marker. Liver, 2(2), pp.104-12.	Incorrect population - cirrhosis patients with / without chronic aggressive hepatitis (mixed alcohol / non-alchoholic)
Singal A K, Kodali S, Vucovich L A, Darley-Usmar V, and Schiano T D. (2016). Diagnosis and Treatment of Alcoholic Hepatitis: A Systematic Review. Alcoholism: Clinical & Experimental Research, 40(7), pp.1390-402.	Incorrect publication type - systematic review of clinical area. Used for cross-checking. No additional relevant studies identified
Singh S, Murad M H, Chandar A K, Bongiorno C M, Singal A K, Atkinson S R, Thursz M R, Loomba R, and Shah V H. (2015). Comparative Effectiveness of Pharmacological Interventions for Severe Alcoholic Hepatitis: A Systematic Review and Network Meta-analysis. Gastroenterology, 149(4), pp.958-70.e12.	Incorrect publication type - network meta-analysis. Used for cross-checking. No additional relevant studies identified.
Yu C H, Xu C F, Ye H, Li L, and Li Y M. (2010). Early mortality of alcoholic hepatitis: A review of data from placebo-controlled clinical trials. World Journal of Gastroenterology, 16(19), pp.2435-2439.	Incorrect publication type - systematic review. Used for cross-checking. No additional relevant studies identified.

Appendix G: Evidence tables

G.1 Blitzer (1977)

Bibliographic reference	**Blitzer B L, Mutchnick M G, Joshi P H, Phillips M M, Fessel J M, and Conn H O. (1977). Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double-blind randomized study. American Journal of Digestive Diseases, 22(6), pp.477-84.**
Study type	RCT
Aim	To study the effect of adrenocorticosteroid treatment of acute alcoholic hepatitis in a double-blind RCT.
Patient characteristics	**Inclusion:** Patients with alcoholic hepatitis who met the following criteria after at least 5 days in hospital were included in the study: (1) recent history of heavy alcohol consumption; (2) hepatomegaly based on physical examination; (3) total serum bilirubin greater than 5mg/100 ml (4) and at least two of the following abnormalities: - serum glutamic oxaloacetic transaminase (SGOT) > 100 Reitman-Frankel units per ml - serum albumin concentration <3g/ml, or - prothrombin time more than 2 seconds greater than control value. Liver biopsies performed where possible but not required for study admission. Patients with serious life-threatening infection were delayed entry to the trial until infection was eradicated. Patients with peptic ulcer or gastrointestinal bleeding were not excluded. **Exclusion:** - Adrenocorticosteroids in the six months prior to admission - Showed evidence of psychotic behaviour precluding their cooperation. **Baseline characteristics:** For those included in analyses (n=28). No baseline information on 5/33 dropouts (all prednisolone group) who were excluded from analyses.

	Prednisolone	**Placebo**

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Blitzer B L, Mutchnick M G, Joshi P H, Phillips M M, Fessel J M, and Conn H O. (1977). Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double-blind randomized study. American Journal of Digestive Diseases, 22(6), pp.477-84.</td></tr>
<tr><td></td><td colspan="3">
<table>
<tr><th></th><th>(n=12)</th><th>(n=16)</th></tr>
<tr><td>Age (years) - mean</td><td>47</td><td>48</td></tr>
<tr><td>Days before study entry</td><td>11.1</td><td>12.6</td></tr>
<tr><td>Men:women</td><td>12:0</td><td>16:0</td></tr>
<tr><td>Ascites* (%)</td><td>65</td><td>82</td></tr>
<tr><td>Encephalopathy* (%)</td><td>25</td><td>10</td></tr>
<tr><td>PTT* (s)</td><td>4</td><td>5.2</td></tr>
<tr><td>Bilirubin mg/100ml</td><td>25.4</td><td>15.4</td></tr>
</table>
*Approximations as read off bar charts. There were no significant differences between the groups at baseline with the exception of serum bilirubin (p<0.05).
</td></tr>
<tr><td>Number of Patients</td><td colspan="3">N=28 in analyses

N=33 initially randomised. N=5 (15%) dropouts - all from prednisolone group: N=3 left the hospital against medical advice, N=2 GI haemorrhage.</td></tr>
<tr><td>Intervention</td><td colspan="3">Prednisolone tablets (n=12) as follows:
10mg four times a day for 14 days
5mg four times a day for 4 days
2.5mg four times a day for 4 days
2.5mg twice a day for 4 days.

All patients (both treatment groups) were encouraged to eat standard hospital 2600-calorie diet and offered supplements if caloric intake seemed inadequate.</td></tr>
<tr><td>Comparison</td><td colspan="3">Placebo (n=16)</td></tr>
<tr><td>Length of follow up</td><td colspan="3">Length of follow up: cumulative survival calculated until day 63</td></tr>
<tr><td>Location</td><td colspan="3">USA (single centre).</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Results
<table>
<tr><th>Outcome</th><th>Prednisolone (n=12)</th><th>Placebo (n=16)</th></tr>
<tr><td>All-cause mortality (cumulative)</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Blitzer B L, Mutchnick M G, Joshi P H, Phillips M M, Fessel J M, and Conn H O. (1977). Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double-blind randomized study. American Journal of Digestive Diseases, 22(6), pp.477-84.**

- Up to 28 days - ≤90 days* - 1 year	2 (17%) 6 (50%) NR	2 (13%) 5 (31%) NR
Liver-related mortality - Up to 28 days - ≤90 days - 1 year	 NR 5 (42%) NR	 NR 5 (31%) NR
Number of people with serious infections - Up to 28 days - ≤90 days - 1 year	 NR 2 (17%)** NR	 NR 0 NR
Number of people with serious adverse events***	NR	NR
Length of stay	NR	NR
Quality of life	NR	NR

*final death day 54

** two patients who developed oral lesions from which Candida was cultured are not included on advice from topic experts that this should not be considered a serious infection

*** serious infections are reported for the study sample as a whole, but other SAEs are not reported (aside from those precipitating a fatality).

Subgroup:

All-cause mortality by severe AH with hepatic encephalopathy at baseline

Outcome	**Prednisolone (n=3)**	**Placebo (n=2)**
All-cause mortality - 28 days	 2/3 (67%)	 1/2 (50%)

Bibliographic reference	**Blitzer B L, Mutchnick M G, Joshi P H, Phillips M M, Fessel J M, and Conn H O. (1977). Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double-blind randomized study. American Journal of Digestive Diseases, 22(6), pp.477-84.**
Source of funding	US Public Health Service training grants. Prednisolone and placebo tablets supplied by Upjohn Co., Kalamazoo, Michigan.
Comments	**Note:** all male study population **Quality assessment** Selection bias: High risk - no information on how random sequence was generated; 'sealed envelope technique' – does not specify if envelopes were opaque and numbered. Performance bias: Low risk - double blind study; only pharmacist aware of treatment allocation Detection bias: Low risk - outcomes measured by investigators who were blinded to treatment allocation. Attrition bias: High risk - N=5 (15%) dropouts - all from prednisolone group. No ITT analysis Reporting bias: Unclear - no study protocol available; outcomes not clearly pre-specified; insufficient information to judge selective reporting. Other bias: High risk –.all male study population; potential 'for profit' bias (medication provided by manufacturers).

G.2 Campra (1973)

Bibliographic reference	**Campra J L, Hamlin E M, Jr , Kirshbaum R J, Olivier M, Redeker A G, and Reynolds T B. (1973). Prednisone therapy of acute alcoholic hepatitis. Report of a controlled trial. Annals of Internal Medicine, 79(5), pp.625-31.**
Study type	RCT
Aim	To examine the effect of prednisolone treatment of clinically severe acute alcoholic hepatitis on the disease course and survival rate.
Patient characteristics	**Inclusion:** - a clinical diagnosis of severe acute alcoholic liver disease randomisation within 10 days of hospitalisation Histologic features of primary diagnostic value were considered to be: intrasinusoidal and pericentral collagen deposition, alcoholic hyaline, cell swelling and hydrepic change, cell necrosis and polymorphonuclear cell infiltration.

<table>
<tr><td>Bibliographic reference</td><td>Campra J L, Hamlin E M, Jr , Kirshbaum R J, Olivier M, Redeker A G, and Reynolds T B. (1973). Prednisone therapy of acute alcoholic hepatitis. Report of a controlled trial. Annals of Internal Medicine, 79(5), pp.625-31.</td></tr>
<tr><td></td><td>All patients were judged to be seriously ill. Diagnostic confirmation by percutaneous liver biopsy was not required for study admission (all but three patients eventually had histological confirmation of diagnosis obtained either by liver biopsy or at autopsy).

Exclusion:
- Prior history of liver disease
- Contraindication to corticosteroid therapy
- Any other known illnesses.
Baseline characteristics:
<table>
<tr><th></th><th>Prednisone (n=20)</th><th>Control (n=25)</th></tr>
<tr><td>Age (years) - mean</td><td>43</td><td>43</td></tr>
<tr><td>Days before study entry</td><td>8.4</td><td>7.0</td></tr>
<tr><td>Men:women</td><td>8:12</td><td>9:16</td></tr>
<tr><td>Ascites (%)</td><td>65%</td><td>48%</td></tr>
<tr><td>Encephalopathy (%)</td><td>40%</td><td>40%</td></tr>
<tr><td>PTT (% of normal control value)</td><td>51%</td><td>52%</td></tr>
<tr><td>Bilirubin mg/100ml</td><td>18.5</td><td>17.8</td></tr>
<tr><td>Creatinine mg/100ml</td><td>1.8</td><td>1.7</td></tr>
</table>

There were no significant differences between the groups at baseline.</td></tr>
<tr><td>Number of Patients</td><td>N=45</td></tr>
<tr><td>Intervention</td><td>Prednisone (n=20)
0.5 mg/kg body weight for 3 weeks
0.25 mg/kg body weight for 3 weeks

Intervention and control group received the same supportive and symptomatic care.</td></tr>
<tr><td>Comparison</td><td>Control (no placebo) (n=25)</td></tr>
</table>

Bibliographic reference	**Campra J L, Hamlin E M, Jr , Kirshbaum R J, Olivier M, Redeker A G, and Reynolds T B. (1973). Prednisone therapy of acute alcoholic hepatitis. Report of a controlled trial. Annals of Internal Medicine, 79(5), pp.625-31.**
Length of follow up	6 weeks
Location	USA (single centre)
Outcomes measures and effect size	**Results**

Outcome	**Prednisone (n=20)**	**Control (n=25)**
All-cause mortality - 28 days - ≤90 days - 1 year	 NR 7 (35%) NR	 NR 9 (36%) NR
Liver-related mortality - 28 days - ≤90 days - 1 year	 NR 7 (35%) NR	 NR 9 (36%) NR
Number of people with serious infections - 28 days - ≤90 days - 1 year	 NR 2 (10%) NR	 NR 0 NR
Number of people with serious adverse events**	NR	NR
Length of stay – mean, (SD)	47 (no SD)	48 (no SD)
Quality of life	NR	NR

*all deaths attributed to progressive hepatic failure, so included under both ‘all-cause’ and ‘liver-related

** States that there was no between-group difference in incidence of GI erosions, ulcerations or bleeding but numbers not reported.

Subgroup:

All-cause mortality by severe AH with hepatic encephalopathy at baseline

Outcome	**Prednisone**	**Control**

Bibliographic reference	**Campra J L, Hamlin E M, Jr , Kirshbaum R J, Olivier M, Redeker A G, and Reynolds T B. (1973). Prednisone therapy of acute alcoholic hepatitis. Report of a controlled trial. Annals of Internal Medicine, 79(5), pp.625-31.**
	<table><tr><th></th><th>(n=8)</th><th>(n=10)</th></tr><tr><td>All-cause mortality - ≤90 days</td><td>4/8 (50%)</td><td>8/10 (80%)</td></tr></table>
Source of funding	Not reported
Comments	**Quality assessment** Selection bias: High risk - no information on how random sequence was generated; 'Previously prepared sealed envelopes' - does not state if envelopes were opaque and numbered. Performance bias: High risk - Participants and investigators not blinded to treatment allocation (comparator was 'no treatment' control group). Detection bias: High risk – Outcome assessors not blinded to treatment allocation. Attrition bias: Unclear - 5/50 (10%) randomised but subsequently withdrew. Not clear if attrition differed between treatment groups. No ITT analysis. Reporting bias: Unclear - no study protocol available; outcomes not clearly pre-specified; insufficient information to judge selective reporting. Other bias: Low risk – no evidence.

G.3 Carithers (1989)

Bibliographic reference	**Carithers R L, Jr , Herlong H F, Diehl A M, Shaw E W, Combes B, Fallon H J, and Maddrey W C. (1989). Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Annals of Internal Medicine, 110(9), pp.685-90.**
Study type	RCT
Aim	To determine the efficacy of a corticosteroid in reducing short-term mortality of patients with severe alcoholic hepatitis.
Patient characteristics	**Inclusion:** - History of long-standing alcoholism - Negative hepatitis B surface antigen within the first 3 days of hospitalisation - No previous history of viral hepatitis - Evaluated as having one or both the following clinical features of alcoholic hepatitis within 3 days of admission: (i) spontaneous hepatic encephalopathy (ii) a discriminant function greater than 32

Bibliographic reference	**Carithers R L, Jr , Herlong H F, Diehl A M, Shaw E W, Combes B, Fallon H J, and Maddrey W C. (1989). Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Annals of Internal Medicine, 110(9), pp.685-90.**

Exclusion:

- GI haemorrhage requiring transfusion
- Insulin-dependent diabetes
- Active infection requiring treatment
- Clinical evidence of acute pancreatitis
- History of recent head trauma
- Known prior heroin addiction
- Pre-existing chronic renal disease with serum creatinine greater than 175 µmol/L

Baseline characteristics:

Corresponds to full recruited sample (n=66) 1

	Methylprednisolone (n=35)	**Placebo (n=31)**
Age (years) - mean	43	44
Days before study entry	4.0	4.5
Men:women	20:15	21:10
Ascites (%)	71%	65%
Encephalopathy (%)	14 (40%)	19 (61%)
PTT	18	18
AST µkat/L	2.6	2.1
Creatinine µmol/L	135.6	132.9
Discriminant function	46.4	46.7

There were no significant differences between the groups at baseline.

Number of Patients	N=66 N=59 completers (89%)
Intervention	Methylprednisolone (n=35) tablets or i.v administration, with following regimen: 32 mg for 28 days

Bibliographic reference	**Carithers R L, Jr , Herlong H F, Diehl A M, Shaw E W, Combes B, Fallon H J, and Maddrey W C. (1989). Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Annals of Internal Medicine, 110(9), pp.685-90.**
	16 mg for 7 days 8 mg for 7 days Discontinued drug therapy if severe infection, GI bleeding or steroid-related complication suspected. All patients in both treatment groups were offered a 3000 calorie diet and the same supportive and symptomatic care.
Comparison	Placebo (n=31)
Length of follow up	28 days
Location	USA (4 centres)
Outcomes measures and effect size	**Results:**

Outcome	**Methylprednisolone (n=35)**	**Placebo (n=31)**
All-cause mortality - 28 days - ≤90 days - 1 year	 2 (6%) NR NR	 11 (35%) NR NR
Liver-related mortality - 28 days - ≤90 days - 1 year	 2 (6%) NR NR	 11 (35%) NR NR
Number of people with serious infections - 28 days - ≤90 days - 1 year	 1 (3%)* NR NR	 3 (10%)** NR NR
Number of people with serious adverse events***	5 (14%)	8 (26%)
Length of stay	NR	NR

Bibliographic reference	**Carithers R L, Jr , Herlong H F, Diehl A M, Shaw E W, Combes B, Fallon H J, and Maddrey W C. (1989). Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Annals of Internal Medicine, 110(9), pp.685-90.**

Quality of life	NR	NR

*one patient developed had gram negative sepsis (non-fatal) – treatment subsequently halted

**3 patients with 'overwhelming sepsis' (all died)

*** includes patients with both fatal and non-fatal SAEs (acute pancreatitis, GI bleeding, sepsis, treatment-related acute psychosis)

Subgroup:

All-cause mortality by severe AH with hepatic encephalopathy at baseline

Outcome	**Methylprednisolone (n=14)**	**Placebo (n=19)**
All-cause mortality - 28 days	1 (7%)	9 (47%)

Source of funding	Research grant from National Institute of Alcohol Abuse and Alcoholism
Comments	**Quality assessment** Selection bias: Unclear. Random code sequence generated for each participating institution and kept by independent source. Block randomisation: within each group of 10 patients recruited at each of four participating centres, 5 received methylprednisolone and 5 placebo. Allocation of later recruited patients may have been possible to anticipate. Performance bias: Low risk - patients and investigators blinded to treatment allocation. Detection bias: Low risk - outcome assessors blinded to treatment allocation. Attrition bias: High risk - 14% attrition in methylprednisolone group vs. 6.5% in placebo group. Two withdrawals (both in methylprednisolone group; 1 was lost to follow-up); 5 treatment discontinuations due to potential drug toxicity (3 methylprednisolone and 2 placebo). No ITT analysis. Reporting bias: Unclear - no study protocol available; outcomes not clearly pre-specified; insufficient information to judge selective reporting. Other bias: Low risk – no evidence. Power analysis conducted.

G.4 De (2014)

<table>
<tr><td>Bibliographic reference</td><td>De B , Mandal S, Sau D, Mani S, Chatterjee S, Mondal S, Bhattacharya K, Sil K, and Bhattacharya R. (2014). Pentoxifylline Plus Prednisolone versus Pentoxifylline Only for Severe Alcoholic Hepatitis: A Randomized Controlled Clinical Trial. Annals of Medical & Health Sciences Research, 4(5), pp.810-6.</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Aim</td><td>To compare the efficacy of combination treatment with prednisolone and pentoxifylline with pentoxifylline alone in the management of acute alcoholic hepatitis (MDF>=32).</td></tr>
<tr><td>Patient characteristics</td><td>
Inclusion:
- History of chronic alcohol intake >50g / day with the following clinical and biochemical features of severe alcoholic hepatitis:
- MDF score >=32
- Aspartate aminotranferase: Alanine aminotransferase (AST:ALT) > 2:1
- Absolute values of AST < 500 I.U/L and ALT <200 I.U/L

Exclusion:
- Other potential aetiology of liver injury (e.g. acute / chronic viral hepatitis, autoimmune liver disease, Wilson's disease), even in the background of chronic alcohol intake.
- History of abstinence from alcohol in the last month
- Positive for HIV antibodies
- Infection, sepsis, spontaneous bacterial peritonitis
- Acute pancreatitis, GI bleeding, hepatorenal syndrome
- Other severe associated disease (uncontrolled diabetes, systemic hypertension, heart failure, pulmonary disease or malignancy) at the time of inclusion or in the previous 3 months.

Baseline characteristics:
<table>
<tr><th></th><th>Prednisolone + Pentoxifylline (n=30)</th><th>Pentoxifylline + placebo (n=30)</th></tr>
<tr><td>Age (years) – mean (SD)</td><td>42.7 (0.4)</td><td>41.3 (7.8)</td></tr>
<tr><td>Male:Female</td><td>30:0</td><td>30:0</td></tr>
<tr><td>Ascites (%)</td><td>28 (93%)</td><td>27 ((90%)</td></tr>
<tr><td>Encephalopathy (%)</td><td>11 (37%)</td><td>10 (33%)</td></tr>
<tr><td>Varices (%)</td><td>25 (83%)</td><td>26 (87%)</td></tr>
<tr><td>Maddrey DF score</td><td>63.1 (31.0)</td><td>56.6 (37.6)</td></tr>
<tr><td>MELD score*</td><td>20.9 (3.3)</td><td>20.1 (4.5)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**De B , Mandal S, Sau D, Mani S, Chatterjee S, Mondal S, Bhattacharya K, Sil K, and Bhattacharya R. (2014). Pentoxifylline Plus Prednisolone versus Pentoxifylline Only for Severe Alcoholic Hepatitis: A Randomized Controlled Clinical Trial. Annals of Medical & Health Sciences Research, 4(5), pp.810-6.**

Glasgow score**	7.9 (0.9)	7.7 (1.1)
Child-Pugh score***	11.9 (1.2)	11.3 (1.5)
Urea (mg/dL)	27.6 (8.7)	31.6 (14.3)
Bilirubin (mg/dL)	4.7 (1.9)	4.8 (3.7)
Creatinine (mg/dL)	1.01 (0.2)	1.04 (0.2)
Albumin (g/dL)	2.9 (0.6)	2.9 (0.6)
INR	2.1 (0.5)	2.1 (0.8)
AST (IU/L)	120.4 (31.2)	117.7 (50.0)
ALT (IU/L)	48.1 (11.9)	42.0 (18.8)

*MELD score ranges from 6 to 40, with higher scores indicating worse prognosis.
**Glasgow score ranges from 5 to 12, with higher scores indicating worse prognosis.
***Child-Pugh score ranges from 5 to 15, with higher scores indicating worse prognosis.
No significant differences between treatment groups at baseline.

Number of Patients	N=60
Intervention	Combination therapy with prednisolone + pentoxifylline (n=30) Prednisolone: 40mg tablet once daily for 4 weeks Pentoxifylline: 400mg tablet 3x per day for 4 weeks Initial double blind treatment phase for 4 weeks. Trial opened after 4 weeks - patients had prednisolone tapered by 5mg/week over next 7 weeks then stopped (while receiving PTX as before) Concomitant treatment with the following was not allowed during study period for patients in either treatment group: salicylates, NSAIDs, budesonide, anti-TNF-alpha agents, vitamin E, s-adenosyl methionine, ursodeoxcholic acid.
Comparison	Pentoxifylline + placebo (n=30) Pentoxifylline: 400mg tablet 3x per day for 4 weeks

<table>
<tr><td>Bibliographic reference</td><td>De B , Mandal S, Sau D, Mani S, Chatterjee S, Mondal S, Bhattacharya K, Sil K, and Bhattacharya R. (2014). Pentoxifylline Plus Prednisolone versus Pentoxifylline Only for Severe Alcoholic Hepatitis: A Randomized Controlled Clinical Trial. Annals of Medical & Health Sciences Research, 4(5), pp.810-6.</td></tr>
<tr><td></td><td>Placebo: tablet in place of prednisolone, once daily for 4 weeks

Initial double blind treatment phase for 4 weeks. Trial opened after 4 weeks - patients who tolerated drug continued with treatment for next 8 weeks, then stopped.</td></tr>
<tr><td>Length of follow up</td><td>Total study follow-up duration: 12 months

Patient recruitment: January 2010 to August 2012.</td></tr>
<tr><td>Location</td><td>India (single centre)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Results
<table>
<tr><th>Outcome</th><th>Prednisolone + Pentoxifylline (n=30)</th><th>Pentoxifylline + placebo (n=30)</th></tr>
<tr><td>All-cause mortality (cumulative)
- Up to 28 days
- ≤90 days
- 1 year</td><td>
1 (3%)
9 (30%)
10 (33%)</td><td>
3 (10%)
5 (17%)
6 (20%)</td></tr>
<tr><td>Liver-related mortality (cumulative)
- Up to 28 days
- ≤90 days
- 1 year</td><td>
1 (3%)
9 (30%)
10 (33%)</td><td>
3 (10%)
5 (17%)
6 (20%)</td></tr>
<tr><td>Number of people with serious infections (cumulative)*
- Up to 28 days
- ≤90 days
- 1 year</td><td>
NR
3 (10%)
5 (17%)</td><td>
NR
1 (3%)
1 (3%)</td></tr>
<tr><td>Number of people with serious adverse events**</td><td>22 (73%)</td><td>5 (17%)</td></tr>
<tr><td>Length of stay</td><td>NR</td><td>NR</td></tr>
<tr><td>Quality of life</td><td>NR</td><td>NR</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**De B , Mandal S, Sau D, Mani S, Chatterjee S, Mondal S, Bhattacharya K, Sil K, and Bhattacharya R. (2014). Pentoxifylline Plus Prednisolone versus Pentoxifylline Only for Severe Alcoholic Hepatitis: A Randomized Controlled Clinical Trial. Annals of Medical & Health Sciences Research, 4(5), pp.810-6.**
	*5 patients in intervention group developed sepsis of whom 3 died; 1 control group patients developed sepsis and died. **reported for 0-3 month timepoint; may include some double-counting of patients who developed more than one of the listed serious adverse events (GI bleed, sepsis, recurrent encephalopathy, worsening ascites, hepatorenal syndrome, impaired glucose tolerance)
Source of funding	No funding support
Comments	**Note:** all male study population **Quality assessment** Selection bias: Unclear. Used 'computer generated randomisation table' but not stated if this was done independently of recruitment & allocation procedure. States that study investigator was blinded but also responsible for treatment allocation and drug administration. Performance bias: Unclear - Patients, caregivers and statisticians were blinded to initial 4-week treatment phase after which treatment was open label for 2 more months. Patients were followed up until 12 months. Detection bias: Unclear - outcome assessor was blinded but only during initial 4-week treatment period, after which the study was opened and patients continued to be assessed. Attrition bias: Low risk - 2 randomised patients discontinued, one per treatment group. No ITT analysis. Reporting bias: Low risk – no evidence of selective reporting. Other bias: High risk – all male study population.

G.5 Depew (1980)

Bibliographic reference	**Depew W, Boyer T, Omata M, Redeker A, and Reynolds T. (1980). Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. Gastroenterology, 78(3), pp.524-9.**
Study type	RCT
Aim	Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy
Patient characteristics	**Inclusion** Alcohol abusers with a clinical diagnosis of severe acute alcoholic hepatitis manifested by: - Hepatomegaly,

<table>
<tr><td>Bibliographic reference</td><td>Depew W, Boyer T, Omata M, Redeker A, and Reynolds T. (1980). Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. Gastroenterology, 78(3), pp.524-9.</td></tr>
<tr><td></td><td>- Leucocytosis, and
- Serum bilirubin greater than 5mg/dl.

Exclusion
- Severe diabetes
- Active TB
- Serious bacterial infection.

All participants had encephalopathy occurring in the absence of gastrointestinal haemorrhage, sedation, diuretic usage, or major electrolyte disturbances. Histologic confirmation of the clinical diagnosis was not required. Liver tissue was eventually obtained in 21 patients with 20 specimens showing features consistent with acute alcoholic hepatitis.

Baseline characteristics
<table>
<tr><th></th><th>Prednisolone (n=15)</th><th>Placebo (n=13)</th></tr>
<tr><td>Age in years – mean</td><td>50</td><td>48</td></tr>
<tr><td>Days before study entry</td><td>8.3</td><td>8.6</td></tr>
<tr><td>Men:women</td><td>10:5</td><td>6:7</td></tr>
<tr><td>Ascites (%)</td><td>87</td><td>92</td></tr>
<tr><td>Encephalopathy (%)</td><td>100</td><td>100</td></tr>
<tr><td>WBC (cells/mm3 x 10-3)</td><td>17.8</td><td>22.2</td></tr>
<tr><td>Bilirubin (mg/dl)</td><td>2.6</td><td>2.1</td></tr>
<tr><td>Creatinine mg/dl</td><td>2.3</td><td>3.0</td></tr>
</table>
Groups were similar at randomisation.</td></tr>
<tr><td>Number of Patients</td><td>N=28</td></tr>
<tr><td>Intervention</td><td>Prednisolone (n=15) 5
40 mg daily by mouth for 28 days followed by tapered withdrawal over the next 14 days</td></tr>
</table>

Bibliographic reference	**Depew W, Boyer T, Omata M, Redeker A, and Reynolds T. (1980). Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. Gastroenterology, 78(3), pp.524-9.**
Comparison	Placebo (n=13)
Length of follow up	Study duration assumed to be duration of hospitalisation. (Mean duration was 66 days for the steroid group and 56 days for placebo).
Location	USA (single centre)
Outcomes measures and effect size	**Results**

Outcome	**Prednisolone (n=15)**	**Placebo (n=13)**
All-cause mortality - 28 days - ≤90 days* - 1 year	 NR 8 (53%) NR	 NR 7 (54%) NR
Liver-related mortality - 28 days - ≤90 days - 1 year	 NR 8 (53%) NR	 NR 7 (54%) NR
Number of people with serious infections - 28 days - ≤90 days - 1 year	 NR 5 (33%)** NR	 NR 2 (15%)*** NR
Number of people with serious adverse events****	NR	NR
Length of stay***** (days) – mean, (SD)	65.6 (no SD)	56.2 (no SD)
Quality of life	NR	NR

*data assumed to relate to total duration of hospital stay (66d for steroid-treated group; 56d for placebo group))

** 3 patients developed pneumonia, 1 septicaemia, 1 peri-nephric abscess at 3 months post-discharge

*** 1 patient developed pneumonia, 1 septicaemia

Bibliographic reference	**Depew W, Boyer T, Omata M, Redeker A, and Reynolds T. (1980). Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. Gastroenterology, 78(3), pp.524-9.**
	****reported as 'instances' rather than numbers of patients *****data are from duration of stay from time of randomisation and relate only to survivors (N=7 steroid group; N=6 placebo group)
Source of funding	Not stated
Comments	**Quality assessment** Selection bias: High risk – no details of sequence generation or treatment allocation procedures. Performance bias: Low risk - patients, investigators and care givers blinded to treatment allocation Detection bias: Low risk - Outcome assessors blinded to treatment allocation. Attrition bias: Low risk – no attrition. Reporting bias: Unclear - no study protocol available; outcomes not clearly pre-specified; insufficient information to judge selective reporting. Other bias: Low risk – no evidence.

G.6 Helman (1971)

Bibliographic reference	**Helman R A, Temko M H, Nye S W, and Fallon H J. (1971). Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. Annals of Internal Medicine, 74(3), pp.311-21.**
Study type	RCT
Aim	To explore the natural history of biopsy-diagnosed alcoholic hepatitis including the effect of prednisolone therapy on the disease course and survival rate.
Patient characteristics	**Inclusion** - Biopsy confirmation of alcoholic hepatitis before inclusion in the study (within 7 days of admission). - Willingness to be hospitalised for four weeks Recruited patients were classified into three groups according to the clinical severity of their disease: - Group I: severely ill and manifesting pre-coma or coma during the first 10 days of admission; - Group II: patients were moderately ill with no evidence of hepatic encephalopathy; - Group III: mildly ill or asymptomatic and ambulatory on admission. **Exclusion**

<table>
<tr><td>Bibliographic reference</td><td>Helman R A, Temko M H, Nye S W, and Fallon H J. (1971). Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. Annals of Internal Medicine, 74(3), pp.311-21.</td></tr>
<tr><td></td><td>Any of the following criteria:
- A biopsy could not be obtained within the first week of hospitalisation;
- Gastrointestinal bleeding (requiring transfusion) occurred during first week of hospitalisation;
- Purified protein derivative (PPD) test was positive

Baseline characteristics
<table>
<tr><th></th><th>Prednisolone (n=20)</th><th>Placebo (n=17)</th></tr>
<tr><td>Severity group:
- Group I
- Group II
- Group III</td><td>
9
6
5</td><td>
6
4
7</td></tr>
</table>
The average age of participants was 47.8 years. There were 12 (32%) men and 25 (68%) women. The differences in age, sex and treatment selection were not different between severity groups. 73% had ascites. 89% had underlying cirrhosis. (NB few patient characteristics are reported by treatment arm).
<table>
<tr><th></th><th>Severity group I</th><th>Severity group II</th><th>Severity group II</th></tr>
<tr><td>WBC x $10^3/mm^3$</td><td>12.8</td><td>11.4</td><td>10.7</td></tr>
<tr><td>Bilirubin mg/100ml</td><td>13.1</td><td>13.3</td><td>5.7</td></tr>
<tr><td>Prothrombin time, sec</td><td>15.8</td><td>14.6</td><td>13.6</td></tr>
<tr><td>Albumin g/100ml</td><td>2.4</td><td>3.4</td><td>3.4</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>N=37</td></tr>
<tr><td>Intervention</td><td>Prednisolone (n=20)
40mg daily for 4 weeks then tapered over a 2 week period

Both treatment groups received same high calorie diet.</td></tr>
<tr><td>Comparison</td><td>Placebo (n=17)
Lactose placebo given for 4 weeks then ‘tapered’ over a 2 week period.</td></tr>
<tr><td>Length of follow up</td><td>4 months</td></tr>
</table>

Bibliographic reference	**Helman R A, Temko M H, Nye S W, and Fallon H J. (1971). Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. Annals of Internal Medicine, 74(3), pp.311-21.**
Location	USA (single centre).
Outcomes measures and effect size	**Results**

Outcome	**Prednisolone (n=20)**	**Placebo (n=17)**
All-cause mortality (cumulative)*		
- 28 days	NR	NR
- ≤90 days	1 (5%)	6 (35%)
- 1 year	NR	NR
Liver-related mortality		
- 28 days	NR	NR
- ≤90 days	1 (5%)	6 (35%)
- 1 year	NR	NR
Number of people with serious infections**	NR	NR
Number of people with serious adverse events**	NR	NR
Length of stay	NR	NR
Quality of life	NR	NR

*all deaths were among patients in most severe group (severity group I)

**states 'there was no evidence of GI ulceration or bleeding, infection or other adverse side effect of prednisolone', but does not data for either treatment group.

Subgroup:

All-cause mortality by Severe* alcoholic hepatitis

Outcome	**Prednisolone (n=9)**	**Placebo (n=6)**
All-cause mortality		
- ≤90 days	1 (11%)	6 (100%)

*Group I: severely ill and manifesting pre-coma or coma during the first 10 days of admission.

Bibliographic reference	**Helman R A, Temko M H, Nye S W, and Fallon H J. (1971). Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. Annals of Internal Medicine, 74(3), pp.311-21.**
Source of funding	Supported in part by grants from the US public health service. Intervention and placebo provided by Upjohn Co., Kalamazoo, Michigan.
Comments	**Quality assessment** Selection bias: High risk – 'Drug treatment was randomly determined by the hospital pharmacist'. No details of sequence generation or allocation procedures. Performance bias: Low risk - patients, investigators and care givers blinded to treatment allocation Detection bias: Low risk - outcome assessors blinded to treatment allocation Attrition bias: Low risk – no attrition. Reporting bias: Unclear - no study protocol available; outcomes not clearly pre-specified; insufficient information to judge selective reporting. Other bias: Unclear risk – potential 'for profit' bias (study medication provided by manufacturer) No power analysis conducted.

G.7 Maddrey (1978)

Bibliographic reference	**Maddrey W C, Boitnott J K, Bedine M S, Weber F L, Jr , Mezey E, White R I, and Jr . (1978). Corticosteroid therapy of alcoholic hepatitis. Gastroenterology, 75(2), pp.193-9.**
Study type	RCT
Aim	To define factors important in determining outcome in alcoholic hepatitis, and further evaluate the effects of corticosteroid therapy on early mortality and progression to cirrhosis.
Patient characteristics	Patients were evaluated for study inclusion within 5 days of hospital admission. **Inclusion** - history of long-standing and recent alcoholism. A percutaneous liver biopsy was performed unless precluded by coagulation abnormalities. **Exclusion** - active gastrointestinal haemorrhage - pancreatitis - history of peptic ulcer disease

Bibliographic reference	**Maddrey W C, Boitnott J K, Bedine M S, Weber F L, Jr , Mezey E, White R I, and Jr . (1978). Corticosteroid therapy of alcoholic hepatitis. Gastroenterology, 75(2), pp.193-9.**

- active infection
- presence of hepatitis B antigen
- history of previous viral hepatitis.

Baseline characteristics

	Prednisolone (n=24)	**Placebo (n=31)**
Age in years - mean	40	42
Days before study entry	8.8	9.5
Men: women	12:12	23:8
Ascites (%)	67	58
Encephalopathy with asterixis (%)	21	32
PTT (sec)	15.5	15.8
Serum creatinine mg/dl	1.2	1.6
Albumin (mg/dl)	2.6	2.4
WBC (x10^3/mm^3)	13.7	9.9
Total bilirubin (mg/dl)	11.8	11.2
Severity: - Clinical group A* - Clinical group B** - Clinical group C***	 7 4 13	 8 5 18

*Group A patients (moderately ill), serum bilirubin >3mg per dl; hepatomegaly; and clotting factors adequate to allow liver biopsy.

**Group B patients (more severely ill), hyperbilirubinemia and hepatomegaly as in A with additional presence of ascites and/or hepatic encephalopathy, but coagulation studies adequate for liver biopsy

***Group C patients (severely ill), hyperbilirubinemia and hepatomegaly as in A and B with or without ascites and/or hepatic encephalopathy but coagulation abnormalities precluded liver biopsy.

Number of Patients	N=55

Bibliographic reference	**Maddrey W C, Boitnott J K, Bedine M S, Weber F L, Jr , Mezey E, White R I, and Jr . (1978). Corticosteroid therapy of alcoholic hepatitis. Gastroenterology, 75(2), pp.193-9.**
Intervention	Prednisolone (n=24) 5mg tablets were given in a single dose of 8 tablets each morning for between 28 to 32 days. All patients offered same 3000 calorie diet and same supportive and symptomatic care
Comparison	Placebo (n=31)
Length of follow up	28 to 30 days of treatment plus 5 days
Location	USA (single centre)
Outcomes measures and effect size	**Results**

Outcome	**Prednisolone (n=24)**	**Placebo (n=31)**
All-cause mortality (cumulative) - Up to 28 days - ≤90 days - 1 year	 1 (4%) 3 (13%) NR	 4 (13%) 6 (19%) NR
Liver-related mortality - 28 days - ≤90 days - 1 year	 1 (4%) 3 (13%) NR	 4 (13%) 6 (19%) NR
Number of people with serious infections - 28 days - ≤90 days - 1 year	 0 1 (4%)* NR	 0 0 NR
Number of people with serious adverse events	4 (17%)**	0
Length of stay	NR	NR
Quality of life	NR	NR

*one patient died 26 days after study completion and was found at post-mortem to have pulmonary cytomegalic inclusion disease, Pneumocystis carinii pneumonia, and monilial oesophagitis.

Bibliographic reference	**Maddrey W C, Boitnott J K, Bedine M S, Weber F L, Jr , Mezey E, White R I, and Jr . (1978). Corticosteroid therapy of alcoholic hepatitis. Gastroenterology, 75(2), pp.193-9.**

**includes 1 case of serious infection (noted above) and 3 cases of treatment-related diabetes requiring insulin.

Subgroup 1:

All-cause mortality by Severe* alcoholic hepatitis

Outcome	**Prednisolone (n=13)**	**Placebo (n=18)**
All-cause mortality		
- Up to 28d	1 (8%)	4 (22%)
- ≤90 days	1 (8%)	6 (33%)

* Group C patients (severely ill), hyperbilirubinemia and hepatomegaly as in A and B with or without ascites and/or hepatic encephalopathy but coagulation abnormalities precluded liver biopsy.

Subgroup 2:

All-cause mortality by severe AH with hepatic encephalopathy at baseline **

Outcome	**Prednisolone (n=5)**	**Placebo (n=10)**
All-cause mortality		
- ≤90 days	1 (20%)	6 (60%)

** Encephalopathy with asterixis

Source of funding	Treatment provided by Upjohn Co.

Comments

Quality assessment

Selection bias: High risk –no details of sequence generation or allocation procedures.

Performance bias: Low risk - patients, investigators and care givers blinded to treatment allocation until end of study period.

Detection bias: Low risk - outcome assessor blinded to treatment allocation

Attrition bias: Low risk – no loss to follow up. 2 discontinuations (one per treatment group: N=1 steroid: bleeding from the oesophageal varices before receiving the study drug; N=1 placebo: an episode of upper gastrointestinal haemorrhage presumably from oesophageal varices after receiving prednisolone for 9 days the study drug was stopped). No ITT analysis.

Reporting bias: Low risk – no evidence of selective reporting.

Other bias: Unclear – potential 'for profit' bias (study medication provided by manufacturer).

Bibliographic reference	**Maddrey W C, Boitnott J K, Bedine M S, Weber F L, Jr , Mezey E, White R I, and Jr . (1978). Corticosteroid therapy of alcoholic hepatitis. Gastroenterology, 75(2), pp.193-9.**
	No power analysis.

G.8 Mendenhall (1984)

Bibliographic reference	**Mendenhall C L, Anderson S, Garcia-Pont P, Goldberg S, Kiernan T, Seeff L B, Sorrell M, Tamburro C, Weesner R, Zetterman R, and et al. (1984). Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. New England Journal of Medicine, 311(23), pp.1464-70.**
Study type	RCT (3-arm design)
Aim	To evaluate short-term and long-term effects of androgenic anabolic steroids and adrenal glucocorticosteroids in patients with moderate or severe alcoholic hepatitis.
Patient characteristics	**Inclusion:** Males with moderate or severe alcoholic hepatitis based on conventional clinical and laboratory changes characteristic of the disease. Histologic confirmation was not required. Following study enrolment patients were grouped according to disease severity estimated by the degree of jaundice (bilirubin) and coagulopathy (prothrombin time). (Precise definition for grouping patients by severity not given) **Exclusion:** - Concomitant conditions that would make interpretation of therapeutic efficacy difficult; - Conditions that contraindicated corticosteroid therapy (e.g. severe infections, active peptic ulcer disease); - Taken corticosteroids within the preceding three months. **Baseline characteristics**

	Prednisolone (n=90)	**Placebo (n=88)**
Age in years - mean	51.5	50.4
Days before study entry	8.5	8.1
Men:women	90:0	88:0
Ascites (%)	93	86
Encephalopathy (%)	70	67

Bibliographic reference	**Mendenhall C L, Anderson S, Garcia-Pont P, Goldberg S, Kiernan T, Seeff L B, Sorrell M, Tamburro C, Weesner R, Zetterman R, and et al. (1984). Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. New England Journal of Medicine, 311(23), pp.1464-70.**
	<table><tr><td>PTT (sec)</td><td>4.1</td><td>4.0</td></tr><tr><td>WBC (x10^3/mm^3)</td><td>11.4</td><td>11.9</td></tr><tr><td>AST (µU/l)</td><td>110.8</td><td>113.8</td></tr><tr><td>Bilirubin (mmol/l)</td><td></td><td></td></tr><tr><td>Creatinine mg/dl</td><td>1.5</td><td>1.6</td></tr><tr><td>Disease severity: - Moderate - Severe</td><td> 46 44</td><td> 45 43</td></tr></table> There were no significant differences between the groups at baseline, including the distribution of cases of cirrhosis.
Number of Patients	N=178 randomised between the two groups of interest Participants enrolled between 3rd and 17th day of hospitalisation. Note: This was a 3-arm trial. Data for anabolic steroid (oxandrolone) treatment group have not been extracted.
Intervention	Prednisolone (n=90) 60 mg for 4 days 40 mg for 4 days 30 mg for 4 days 20 mg for 4 days 10 mg for 7 days 5 mg for 7 days
Comparison	Placebo (n=88)
Length of follow up	30-day treatment period and monthly follow-up outpatient appointments. 24 patients relapsed and consented to re-treatment (in group to which they were originally assigned). Median follow-up: Placebo: 180 days

<table>
<tr><td>Bibliographic reference</td><td>Mendenhall C L, Anderson S, Garcia-Pont P, Goldberg S, Kiernan T, Seeff L B, Sorrell M, Tamburro C, Weesner R, Zetterman R, and et al. (1984). Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. New England Journal of Medicine, 311(23), pp.1464-70.</td></tr>
<tr><td></td><td>Prednisolone: 320 days</td></tr>
<tr><td>Location</td><td>USA (6 Veterans Administration Medical Centres)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Results
<table>
<tr><th>Outcome</th><th>Prednisolone (n=90)</th><th>Placebo (n=88)</th></tr>
<tr><td>All-cause mortality
- 28 days
- ≤90 days
- 1 year**</td><td>
15/91* (16%)
NR
55/90 (61%)</td><td>
17/88* (19%)
NR
50/88 (57%)</td></tr>
<tr><td>Liver-related mortality</td><td>NR</td><td>NR</td></tr>
<tr><td>Number of people with serious infections</td><td>NR</td><td>NR</td></tr>
<tr><td>Number of people with serious adverse events***</td><td>NR</td><td>NR</td></tr>
<tr><td>Length of stay</td><td>NR</td><td>NR</td></tr>
<tr><td>Quality of life</td><td>NR</td><td>NR</td></tr>
</table>
*data from Mathurin et al. 2002 (Mendenhall does not give patient numbers and p-values by treatment group, only survival curves are shown). Not clear why Mathurin has +1 as steroid group denominator.
**timepoint = overall duration of follow-up (median: placebo: 180 days; prednisolone: 320 days); from initiation of therapy to the end of the study (4.4 years) the overall survival curves did not differ between treatment groups – no p-value reported).
***limits reporting to only two SAEs where there was a significant difference between treatment groups: hyperglycaemia (favouring placebo: 22% vs. 6%, p=0.005), and hepatocellular carcinoma (affecting 2 placebo patients and none in steroid group). Otherwise state ‘complication observed during treatment were those anticipated in severe liver disease’.

<u>Subgroup:</u>
All-cause mortality by DF≥32 at baseline***</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Mendenhall C L, Anderson S, Garcia-Pont P, Goldberg S, Kiernan T, Seeff L B, Sorrell M, Tamburro C, Weesner R, Zetterman R, and et al. (1984). Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. New England Journal of Medicine, 311(23), pp.1464-70.</td></tr>
<tr><td></td><td>
<table>
<tr><th>Outcome</th><th>Prednisolone (n=52)</th><th>Placebo (n=44)</th></tr>
<tr><td>All-cause mortality
- 28 days</td><td>11/52 (21%)</td><td>14/44 (32%)</td></tr>
</table>
***reported in Mathurin et al. 2002
Subgroup:
All-cause mortality by severe AH with hepatic encephalopathy at baseline ****
<table>
<tr><th>Outcome</th><th>Prednisolone (n=31)</th><th>Placebo (n=30)</th></tr>
<tr><td>All-cause mortality
- 28 days</td><td>11/31 (35%)</td><td>10/30 (33%)</td></tr>
</table>
****reported in Imperiale & McCullough 1990
</td></tr>
<tr><td>Source of funding</td><td>The Cooperative Studies Program of the Veterans Administration Medical Research Services. Treatment & matching placebos supplied by Upjohn Co., and G.D. Searle & Co.</td></tr>
<tr><td>Comments</td><td>Quality assessment:
Selection bias: High risk – No details of randomisation or treatment allocation procedures; only states “Treatment assignments were made by the Coordinating Center (Hines, Ill.)”.
Performance bias: Low risk – participants, clinicians and hospital pharmacy were all blind to which treatment patient was given.
Detection bias: Low risk – outcome assessors blinded to treatment allocation.
Attrition bias Low risk – no difference between groups in attrition rate. Treatment drop-outs: N=8 (N=3 prednisolone (3.3%), N=5 placebo (5.7%); Loss to follow-up: N=24 (N=11 prednisolone (12.2%), N=13 placebo (14.4%)). For patients lost to follow-up after discharge, Veterans Records System was sued to determine status (living / dead) and date of death. ITT analysis conducted.
Reporting bias: Low risk - Primary end points were pre-specified. No evidence of selective reporting.
Other bias: High risk – all-male study population; potential ‘for profit’ bias (study medication provided by manufacturer).

Power analysis undertaken.</td></tr>
</table>

Bibliographic reference	**Mendenhall C L, Anderson S, Garcia-Pont P, Goldberg S, Kiernan T, Seeff L B, Sorrell M, Tamburro C, Weesner R, Zetterman R, and et al. (1984). Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. New England Journal of Medicine, 311(23), pp.1464-70.**
	Secondary publications: Imperiale T F, and McCullough A J. (1990). Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. Annals of Internal Medicine, 113(4), pp.299-307 Mathurin P ; Mendenhall C L; Carithers R L; Jr ; Ramond M J; Maddrey W C; Garstide P ; Rueff B ; Naveau S ; Chaput J C; Poynard T (2002). Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. Journal of Hepatology 36: 480-7.

G.9 Porter (1971)

Bibliographic reference	**Porter H P, Simon F R, Pope C E, 2nd , Volwiler W, and Fenster L F. (1971). Corticosteroid therapy in severe alcoholic hepatitis. A double-blind drug trial. New England Journal of Medicine, 284(24), pp.1350-5.**
Study type	RCT
Aim	To examine the effects of glucocorticosteroid treatment on severe, life-threatening alcoholic hepatitis.
Patient characteristics	Inclusion: For inclusion, all three of the following absolute criteria were required: - a history of recent, heavy alcohol ingestion; - a serum total bilirubin concentration of 5mg per 100ml or more, - clinical and laboratory deterioration over the first five hospital days, a striking lack of improvement in the patient's clinical and biochemical status over this same period; or rapid, marked deterioration in less than 24 hours. In addition, two or more major criteria or one major and four or more minor criteria had to be met. The major criteria were: - liver biopsy showing alcoholic hepatitis; - hepatic encephalopathy, persistent or progressive azotemia unexplained by another process, with either a blood urea nitrogen over 20mg or a creatinine over 1.5mg per 100ml; - a total bilirubin over 20mg per 100ml.

Bibliographic reference	**Porter H P, Simon F R, Pope C E, 2nd , Volwiler W, and Fenster L F. (1971). Corticosteroid therapy in severe alcoholic hepatitis. A double-blind drug trial. New England Journal of Medicine, 284(24), pp.1350-5.**

The minor criteria were as follows:

- fever not obviously secondary to another process;
- white cell count greater than 12,000 not obviously secondary to another process;
- anorexia or nausea or vomiting;
- palpable splenomegaly;
- oesophageal varices on barium swallow x-ray study or endoscopy;
- spider angiomas;
- fluid retention (oedema or ascites);
- palmar erythema;
- a prothrombin time prolonged 3 or 4 more seconds over control.

Patient eligibility required agreement by two study investigators that inclusion criteria had been met.

Only 7 patients could be biopsied before treatment began. 11 others were obtained post-mortem. All 7 pre-treatment biopsies showed the histologic features of severe alcoholic hepatitis, one with clear-cut cirrhosis. All 11 autopsied patients showed severe confluent necrosis, 9 with established cirrhosis.

Exclusion:

- active gastrointestinal bleeding
- pancreatitis
- radiologic evidence of peptic-ulcer disease
- active TB
- potentially life-threatening bacterial infections.

Baseline characteristics

	6-methylprednisolone (n=11)	**Placebo (n=9)**
Age in years - mean	45	50
Days before study entry	14	11
Men:women	7:4	6:3
Ascites - n (%)	9 (82%)	100
Encephalopathy - n (%)	7 (64%)	8 (89%)

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Porter H P, Simon F R, Pope C E, 2nd , Volwiler W, and Fenster L F. (1971). Corticosteroid therapy in severe alcoholic hepatitis. A double-blind drug trial. New England Journal of Medicine, 284(24), pp.1350-5.</td></tr>
<tr><td></td><td colspan="3">
<table>
<tr><td>Serum total bilirubin (mg/100 ml)</td><td>24.6</td><td>24.3</td></tr>
<tr><td>White cell count (x10^3/mm^3)</td><td>16.8</td><td>20.0</td></tr>
</table>

There were no significant differences between the groups at baseline.
</td></tr>
<tr><td>Number of Patients</td><td colspan="3">N=20</td></tr>
<tr><td>Intervention</td><td colspan="3">6-methylprednisolone (n=11)
40mg* per day in 3 divided doses, parenterally for the first 10 days.

If clinical improvement occurred over this interval and if nausea and vomiting were absent, the drug was administered orally and the dose gradually tapered over 35 days. If there was no clinical improvement within 10 days, the initial
parenteral dose of 40mg daily was continued until improvement or death occurred.

All patients were given a minimum of 4 days of therapy.

*equivalent to 50mg prednisone</td></tr>
<tr><td>Comparison</td><td colspan="3">Placebo (n=9)</td></tr>
<tr><td>Length of follow up</td><td colspan="3">40 days</td></tr>
<tr><td>Location</td><td colspan="3">USA (3 centres)</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Results:

<table>
<tr><td>Outcome</td><td>6-methylprednisolone (n=11)</td><td>Placebo (n=9)</td></tr>
<tr><td>All-cause mortality
- 28 days*
- ≤90 days**
- 1 year</td><td>
6 (55%)
6 ((55%)
NR</td><td>
5 (56%)
7 (78%)
NR</td></tr>
<tr><td>Liver-related mortality</td><td>NR</td><td>NR</td></tr>
<tr><td>Number of people with serious infections</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Porter H P, Simon F R, Pope C E, 2nd , Volwiler W, and Fenster L F. (1971). Corticosteroid therapy in severe alcoholic hepatitis. A double-blind drug trial. New England Journal of Medicine, 284(24), pp.1350-5.**

- 28 days - ≤90 days - 1 year	NR 1*** (9%) NR	NR 0 NR
Number of people with serious adverse events	4 (36%)	2 (22%)
Length of stay	NR	NR
Quality of life	NR	NR

*estimated from survival curve

**by end of study (day 40)

***tuberculosis lymphadenitis developed after 34 days in study, despite initially normal chest x-ray and negative skin tests

Note: 28d mortality data reported in Imperiale & McCullough (1990) for patients with hepatic encephalopathy at baseline were not used in analyses because one of the denominators reported in the secondary publication cannot be verified with reference to data presented in the original published study.

Source of funding	Supported in part by grants from the National Institute of Arthritis and Metabolic Diseases Medication and the National Institute of Health. Treatment prepared and supplied by Upjohn Co.
Comments	**Quality assessment:** Selection bias: High risk – no information about randomisation sequence; allocation procedure involved “a number drawn from a pool” (this corresponded to a number on treatment packaging). Performance bias: Low risk - patients and their care givers were unaware of treatment allocation until study was completed. Detection bias: Unclear – outcomes assessed by principal study investigator (does not state whether treatment allocation was known). Attrition bias: High risk - 3/23 randomised patients (13%) were not included in analyses as they died within 36 hrs of start of therapy so “did not have adequate medication”. Reporting bias: Unclear – no study protocol available; outcomes not clearly pre-specified; insufficient information to judge selective reporting. Other bias: Unclear risk – potential ‘for profit’ bias (study medication provided by manufacturer). No power analysis (but described as a pilot study)

G.10 Ramond (1992)

Bibliographic reference	**Ramond M J, Poynard T, Rueff B, Mathurin P, Theodore C, Chaput J C, and Benhamou J P. (1992). A randomized trial of prednisolone in patients with severe alcoholic hepatitis. New England Journal of Medicine, 326(8), pp.507-12.**
Study type	RCT
Aim	To test the hypothesis that corticosteroid therapy can improve short-term survival in patients with severe alcoholic hepatitis (defined by discriminant function >32)
Patient characteristics	**Inclusion** - biopsy-proven alcoholic hepatitis (characterised by hyaline necrosis and infiltration of polymorphonuclear leukocytes) - spontaneous hepatic encephalopathy or a discriminant function value higher than 32* (or both). *The discriminant function used was as follows: 4.6 (prothrombin time - control time [in seconds] + serum bilirubin (in micromoles per litre)/17. **Exclusion** - gastrointestinal bleeding or bacterial infection (unless they could be effectively treated within 48 hours) - gastric or duodenal ulcer or ulcerated oesophagitis at endoscopy; - neoplastic disease - presence of hepatitis B surface antigen - presence of HIV antibodies - anticoagulation therapy. Patients were clinically evaluated at admission and at weekly intervals until all data for inclusion or exclusion were obtained. **Baseline characteristics**

	Prednisolone (n=32)	Placebo (n=29)
Age in years - mean	48	48
Days before study entry	14	17
Men: women	10:22	9:20
Ascites – n (%)	24 (75%)	25 (86%)
Encephalopathy – n (%)	9 (28%)	10 (34%)
PTT (% of normal)	38.6	37.4

Bibliographic reference	**Ramond M J, Poynard T, Rueff B, Mathurin P, Theodore C, Chaput J C, and Benhamou J P. (1992). A randomized trial of prednisolone in patients with severe alcoholic hepatitis. New England Journal of Medicine, 326(8), pp.507-12.**
	AST (no of times upper limit of normal): 3.7 / 3.3 Serum albumin µmol/L (mean): 414 / 388 Serum creatinine µmol/L (mean): 83.3 / 103.1 Serum bilirubin µmol/L (mean): 213 / 284 Discriminant function (mean): 51 / 60 There were no significant differences between the groups at baseline
Number of Patients	N=61 Completed treatment: N=57 (93%) Discontinuations: N=4 (N=1 lost to follow-up) Recruitment period: March 1987 to June 1990.
Intervention	Prednisolone (n=32) 40 mg for 28 days (tablets or i.v.) Drug therapy was interrupted by the attending physician if there was severe bacterial infection or gastrointestinal bleeding or if a corticosteroid-related complication was suspected. The remaining study drug tablets were replaced with placebo.
Comparison	Placebo (n=29)
Length of follow up	2 months Secondary publication (Mathurin 1996) reports 2-year outcomes
Location	France (2 centres)
Outcomes measures and effect size	**Results:** Outcome: **Prednisolone (n=32)** / **Placebo (n=29)** All-cause mortality - 28 days: 4 (13%) / 11 (38%)

Bibliographic reference	**Ramond M J, Poynard T, Rueff B, Mathurin P, Theodore C, Chaput J C, and Benhamou J P. (1992). A randomized trial of prednisolone in patients with severe alcoholic hepatitis. New England Journal of Medicine, 326(8), pp.507-12.**

- ≤90 days* - 1 year**	4 (13%) 10 (31%)	16 (55%) 17 (59%)
Liver-related mortality	NR	NR
Number of people with serious infections	NR	NR
Number of people with serious adverse events	NR	NR
Length of stay	NR	NR
Quality of life	NR	NR

*final death day 66

**data from Mathurin et al. 1996. 2-year data are also reported which show 6 further deaths in steroid-treated group vs. none in placebo group (mortality rate: 16/32 (50%) vs. 17/29 (59%) – no significant difference).

Subgroups:

All-cause mortality (90 days) by DF>32 without hepatic encephalopathy at baseline

Outcome	**Prednisolone (n=23)**	**Placebo (n=19)**
All-cause mortality - ≤90 days	2/23 (8.7%)	9/19 (47%)

All-cause mortality (90 days) by severe AH with hepatic encephalopathy at baseline

Outcome	**Prednisolone (n=9)**	**Placebo (n=10)**
All-cause mortality - ≤90 days	2/9 (22%)	7/10 (70%)

Source of funding	Not stated
Comments	**Quality assessment:**

Bibliographic reference	**Ramond M J, Poynard T, Rueff B, Mathurin P, Theodore C, Chaput J C, and Benhamou J P. (1992). A randomized trial of prednisolone in patients with severe alcoholic hepatitis. New England Journal of Medicine, 326(8), pp.507-12.**
	Selection bias: Low risk – computer-generated randomisation sequence; blocked randomisation within each participating centre stratified by gender; random sequences of drug or placebo prepared by the pharmacist at each hospital. Performance bias: Low risk – patients, clinicians and study investigators were unaware of treatment allocation Detection bias: Low risk – outcome assessors blinded to treatment allocation Attrition bias: Low risk – 3/32 (9.4%) discontinuations in prednisolone group (N=1 self-discharge and loss to follow-up); 1/29 (3.4%) discontinuations in placebo group. ITT analysis undertaken. Reporting bias: Low risk - Primary end points were pre-specified. No evidence of selective reporting. Other bias: Low risk - no evidence. Power analysis conducted. Secondary publication: Mathurin P, Duchatelle V, Ramond M, Degott C, Bedossa P, et al. (1996) Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. Gastroenterology 110: 1847-1853.

G.11 Shumaker (1978)

Bibliographic reference	**Shumaker J B, Resnick R H, Galambos J T, Makopour H, and Iber F L. (1978). A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. American Journal of Gastroenterology, 69(4), pp.443-9.**
Study type	RCT
Aim	To examine the value of corticosteroids in the treatment of alcoholic hepatitis.
Patient characteristics	**Inclusion:** Patients with a clinical diagnosis of alcoholic hepatitis - minimal criteria for admission being: ○ a history of recent alcohol ingestion; ○ a serum bilirubin >5mg; ○ hospitalisation for at least 5 days without improvement in liver tests, or rapid deterioration of the clinical condition during a 24hr period under observation.

Bibliographic reference	**Shumaker J B, Resnick R H, Galambos J T, Makopour H, and Iber F L. (1978). A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. American Journal of Gastroenterology, 69(4), pp.443-9.**
	Additionally, a patient had to have a minimum of two major criteria or one major or two minor to be placed in the study, as follows: Major criteria: - liver biopsy showing alcoholic hepatitis - hepatic encephalopathy - azotemia unexplained by another process - bilirubin >20mg.% - creatinine >1.5mg.% - prothrombin time prolonged more than 4 seconds over control. Minor criteria: - fever not obviously secondary to any other process - WBC greater than 12,000 - hepatomegaly (span >14cm) - splenomegaly - liver stigmas spider telangiectasia, palmar erythema, ascites, oedema, etc.) **Exclusion:** - serum glutamic oxaloacetic transaminase (SGOT) >500 μ/ml - active gastrointestinal bleeding (evidence by falling haematocrit, guaiac positive stools, hematemesis) - pancreatitis - x-ray evidence of peptic ulcer disease - active or suspected TB - acute infection - severe psychiatric disorder. Patients with positive tuberculin tests were not excluded, but were treated with INH and pyridoxine. **Baseline characteristics** Patients were stratified into two groups: those with prothrombin times <4 seconds prolonged were placed in the “biopsy feasible” group (BF). All others constituted “biopsy disallowed” (BD).

Bibliographic reference	**Shumaker J B, Resnick R H, Galambos J T, Makopour H, and Iber F L. (1978). A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. American Journal of Gastroenterology, 69(4), pp.443-9.**

Characteristics in BF patients	Methylprednisolone (n=4)	Placebo (n=6)
Age in years	44	46
Male:female	3:1	3:3
Bilirubin (mg.%)	9	16
PPT (sec)	2.1	3.3
Albumin (gm.%)	2.8	2.8
WBC (x10^3/cu.mm)	15.2	18.5

Characteristics in BD patients	Methylprednisolone (n=8)	Placebo (n=9)
Age in years - mean	47	43
Male:female	2:6	4:5
Bilirubin (mg.%)	29.1	20.3
PPT (sec)	5.6	5.8
Albumin (gm.%)	2.2	2.3
WBC (x10^3/cu.mm)	20	20.9

No significant differences were noted between steroid treated and placebo treated patients in either the BF or BD stratifications. (Characteristics not reported for treatment groups unstratified by 'biopsy feasible/disallowed').

Number of Patients	N=27
Intervention	6-methylprednisolone (tablets or i.v. if gastrointestinal function precluded oral intake) (n=12) 80mg for 4 to 7 days, then tapered on a flexible schedule with cessation of therapy planned for 4 weeks. Mean duration of steroid therapy was 8.5 days.

<table>
<tr><td>Bibliographic reference</td><td>Shumaker J B, Resnick R H, Galambos J T, Makopour H, and Iber F L. (1978). A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. American Journal of Gastroenterology, 69(4), pp.443-9.</td></tr>
<tr><td></td><td>Note: treatment withdrawals due to side-effects occurred more frequently in BD group than BF group (only 1/8 of the steroid treated BD patients remained in the protocol longer than 21 days)

All patients received same supportive care.</td></tr>
<tr><td>Comparison</td><td>Placebo (n=15)

Mean duration of placebo treatment was 16.4 days.
Note: treatment withdrawals due to side-effects occurred more frequently in BD group than BF group (only 2/9 of the placebo-treated BD patients remained in the protocol longer than 21 days)</td></tr>
<tr><td>Length of follow up</td><td>4 weeks</td></tr>
<tr><td>Location</td><td>USA (unclear no. of centres)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Results:
<table>
<tr><th>Outcome</th><th>Methylprednisolone (n=12)</th><th>Placebo (n=15)</th></tr>
<tr><td>All-cause mortality (cumulative)
- up to 28 days
- ≤90 days
- 1 year</td><td>
6/12 (50%)
NR
NR</td><td>
7/15 (47%)
NR
NR</td></tr>
<tr><td>Liver-related mortality (cumulative)
- Up to 28 days
- ≤90 days
- 1 year</td><td>
5/12 (42%)*
NR
NR</td><td>
6/15 (40%)**
NR
NR</td></tr>
<tr><td>Number of people with serious infections</td><td>NR</td><td>NR</td></tr>
<tr><td>Number of people with serious adverse events***</td><td>NR</td><td>NR</td></tr>
<tr><td>Length of stay</td><td>NR</td><td>NR</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Shumaker J B, Resnick R H, Galambos J T, Makopour H, and Iber F L. (1978). A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. American Journal of Gastroenterology, 69(4), pp.443-9.**

Quality of life	NR	NR

*includes 3 deaths due to GI bleed and 2 due to hepatic failure (all steroid group deaths were in 'BD' patients)

**includes 3 deaths due to GI bleed and 2 due to sepsis (all 5 were 'BD' placebo-treated patients), and 1 'BF' death due to massively bleeding oesophageal varices.

*** reports 'nonlethal' complications (including sepsis) for biopsy disallowed (BD) patients only, but unclear if data are no. of events or no. of patients.

Subgroup:

All-cause mortality (28 days) by severe AH with hepatic encephalopathy at baseline

Outcome	**Methylprednisolone (n=6)**	**Placebo (n=6)**
All-cause mortality - 28 days	2/6 (33%)	4/6 (67%)

Source of funding	Upjohn Co supplied and prepared the medications and placebo.
Comments	**Quality assessment:** Selection bias: Unclear – patients stratified according to presence or absence of criteria permitting biopsy (based on PTT time) then 'randomised into a predetermined code provided by the drug manufacturer'. No further details. Performance bias: Low risk - patients and clinical staff were blinded to treatment allocation. Detection bias: Low risk – clinical evaluation carried out by clinicians blinded to treatment allocation. Attrition bias: Low risk – N=1 steroid-treated 'biopsy-feasible' patient withdrew after 8 days but was kept in analysis. ITT analysis. Reporting bias: Unclear – no study protocol available; outcomes not clearly pre-specified; insufficient information to judge selective reporting. Other bias: Unclear risk – potential 'for profit' bias (study medication provided by manufacturer).

G.12 Theodossi (1982)

Bibliographic reference	**Theodossi A, Eddleston A L, and Williams R. (1982). Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. Gut, 23(1), pp.75-9.**
Study type	RCT

Bibliographic reference	**Theodossi A, Eddleston A L, and Williams R. (1982). Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. Gut, 23(1), pp.75-9.**
Aim	To assess the efficacy of a 3-day large dose regimen of methylprednisolone (effective in reversing transplant rejection) in patients with severe alcoholic hepatitis.
Patient characteristics	**Inclusion:** Patients referred from other hospitals with severe alcoholic hepatitis who met all the following criteria: - a history of alcohol intake of ≥ 80g or more daily for at least 5 years, - serum bilirubin concentration > than 80 µmol/L, - serum AST level at least twice the limit of normal, and - a PPT prolonged by at least 9 seconds. Presence of complications such as GI bleeding, renal failure and sepsis did not invalidate entry to trial. **Exclusion:** - recent MI or cerebrovascular accident (including evidence of subdural haematoma) - hepatoma - active tuberculosis. **Baseline characteristics**

	Methylprednisolone (n=27)	**Control (n=28)**
Age*	Not reported	Not reported
Men:women	19:8	12:16
Ascites (%)	93	71
Encephalopathy (%)	74	50
Spider naevi (%)	100	89
Serum creatinine (µmol/L) - median	100	115
Bilirubin (µmol/L) - median	188	300
Albumin (g/L) - median	25	28
AST (IU/l) - median	177	149
PTT (secs prolonged)	10	11
White cell count - median	10.7	15.2

*mean age of overall study sample was reported, as per Summary of Included Studies (Table 1)

Bibliographic reference	**Theodossi A, Eddleston A L, and Williams R. (1982). Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. Gut, 23(1), pp.75-9.**
Number of Patients	N=60 randomised N=55 included in final analysis
Intervention	Methylprednisolone (i.v.) (n=27) 1g daily for 3 days
Comparison	Control (no treatment) (n=28)
Length of follow up	Duration of follow-up: unclear. Laboratory data reported for 10 days post-randomisation timepoint. Mortality rates reported for 'during the study'. Mean length of hospital stay: - Steroid group : 24.2 days - Control group: 28.1 days
Location	UK (single centre)
Outcomes measures and effect size	**Results:**

Outcome	**Methylprednisolone (n=27)**	**Control (n=28)**
All-cause mortality - 28 days* - ≤90 days - 1 year	 17/27 (63%) NR NR	 16/28 (57%) NR NR
Liver-related mortality	NR	NR
Number of people with serious infections**	NR	NR
Number of people with serious adverse events**	NR	NR
Length of stay (days) – mean (SD)	24.2 (no SD)	28.1 (no SD)
Quality of life	NR	NR

<table>
<tr><td>Bibliographic reference</td><td>Theodossi A, Eddleston A L, and Williams R. (1982). Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. Gut, 23(1), pp.75-9.</td></tr>
<tr><td></td><td>*timepoint not clear; treatment phase was for 3 days so timepoint assumed to correspond to no longer than duration of hospital stay
**selective reporting of SAEs and infections – not clear if figures correspond to whole study population.

<u>Subgroup:</u>
All-cause mortality (28 days) by severe AH with hepatic encephalopathy at baseline
<table>
<tr><td>Outcome</td><td>Methylprednisolone (n=13)</td><td>Control (n=14)</td></tr>
<tr><td>All-cause mortality
- 28 days*</td><td>12/13 (92%)</td><td>10/14 (71%)</td></tr>
</table>
*only %’s are given; raw numbers back-calculated by reviewer from denominators given for no. with encephalopathy at baseline in each treatment group, but re-calculated %’s do not match those reported by authors (94% vs. 69%)</td></tr>
<tr><td>Source of funding</td><td>Not stated.</td></tr>
<tr><td>Comments</td><td>Quality assessment:
<u>Selection bias</u>: High risk - no information on how random sequence was generated; ‘sealed envelope technique' – does not specify if envelopes were opaque and numbered.
<u>Performance bias</u>: High risk - open label trial (no placebo group)
<u>Detection bias</u>: High risk - open label trial (no placebo group)
<u>Attrition bias</u>: High risk - 1/28 (3.6%) randomised to treatment group and 4/32 (12.5%) randomised to control group were not included in final analysis due to doubt about initial diagnosis (N=4) or because referring hospital had already given corticosteroid treatment (N=1). No ITT analysis.
<u>Reporting bias</u>: Unclear - no study protocol available; outcomes not clearly pre-specified; insufficient information to judge selective reporting.
<u>Other bias</u>: Low risk – no evidence.

No power analysis.</td></tr>
</table>

G.13 Thursz (2015)

Bibliographic reference	**Thursz M, Forrest E, Roderick P, Day C, Austin A, O'Grady J, Ryder S, Allison M, Gleeson D, McCune A, Patch D, Wright M, Masson S, Richardson P, Vale L, Mellor J, Stanton L, Bowers M, Ratcliffe I, Downs N, Kirkman S, Homer T, and Ternent L. (2015). The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2x2 factorial randomised controlled trial. Health Technology Assessment (Winchester, and England), 19(102), pp.1-104.**
Study type	RCT (factorial 2x2 design)
Aim	To determine whether prednisolone or pentoxifylline, administered for 28-days, reduced short-term and medium-term mortality among patients admitted to hospital with severe alcoholic hepatitis.

Patient characteristics	**Inclusion**
	• aged ≥18 years
	• admitted to hospital with clinical AH:
	  ○ serum bilirubin level >80 µmol/L
	  ○ history of excess alcohol (>80g / day for males, >60g / day for females) to within 2 months of randomisation
	• less than 4 weeks since admission to hospital
	• discriminant function (DF) ≥32
	
	Exclusion:
	• Abstinence of >2 months prior to randomisation
	• Duration of clinically apparent jaundice >3 months
	• Other causes of liver disease, inc:
	  ○ Evidence of chronic viral hepatitis (B or C)
	  ○ Biliary obstruction
	  ○ Hepatocellular carcinoma
	• Evidence of current malignancy (except non-melanotic skin cancer0
	• Use of prednisolone or pentoxifylline (PTX) within 6 weeks of admission
	• AST level of > 500 IU, or ALT level of >300 IU (not compatible with AH)
	• Serum creatinine of > 500 µmol/L or requiring renal support
	• Dependence on inotropic support (adrenaline or noradrenaline); terlipressin is allowed
	• Active GI bleeding
	• Untreated sepsis
	• Known hypersensitivity to PTX, other methylxanthines or any of the excipients
	• Cerebral haemorrhage, extensive retinal haemorrhage, acute MI (within the last 6 weeks) or severe cardiac arrhythmias (not including atrial fibrillation)

Bibliographic reference	**Thursz M, Forrest E, Roderick P, Day C, Austin A, O'Grady J, Ryder S, Allison M, Gleeson D, McCune A, Patch D, Wright M, Masson S, Richardson P, Vale L, Mellor J, Stanton L, Bowers M, Ratcliffe I, Downs N, Kirkman S, Homer T, and Ternent L. (2015). The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2x2 factorial randomised controlled trial. Health Technology Assessment (Winchester, and England), 19(102), pp.1-104.**

Note: patients with evidence of sepsis, GI bleeding or renal failure (creatinine level 500 µmol/L or requiring renal-replacement therapy) were excluded from trial eligibility only if they could not be stabilised with treatment in the first 7 days after admission to hospital.

Baseline characteristics - Comparison A:

Prednisolone + placebo Vs placebo + placebo

	Prednisolone + placebo (n=274)	**Placebo + placebo (n=272)**
Age (years) - mean	49.3	48.8
Men:women	177:97	162:110
Time from admission to start of study treatment (days)	6.5	6.1
Encephalopathy* (%) - None - Grade 1 - Grade 2 - Grade 3 - Grade 4	 75 14 7 <0.5 0	 70 17 7 2 0
Bilirubin (µmol/L) – mean	298	306
Albumin (g/L) – mean	25.2	25.6
AST (U/L) – mean	133.6	143.7
Creatinine (µmol/L) – mean	79.6	73.4
White cell count (per mm^3) - mean	10,600	10,100
PTT (sec) – mean	20.8	21.1
Discriminant function	60.7	61.9
MELD score**	21.2	20.7
Glasgow score***	8.4	8.3

Bibliographic reference	**Thursz M, Forrest E, Roderick P, Day C, Austin A, O'Grady J, Ryder S, Allison M, Gleeson D, McCune A, Patch D, Wright M, Masson S, Richardson P, Vale L, Mellor J, Stanton L, Bowers M, Ratcliffe I, Downs N, Kirkman S, Homer T, and Ternent L. (2015). The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2x2 factorial randomised controlled trial. Health Technology Assessment (Winchester, and England), 19(102), pp.1-104.**

Baseline characteristics - Comparison B:

Prednisolone + pentoxifylline Vs. Pentoxifylline + placebo

	Prednisolone + pentoxifylline (n=273)	**Pentoxifylline + placebo (n=273)**
Age (years) - mean	48.6	47.9
Men:women	182:91	164:109
Time from admission to start of study treatment (days)	6.5	6.7
Encephalopathy - None - Grade 1 - Grade 2 - Grade 3 - Grade 4	 70 18 4 3 0	 77 12 6 2 0
Bilirubin (µmol/L) – mean	306.1	292.4
Albumin (g/L) – mean	25.3	25.1
AST (U/L) – mean	143.4	134.3
Creatinine (µmol/L) – mean	81.3	78.7
White cell count (per mm^3) - mean	9,800	9,900
PTT (sec) – mean	21.1	22.1
Discriminant function	62.4	65.6
MELD score	21.5	21.4
Glasgow score	8.4	8.4

*Encephalopathy grade 1 = mild confusion and impaired attention; grade 2 = lethargy, personality change and inappropriate behaviour; grade 3 = comatose behaviour with responsiveness to verbal and noxious stimuli; grade 4 = coma without responsiveness to verbal or noxious stimuli.

**MELD score ranges from 6 to 40, with higher scores indicating worse prognosis.

Bibliographic reference	**Thursz M, Forrest E, Roderick P, Day C, Austin A, O'Grady J, Ryder S, Allison M, Gleeson D, McCune A, Patch D, Wright M, Masson S, Richardson P, Vale L, Mellor J, Stanton L, Bowers M, Ratcliffe I, Downs N, Kirkman S, Homer T, and Ternent L. (2015). The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2x2 factorial randomised controlled trial. Health Technology Assessment (Winchester, and England), 19(102), pp.1-104.**
	***Glasgow score ranges from 5 to 12, with higher scores indicating worse prognosis.
Number of Patients	N=1103 randomised N=1053 (95.5%) available for analysis of primary end-point (28-day mortality) Cumulative dropout rates*: Comparison A: Prednisolone + placebo: 8/274 (2.9%) by 28 days; 33/274 (12%) by 90 days; 84/274 (30.7%) by 1 year Placebo + placebo: 3/272 (1.1%) by 28 days; 23/272 (8.5%) by 90 days; 80/272 (29.4%) by 1 year Comparison B: Prednisolone + pentoxifylline: 13/273 (4.8%) by 28 days; 30/273 (11%) by 90 days; 92/273 (33.7%) Pentoxifylline + placebo: 15/273 (5.5%) by 28 days; 38/273 (13.9%) by 90 days; 89/273 (32.6%) * dropouts = loss to follow-up, or patient withdrawal of consent - but allowed use of data collection up to point of withdrawal - or (for 90 day and 1 year timepoints only), early cessation of follow-up (recruitment extended to end of February 2014, but follow-up for all patients ceased end March 2013, so that primary end-point data could be collected for all patients).
Intervention	Intervention A: Prednisolone + placebo (n=274) 40mg prednisolone daily for 28 days + pentoxifylline-matched placebo Intervention B: Prednisolone + pentoxifylline (n=273) 40mg prednisolone daily + 400mg pentoxifylline three times daily for 28 days Standard supportive care and nutritional support given to all patients.
Comparison	Comparator A: Placebo + placebo (n=272) Prednisolone-matched placebo and pentoxifylline-matched placebo for 28 days Comparator B: Pentoxifylline + placebo (n=273)

<table>
<tr><td>Bibliographic reference</td><td>Thursz M, Forrest E, Roderick P, Day C, Austin A, O'Grady J, Ryder S, Allison M, Gleeson D, McCune A, Patch D, Wright M, Masson S, Richardson P, Vale L, Mellor J, Stanton L, Bowers M, Ratcliffe I, Downs N, Kirkman S, Homer T, and Ternent L. (2015). The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2x2 factorial randomised controlled trial. Health Technology Assessment (Winchester, and England), 19(102), pp.1-104.</td></tr>
<tr><td></td><td>400mg pentoxifylline three times daily + prednisolone-matched placebo.

Standard supportive care and nutritional support given to all patients.</td></tr>
<tr><td>Length of follow up</td><td>1 year
Recruitment: January 2011 to February 2014</td></tr>
<tr><td>Location</td><td>UK (65 centres)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Results

Comparison A: Prednisolone + placebo vs. Placebo + placebo
<table>
<tr><th>Outcome</th><th>Prednisolone + placebo (n=variable)**</th><th>Placebo + placebo (n=variable)**</th></tr>
<tr><td>All-cause mortality (cumulative)*
- Up to 28 days
- ≤90 days
- 1 year</td><td>
38/266 (14%)
80/241 (33%)
110/190 (58%)</td><td>
45/269 (17%)
66/249 (27%)
106/192 (55%)</td></tr>
<tr><td>Liver-related mortality (cumulative)***
- Up to 28 days
- ≤90 days
- 1 year</td><td>
NR
NR
109/190 (57%)</td><td>
NR
NR
99/192 (52%)</td></tr>
<tr><td>Number of people with serious infections****
- 28 days
- ≤90 days
- 1 year</td><td>
NR
42/274 (15%)****
NR</td><td>
NR
22/272 (8%)
NR</td></tr>
<tr><td>Number of people with serious adverse events*****</td><td>128/274 (47%)</td><td>106/272 (39%)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Thursz M, Forrest E, Roderick P, Day C, Austin A, O'Grady J, Ryder S, Allison M, Gleeson D, McCune A, Patch D, Wright M, Masson S, Richardson P, Vale L, Mellor J, Stanton L, Bowers M, Ratcliffe I, Downs N, Kirkman S, Homer T, and Ternent L. (2015). The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2x2 factorial randomised controlled trial. Health Technology Assessment (Winchester, and England), 19(102), pp.1-104.**

Length of stay (days) – mean (SD), n ******	12.11 (24.73), n=104	12.17 (23.17), n=106
Quality of life (EQ-5D utility value) – survivors only - mean (SD), n - On discharge - 90 days - 1 year	 0.615 (0.33), n=147 0.545 (0.36), n=100 0.566 (0.38), n=48	 0.654 (0.32), n=143 0.582 (0.37), n=103 0.673 (0.31), n=46

Comparison B: Prednisolone + pentoxifylline vs. Pentoxifylline + placebo

Outcome	**Prednisolone + pentoxifylline (n=variable)****	**Pentoxifylline + placebo (n=variable)****
All-cause mortality (cumulative)* - Up to 28 days - ≤90 days - 1 year	 35/260 (13%) 64/243 (26%) 100/181 (55%)	 50/258 (19%) 75/235 (32%) 105/184 (57%)
Liver-related mortality (cumulative)*** - Up to 28 days - ≤90 days - 1 year	 NR NR 87/181 (48%)	 NR NR 101/184 (55%)
Number of people with serious infections - 28 days - ≤90 days - 1 year	 NR 29/273 (11%)**** NR	 NR 16/273 (6%) NR
Number of people with serious adverse events*****	116/273 (42%)	111/273 (41%)
Length of stay (days) – mean (SD), n ******	11.38 (21.52), n=107	10.36 (17.76), n=94

Bibliographic reference	**Thursz M, Forrest E, Roderick P, Day C, Austin A, O'Grady J, Ryder S, Allison M, Gleeson D, McCune A, Patch D, Wright M, Masson S, Richardson P, Vale L, Mellor J, Stanton L, Bowers M, Ratcliffe I, Downs N, Kirkman S, Homer T, and Ternent L. (2015). The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2x2 factorial randomised controlled trial. Health Technology Assessment (Winchester, and England), 19(102), pp.1-104.**

Quality of life (EQ-5D utility value) – survivors only - mean (SD)		
- On discharge	0.635 (0.33), n=128	0.616 (0.35), n=119
- 90 days	0.561 (0.35), n=91	0.604 (0.33), n=83
- 1 year	0.604 (0.32), n=40	0.477 (0.38), n=36

*data are reported for 'deceased / liver transplantation'

**denominators vary due to dropouts (loss to follow-up; withdrawal or early cessation of data-collection)

***includes deaths categorised by study investigators as 'Liver-related' and 'Both liver and non-liver related'

**** percentages based on no. patients in the ITT population.

*****serious adverse event (including infections) data taken from Thursz et al. NEJM (2105) because SAE data in HTA report is no. of events (not no. of patients); data presented for no. of patients with infections up to 28 days and 29-54 days compares all patients treated with prednisolone vs. no prednisolone (that is, combined analysis across comparison A and B in this review).

****** reported as liver-related inpatient stay (mean no. of nights) by 90-day follow-up. These data were not included in analyses due to validity issues: while the data include the index inpatient stay (during which the patient was recruited to the study), it is stated that some patients received their allocated treatment after discharge from hospital; it is also unclear what proportion of patients had further liver-related inpatient care after their index admission.

<u>Note re: subgroup analysis</u>

Data are not reported to enable a subgroup analysis of patients with encephalopathy at baseline. A within-trial multivariate analysis of factors associated with 28-day mortality showed hepatic encephalopathy to be a significant independent predictor of mortality (OR 3.07 (95%CIs 2.05 to 4.60), p<0.001).

<u>Serious adverse events</u>

The following data were extracted on two categories of serious adverse event of particular interest to the review: GI disorders (including bleeds) and infections. The data are reported in the STOPAH trial HTA as number of episodes recorded. These data could not be used in analyses for this update as the review protocol specified rate of SAEs / infections *per patient*.

Bibliographic reference	**Thursz M, Forrest E, Roderick P, Day C, Austin A, O'Grady J, Ryder S, Allison M, Gleeson D, McCune A, Patch D, Wright M, Masson S, Richardson P, Vale L, Mellor J, Stanton L, Bowers M, Ratcliffe I, Downs N, Kirkman S, Homer T, and Ternent L. (2015). The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2x2 factorial randomised controlled trial. Health Technology Assessment (Winchester, and England), 19(102), pp.1-104.**

	Comparison A		Comparison B	
	Steroid	Placebo	Steroid + PTX	Placebo + PTX
Total no. SAEs	184	136	159	145
All GI disorders	27%	23%	30%	39%
- Upper GI bleed	7%	4%	11%	7%
- Oesophageal varices / bleed	4%	6%	3%	5%
- Lower GI bleed	1%	1%	0	0
- Gastric / rectal bleed	2%	0	1%	1%
- Other GI SAE	16%	12%	17%	27%
All infections	24%	20%	19%	11%
Lung*	11%	8%	11%	4%
Sepsis	6%	6%	2%	4%
Hepatic	1%	0	1%	0
Other	7%	6%	6%	3%

Bibliographic reference	**Thursz M, Forrest E, Roderick P, Day C, Austin A, O'Grady J, Ryder S, Allison M, Gleeson D, McCune A, Patch D, Wright M, Masson S, Richardson P, Vale L, Mellor J, Stanton L, Bowers M, Ratcliffe I, Downs N, Kirkman S, Homer T, and Ternent L. (2015). The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2x2 factorial randomised controlled trial. Health Technology Assessment (Winchester, and England), 19(102), pp.1-104.**
	* STOPAH report states that 69% of all reported lung infections occurred in steroid-treated patients ($p<0.05$ compared with no steroid treatment). No other significant treatment group differences are reported for the types of GI disorder listed, or for other types of emergent infection.
Source of funding	Supported by NIHR Health Technology Assessment grant.
Comments	**Quality assessment:** Selection bias: Low risk – randomisation & allocation was computer-generated and undertaken centrally with treatment allocation blinded to site staff and patient via a unique, 4-digit patient pack number. Randomisation was in block size of four, stratified according to geographic area and risk category (high risk patients were those who had had an occurrence of GI bleeding, renal impairment or sepsis prior to randomisation; all other patients were classed 'intermediate risk'). Performance bias: Low risk - care givers and patients all blinded to treatment allocation. Detection bias: Low risk – investigators and outcome assessors all blinded to treatment allocation (only statisticians were unblinded for analysis purposes). Attrition bias: Low risk - high dropout rates by 1 year follow-up (32% overall), but no marked differences between treatment arms for either comparison (A or B) and majority of 'dropouts' due to early cessation of follow-up; ITT analysis conducted. Reporting bias: Low risk - trial protocol paper available. All reported outcomes were specified a priori. No evidence of selective reporting. Other bias: Low risk - no evidence. Secondary publications: Forrest E, Mellor J, Stanton L, Bowers M, Ryder P, Austin A, Day C, Gleeson D, O'Grady J, Masson S, McCune A, Patch D, Richardson P, Roderick P, Ryder S, Wright M, and Thursz M. (2013). Steroids or pentoxifylline for alcoholic hepatitis (STOPAH): study protocol for a randomised controlled trial. Trials, 14, pp.262. Thursz M R, Richardson P, Allison M, Austin A, Bowers M, Day C P, Downs N, Gleeson D, MacGilchrist A, Grant A, Hood S, Masson S, McCune A, Mellor J, O'Grady J, Patch D, Ratcliffe I, Roderick P, Stanton L, Vergis N, Wright M, Ryder S, Forrest E H, and Trial Stopah. (2015). Prednisolone or pentoxifylline for alcoholic hepatitis. New England Journal of Medicine, 372(17), pp.1619-28.

Appendix H: GRADE profiles

Steroid versus 'no steroid' treatment

Quality assessment							No of patients		Effect estimate		
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (Steroid)	Comparator (No steroid)	Relative (95% CI)	Absolute	Quality
Outcome1a: All-cause mortality – within 28 days (see Appendix I: Figure 1)											
10[1]	RCTs	No serious[2]	No serious[3]	No serious[4]	Serious[5]	None	127/800 (15.9%)	171/804 (21.3%)	RR 0.78 (0.58 to 1.05)	47 fewer per 1000 (from 89 fewer to 11 more)	MOD
Subgroup analysis: All-cause mortality – within 28 days BY Subgroup (i): Severe (baseline DF≥32 and / or hepatic encephalopathy or otherwise defined 'severe' AH) (see Appendix I: Figure 2)											
9[6]	RCTs	No serious[2]	No serious[3]	No serious[4]	Serious[7]	None	108/710 (15.2%)	153/701 (21.8%)	RR 0.65 (0.42 to 1.00)	76 fewer per 1000 (from 127 fewer to 0 more)	MOD
Subgroup analysis: All-cause mortality – within 28 days BY Subgroup (ii): DF≥32 (see Appendix I: Figure 3)											
5[8]	RCTs	No serious[2]	No serious[9]	No serious[4]	No serious[10]	None	90/661 (13.6%)	125/642 (19.5%)	RR 0.70 (0.55 to 0.90)	58 fewer per 1000 (from 19 fewer to 88 fewer)	HIGH
Subgroup analysis: All-cause mortality – within 28 days BY Subgroup (iii): Hepatic encephalopathy at baseline (see Appendix I: Figure 4)											
5[11]	RCTs	Serious [12]	No serious[13]	No serious[4]	Very serious[14]	None	28/67 (41.8%)	34/71 (47.9%)	RR 0.88 (0.46 to 1.67)	57 fewer per 1000 (from 259 fewer to 321 more)	VERY LOW
Outcome1b: All-cause mortality – within 90 days (see Appendix I: Figure 5)											
9[15]	RCTs	No serious[2]	No serious[16]	No serious[4]	Serious[5]	None	188/648 (29.0%)	202/654 (30.9%)	RR 0.85 (0.59 to 1.21)	46 fewer per 1000 (from 127 fewer to 65 more)	MOD

Quality assessment							No of patients		Effect estimate		
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (Steroid)	Comparator (No steroid)	Relative (95% CI)	Absolute	Quality
Subgroup analysis: All-cause mortality – within 90 days BY Subgroup (i): Severe (baseline DF≥32 and / or hepatic encephalopathy) (see Appendix I: Figure 6)											
8[17]	RCTs	No serious[2]	No serious[16]	No serious[4]	Serious[5]	None	173/594 (29.1%)	190/592 (32.1%)	RR 0.69 (0.42 to 1.13)	99 fewer per 1000 (from 186 fewer to 42 more)	MOD
Subgroup analysis: All-cause mortality – within 90 days BY Subgroup (ii): DF≥32 (see Appendix I: Figure 7)											
3[18]	RCTs	No serious [19]	No serious[20]	No serious[4]	Very serious[14]	None	155/537 (28.9%)	155/533 (29.1%)	RR 0.83 (0.34 to 2.05)	49 fewer per 1000 (from 192 fewer to 305 more)	LOW
Subgroup analysis: All-cause mortality – within 90 days BY Subgroup (iii): hepatic encephalopathy at baseline (see Appendix I: Figure 8)											
6[21]	RCTs	Serious [22]	No serious[23]	No serious[4]	Serious[5]	None	18/49 (36.7%)	35/51 (68.6%)	RR 0.57 (0.32 to 1.02)	295 fewer per 1000 (from 467 fewer to 14 more)	LOW
Outcome 1c: All-cause mortality – within 1 year (see Appendix I: Figure 9)											
4[24]	RCTs	No serious [25]	No serious[26]	No serious[4]	Serious[5]	None	285/523 (54.5%)	284/523 (54.3%)	RR 0.99 (0.79 to 1.24)	5 fewer per 1000 (from 114 fewer to 130 more)	MOD
Subgroup analysis: All-cause mortality – within 1 year BY Subgroup (i): DF≥32 and/or hepatic encephalopathy (see Appendix I: Figure 10)											
3[27]	RCTs	No serious [19]	No serious[28]	No serious[4]	Serious[5]	None	230/433 (53.1%)	234/435 (53.8%)	RR 0.92 (0.56 to 1.51)	43 fewer per 1000 (from 237 fewer to 274 more)	MOD
Outcome 2a: Liver-related mortality – within 28 days (see Appendix I: Figure 11)											
4[29]	RCTs	Serious [22]	No serious[28]	No serious[4]	Very serious[14]	None	9/101 (8.9%)	24/107 (22.4%)	RR 0.42 (0.14 to 1.24)	130 fewer per 1000 (from 193 fewer to 54 more)	VERY LOW

Quality assessment							No of patients		Effect estimate		
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (Steroid)	Comparator (No steroid)	Relative (95% CI)	Absolute	Quality
Subgroup analysis: Liver-related mortality – within 28 days BY Subgroup (i): Severe (baseline DF≥32 and / or hepatic encephalopathy) (see Appendix I: Figure 12)											
3[30]	RCTs	Serious[22]	No serious[28]	No serious[4]	No serious[10]	None	4/78 (5.1%)	18/79 (22.8%)	RR 0.23 (0.08 to 0.65)	175 fewer per 1000 (from 80 fewer to 210 fewer)	MOD
Outcome 2b: Liver-related mortality – within 90 days (see Appendix I: Figure 13)											
6[31]	RCTs	Serious[22]	No serious[16]	No serious[4]	Serious[5]	None	33/121 (27.3%)	38/132 (28.8%)	RR 1.00 (0.65 to 1.55)	0 fewer per 1000 (from 101 fewer to 158 more)	LOW
Subgroup analysis: Liver-related mortality – within 90 days BY Subgroup (i): Severe (baseline DF≥32 and / or hepatic encephalopathy) (see Appendix I: Figure 14)											
5[32]	RCTs	Serious[22]	No serious[16]	No serious[4]	Very serious[14]	None	23/75 (30.7%)	32/77 (41.6%)	RR 0.67 (0.33 to 1.38)	137 fewer per 1000 (from 278 fewer to 158 more)	VERY LOW
Outcome 2c: Liver-related mortality – within 1 year (see Appendix I: Figure 15) **Note: in both studies contributing evidence to this outcome all included patients were DF≥32**											
2[33]	RCTs	No serious[34]	No serious[35]	No serious[4]	Serious[5]	None	206/401 (51.4%)	206/406 (50.7%)	RR 1.07 (0.75 to 1.52)	36 more per 1000 (from 127 fewer to 264 more)	MOD
Outcome 3a: Serious infections - within 28 days (see Appendix I: Figure 16) **Note: all patients included in this single study were DF≥32 and / or encephalopathy at baseline.**											
1[36]	RCT	Serious[37]	No serious[38]	n/a (single study)	Very serious[39]	None	1/35 (2.9%)	3/31 (9.7%)	RR 0.30 (0.03 to 2.69)	68 fewer per 1000 (from 94 fewer to 164 more)	VERY LOW
Outcome 3b: Serious infections - within 90 days (see Appendix I: Figure 17)											

Quality assessment							No of patients		Effect estimate		
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (Steroid)	Comparator (No steroid)	Relative (95% CI)	Absolute	Quality
7[40]	RCTs	No serious[2]	No serious[16]	No serious[4]	No serious[41]	None	85/659 (12.9%)	41/669 (6.1%)	RR 1.99 (1.40 to 2.82)	61 more per 1000 (from 25 more to 112 more)	HIGH
Subgroup analysis: Serious infections - within 90 days BY Subgroup (i): Severe (baseline DF≥32 and / or encephalopathy) (see Appendix I: Figure 18)											
3[42]	RCTs	No serious [43]	No serious[35]	No serious[4]	No serious[41]	None	79/592 13.3%	41/588 (7.0%)	RR 1.90 (1.33 to 2.72)	63 more per 1000 (from 23 more to 120 more)	HIGH
Outcome 3c: Serious infections - within 1 year (see Appendix I: Figure 19) Note: all patients included in this single study were DF≥32											
1[44]	RCT	Serious [45]	Serious[46]	n/a (single study)	Very serious[39]	None	5/30 (16.7%)	1/30 (3.3%)	RR 5.00 (0.62 to 40.28)	133 more per 1000 (from 13 fewer to 1000 more)	VERY LOW
Outcome 4: Serious adverse events (liver- and non-liver related; including serious infections) (see Appendix I: Figure 20)											
5[47]	RCTs	Serious [48]	No serious[20]	No serious[4]	Very serious[39]	None	279/647 (43.1%)	232/646 (35.9%)	RR 1.64 (0.74 to 3.62)	230 more per 1000 (from 93 fewer to 941 more)	VERY LOW
Subgroup analysis: Serious adverse events BY Subgroup (i): Severe (baseline DF≥32 and / or encephalopathy) (see Appendix I: Figure 21)											
3[49]	RCTs	Serious [48]	No serious[20]	No serious[4]	Very serious[39]	None	271/612 (44.3%)	230/606 (38.0%)	RR 1.41 (0.55 to 3.64)	156 more per 1000 (from 171 fewer to 1000 more)	VERY LOW
Outcome 5a: Quality of life (EQ-5D utility score: higher = better QoL) – at discharge (see Appendix I: Figure 22)											
1[50]	RCT	No serious [51]	No serious[38]	n/a (single study)	Serious[52]	None	N=275	N=262	-	MD 0.01 lower (0.07 lower to 0.04 higher)	MOD
Outcome 5b: Quality of life (EQ-5D utility score: higher = better QoL) – at 90 day follow-up (see Appendix I: Figure 23)											

Quality assessment							No of patients		Effect estimate		
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (Steroid)	Comparator (No steroid)	Relative (95% CI)	Absolute	Quality
1[50]	RCT	No serious [53]	No serious	n/a (single study)	Serious[54]	None	N=191	N=186	-	MD 0.04 lower (0.11 lower to 0.03 higher)	LOW
Outcome 5c: Quality of life (EQ-5D utility score: higher = better QoL) – at 1 year follow-up (see Appendix I: Figure 24)											
1[50]	RCT	No serious [53]	No serious	n/a (single study)	Very serious[55]	None	N=88	N=82	-	MD 0 higher (0.11 lower to 0.10 higher)	VERY LOW

1.Blitzer 1977; Carithers 1989; De 2014; Maddrey 1978; Mendenhall 1984; Porter 1971; Ramond 1992; Shumaker 1978; Theodossi 1982; Thursz 2015 (treatment comparison A and B combined)
2. Majority of studies were double-blind; some studies with poorly reported randomisation and treatment allocation but largest study contributing to the analysis (Thursz 2015) had adequate methodological rigour
3. Population, interventions and outcomes match those specified in review protocol. Three studies had all-male populations (Blitzer 1977; De 2014; Mendenhall 1984). However, the studies contributing most (>50% weight) to the analysis were mixed-gender.
4. No serious inconsistency: Tau^2 <1.00
5. 95%CIs cross the MID (line of no effect) indicating imprecision in the effect estimate.
6. Blitzer 1977 (subsample with encephalopathy at baseline); Carithers 1989; De 2014; Maddrey 1978 (subsample in severity group C); Mendenhall 1984 (subsample with DF≥32); Ramond 1992; Shumaker 1978 (subsample with hepatic encephalopathy at baseline); Theodossi 1982 (subsample with hepatic encephalopathy at baseline); Thursz 2015 (treatment comparison A and B combined)
7. Upper 95%CI reaches the MID (line of no effect), indicating imprecision in the effect estimate
8. Carithers 1989 (subsample with DF>32 and no hepatic encephalopathy at baseline); De 2014; Mendenhall 1984 (subsample with DF≥32); Ramond 1992; Thursz 2015 (treatment comparison A and B combined)
9. Population, interventions and outcomes match those specified in review protocol. Two studies had all-male populations (De 2014; Mendenhall 1984). However, the studies contributing most (>50% weight) to the analysis were mixed-gender.
10. 95%CIs do not cross the MID (line of no effect), indicating a precise and clinically important effect estimate.
11. Data from subsamples with hepatic encephalopathy at baseline from the following studies: Blitzer 1977; Carithers 1989; Mendenhall 1984; Shumaker 1978; Theodossi 1982
12. Majority of studies contributing to the analysis had poorly reported randomisation and treatment allocation procedures and risk of attrition bias
13. Population, interventions and outcomes match those specified in review protocol. Two studies had all-male populations (Blitzer 1977; Mendenhall 1984). However, the studies contributing most (>50% weight) to the analysis were mixed-gender.
14. 95%CIs are very wide and cross the MID (line of no effect), indicating very serious uncertainty in the effect estimate.
15. Blitzer 1977; Campra 1973; De 2014; Depew 1980; Helman 1971; Maddrey 1978; Porter 1971; Ramond 1992; Thursz 2015 (treatment comparison A and B combined)
16. Population, interventions and outcomes match those specified in review protocol. Two included studies had all-male populations (Blitzer 1977; De 2014). However, the studies contributing most (>50%) to the analysis were mixed-gender.
17. Blitzer 1977 (subsample with encephalopathy); Campra 1973 (subsample with encephalopathy); De 2014; Depew 1980; Helman 1971 (subsample in severity group I); Maddrey 1978 (subsample in severity group C); Ramond 1992; Thursz 2015 (treatment comparison A and B combined)
18. De 2014; Ramond 1992 (subsample with DF>32 and without encephalopathy at baseline); Thursz 2015 (treatment comparison A and B combined)
19. All studies were double-blind for treatment period and had adequate randomisation and treatment allocation procedures and low risk of attrition bias

20. Population, interventions and outcomes match those specified in review protocol. De (2014) had an all-male population but the other included studies were mixed-gender populations.
21. Blitzer 1977 (subsample with encephalopathy); Campra 1973 (subsample with encephalopathy); Depew 1980; Helman 1971 (subsample in severity group I); Maddrey 1978 (subsample in severity group C); Ramond 1992
22. High risk of selection bias in majority of studies contributing to analysis due to inadequate reporting of randomisation and treatment allocation procedures
23. Population, interventions and outcomes match those specified in review protocol. Blitzer (1977) had an all-male population but the other studies contributing to the analysis were in mixed-gender populations.
24. De 2014; Mendenhall 1984; Ramond 1992; Thursz 2015 (treatment comparison A and B combined)
25. All studies were double-blind for treatment period and most had adequate randomisation and treatment allocation procedures and low risk of attrition bias.
26. Population, interventions and outcomes match those specified in review protocol. De 2014 and Mendenhall 1984 had all-male populations but the studies contributing most (>50%) to the analysis were mixed-gender.
27. De 2014; Ramond 1992; Thursz 2015 (treatment comparison A and B).
28. Population, interventions and outcomes match those specified in review protocol. De 2014 had an all-male population but the other studies contributing to the analysis were mixed-gender.
29. Carithers 1989; De 2014; Maddrey 1978; Shumaker 1978
30. Carithers 1989; De 2014; Maddrey 1978 (subsample in severity group C)
31. Blitzer 1977; Campra 1973; De 2014; Depew 1980; Helman 1971; Maddrey 1978
32. Campra 1973 (subsample with encephalopathy); De 2014; Depew 1980; Helman 1971 (subsample in severity group I); Maddrey 1978 (subsample in severity group C).
33. De 2014; Thursz 2015(comparison A and B combined)
34. Majority of weight in analysis is from study by Thursz 2015, which had adequate methodological rigour
35. Population, interventions and outcomes match those specified in review protocol. De 2014 had an all-male population but majority of weight in analysis (>50%) is from the study by Thursz 2015, which was a mixed-gender population.
36. Carithers 1989
37. Study had unclear treatment allocation concealment and high risk of attrition bias.
38. Population, intervention and outcomes match those specified in review protocol.
39. 95%CIs cross both default GRADE MIDs (RR 0.8 and 1.25)
40. Blitzer 1977; Campra 1973; De 2014; Depew 1980; Maddrey 1978; Porter 1971; Thursz 2015 (treatment comparison A and B combined).
41. 95% CIs do not cross either of the GRADE default MIDs, indicating the effect estimate is precise and clinically important.
42. De 2014; Depew 1980; Thursz 2015 (treatment comparison A and B combined)
43. All studies were double-blind for treatment period; majority of weight in analysis is from study by Thursz 2015, which had adequate methodological rigour.
44. De 2014
45. Unclear treatment allocation concealment and risk of detection bias (study was double-blind during initial 4-week treatment phase then opened for additional 7 weeks of treatment tapering, so assessment of infection rates at 1 year were not blind)
46. Downgraded 1 level: the study was conducted in all-male population; results may not be generalizable to the wider population with severe AH.
47. Carithers 1989; De 2014; Maddrey 1978; Porter 1971; Thursz 2015 (treatment comparison A and B combined)
48. Majority of studies contributing to analysis had unclear randomisation and treatment allocation; risk of detection bias in De 2014 (after 4-week double-blind treatment phase, study was opened for additional 7 weeks of treatment tapering, so assessment of serious adverse events at 1 year were not blind)
49. Carithers 1989; De 2014; Thursz 2015 (treatment comparison A and B combined)
50. Thursz 2015 (treatment comparison A and B combined)
51. Double-blind study with adequate methodological rigour
52. Lower 95%CI reaches MID threshold for this outcome (MD -0.07) indicating serious imprecision in effect estimate
53. Response bias - results may not generalise to wider population with AH due to large amounts of missing data at follow-up (response rate among survivors fell by 30% between discharge and 90 day follow-up, and a further 40% by 1 year follow-up)
54. 95%CIs cross one MID for this outcome (MD -0.07) indicating serious imprecision in effect estimate
55. 95%CIs cross two MIDs for this outcome (MD -0.07 and +0.07), indicating very serious imprecision in effect estimate

Appendix I: Forest plots

Steroid versus 'no steroid' treatment

Figure 1: All-cause mortality – within 28 days

All participants and levels of severity

Study or Subgroup	Steroid Events	Steroid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Blitzer 1977	2	12	2	16	2.4%	1.33 [0.22, 8.16]
Carithers 1989	2	35	11	31	3.8%	0.16 [0.04, 0.67]
De 2014	1	30	3	30	1.7%	0.33 [0.04, 3.03]
Maddrey 1978	1	24	4	31	1.8%	0.32 [0.04, 2.71]
Mendenhall 1984	15	91	17	88	13.9%	0.85 [0.45, 1.60]
Porter 1971	6	11	5	9	10.0%	0.98 [0.44, 2.17]
Ramond 1992	4	32	11	29	6.7%	0.33 [0.12, 0.92]
Shumaker 1978	6	12	7	15	10.3%	1.07 [0.49, 2.34]
Theodossi 1982	17	27	16	28	21.0%	1.10 [0.72, 1.70]
Thursz 2015 (combined)	73	526	95	527	28.5%	0.77 [0.58, 1.02]
Total (95% CI)		**800**		**804**	**100.0%**	**0.78 [0.58, 1.05]**
Total events	127		171			

Heterogeneity: Tau² = 0.06; Chi² = 13.04, df = 9 (P = 0.16); I² = 31%
Test for overall effect: Z = 1.65 (P = 0.10)

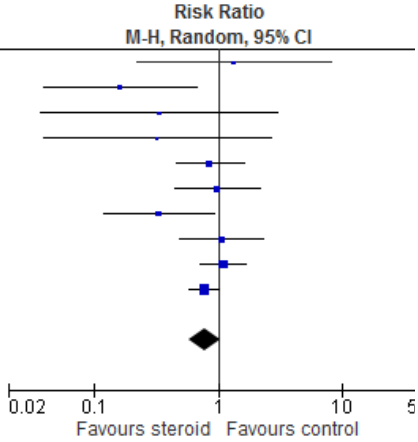


Figure 2: All-cause mortality – within 28 days

Subgroup (i): Severe AH = DF≥32 and/or hepatic encephalopathy at baseline (or otherwise defined 'severe' AH)

Study or Subgroup	Steroid Events	Steroid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Blitzer 1977	2	3	1	2	5.7%	1.33 [0.27, 6.61]
Carithers 1989	2	35	11	31	6.8%	0.16 [0.04, 0.67]
De 2014	1	30	3	30	3.3%	0.33 [0.04, 3.03]
Maddrey 1978	1	13	4	18	3.7%	0.35 [0.04, 2.75]
Mendenhall 1984	11	52	14	44	15.9%	0.66 [0.34, 1.31]
Ramond 1992	4	32	11	29	10.5%	0.33 [0.12, 0.92]
Shumaker 1978	2	6	4	6	8.0%	0.50 [0.14, 1.77]
Theodossi 1982	12	13	10	14	22.2%	1.29 [0.90, 1.86]
Thursz 2015 (combined)	73	526	95	527	23.8%	0.77 [0.58, 1.02]
Total (95% CI)		**710**		**701**	**100.0%**	**0.65 [0.42, 1.00]**
Total events	108		153			

Heterogeneity: Tau² = 0.18; Chi² = 19.44, df = 8 (P = 0.01); I² = 59%
Test for overall effect: Z = 1.94 (P = 0.05)

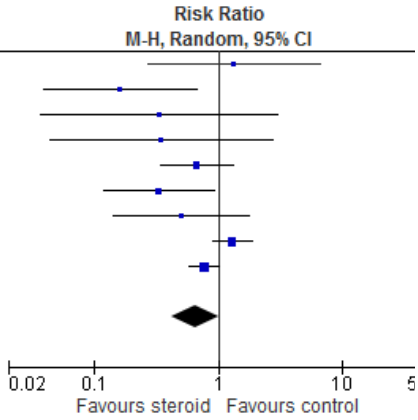


Figure 3: All-cause mortality – within 28 days

Subgroup (ii): Severe = DF≥32

Study or Subgroup	Steroid Events	Steroid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Carithers 1989	1	21	2	12	1.2%	0.29 [0.03, 2.83]
De 2014	1	30	3	30	1.3%	0.33 [0.04, 3.03]
Mendenhall 1984	11	52	14	44	13.3%	0.66 [0.34, 1.31]
Ramond 1992	4	32	11	29	5.8%	0.33 [0.12, 0.92]
Thursz 2015 (combined)	73	526	95	527	78.4%	0.77 [0.58, 1.02]
Total (95% CI)		**661**		**642**	**100.0%**	**0.70 [0.55, 0.90]**
Total events	90		125			

Heterogeneity: Tau² = 0.00; Chi² = 3.55, df = 4 (P = 0.47); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)

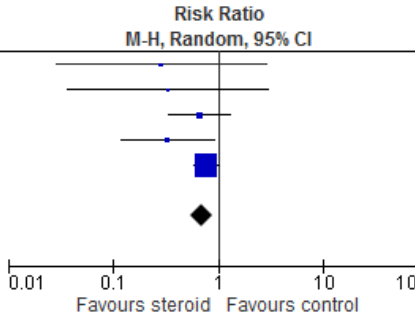


Figure 4: All-cause mortality – within 28 days

Subgroup (iii): Severe = hepatic encephalopathy at baseline

Study or Subgroup	Steroid Events	Steroid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Blitzer 1977	2	3	1	2	11.5%	1.33 [0.27, 6.61]
Carithers 1989	1	14	9	19	8.6%	0.15 [0.02, 1.06]
Mendenhall 1984	11	31	10	30	27.8%	1.06 [0.53, 2.13]
Shumaker 1978	2	6	4	6	15.8%	0.50 [0.14, 1.77]
Theodossi 1982	12	13	10	14	36.3%	1.29 [0.90, 1.86]
Total (95% CI)		**67**		**71**	**100.0%**	**0.88 [0.46, 1.67]**
Total events	28		34			

Heterogeneity: Tau² = 0.26; Chi² = 9.21, df = 4 (P = 0.06); I² = 57%
Test for overall effect: Z = 0.39 (P = 0.69)

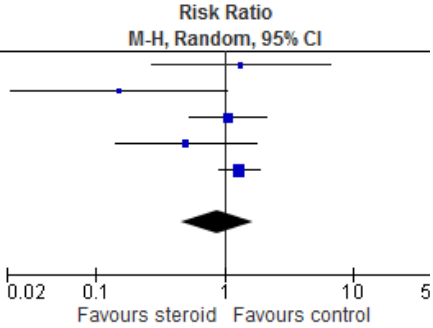


Figure 5: All-cause mortality – within 90 days

All participants and levels of severity

Study or Subgroup	Steroid Events	Steroid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Blitzer 1977	6	12	5	16	9.6%	1.60 [0.64, 4.02]
Campra 1973	7	20	9	25	11.5%	0.97 [0.44, 2.15]
De 2014	9	30	5	30	9.0%	1.80 [0.68, 4.74]
Depew 1980	8	15	7	13	13.3%	0.99 [0.50, 1.98]
Helman 1971	1	20	6	17	2.8%	0.14 [0.02, 1.06]
Maddrey 1978	3	24	6	31	6.1%	0.65 [0.18, 2.32]
Porter 1971	6	11	7	9	14.3%	0.70 [0.37, 1.33]
Ramond 1992	4	32	16	29	9.0%	0.23 [0.09, 0.60]
Thursz 2015 (combined)	144	484	141	484	24.3%	1.02 [0.84, 1.24]
Total (95% CI)		**648**		**654**	**100.0%**	**0.85 [0.59, 1.21]**
Total events	188		202			

Heterogeneity: Tau² = 0.13; Chi² = 16.50, df = 8 (P = 0.04); I² = 52%
Test for overall effect: Z = 0.91 (P = 0.36)

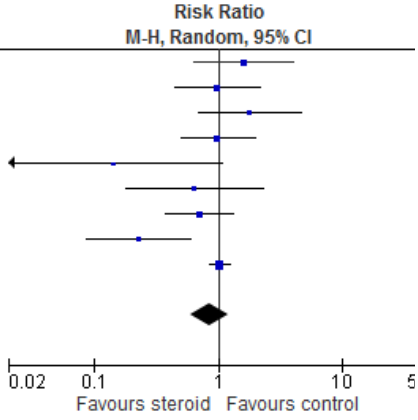


Figure 6: All-cause mortality – within 90 days

Subgroup (i): Severe = DF≥32 and/or hepatic encephalopathy at baseline (or otherwise defined 'severe' AH)

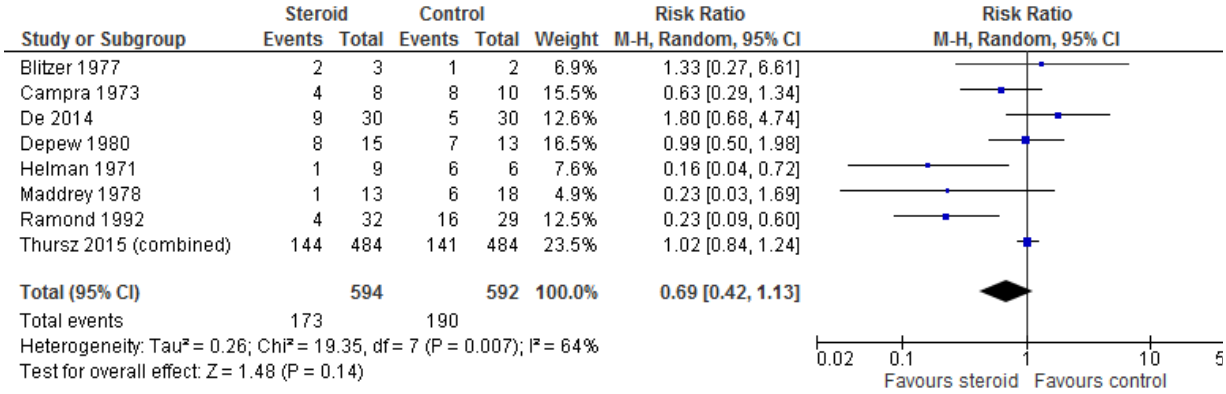


Figure 7: All-cause mortality – within 90 days

Subgroup (ii): Severe = DF≥32

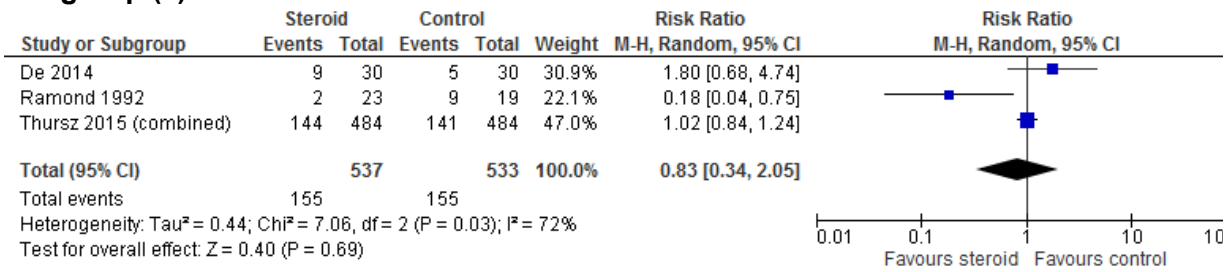


Figure 8: All-cause mortality – within 90 days

Subgroup (iii): Severe = hepatic encephalopathy at baseline

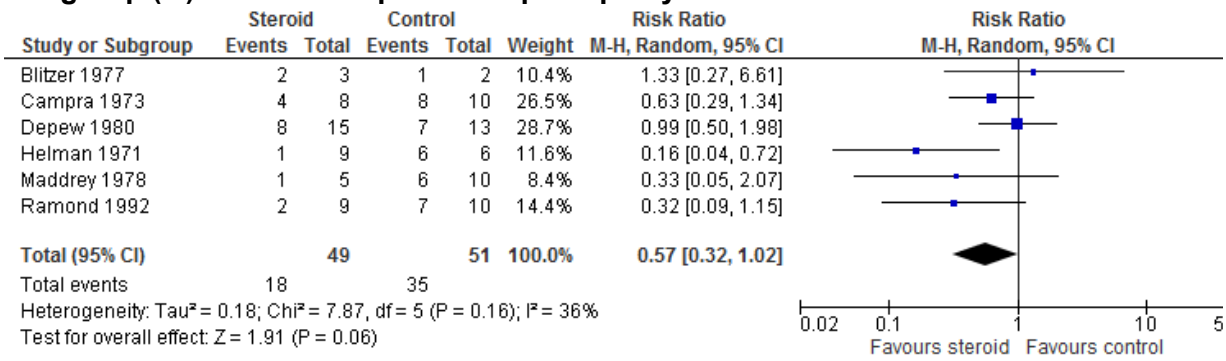


Figure 9: All-cause mortality – within 1 year

All participants and levels of severity

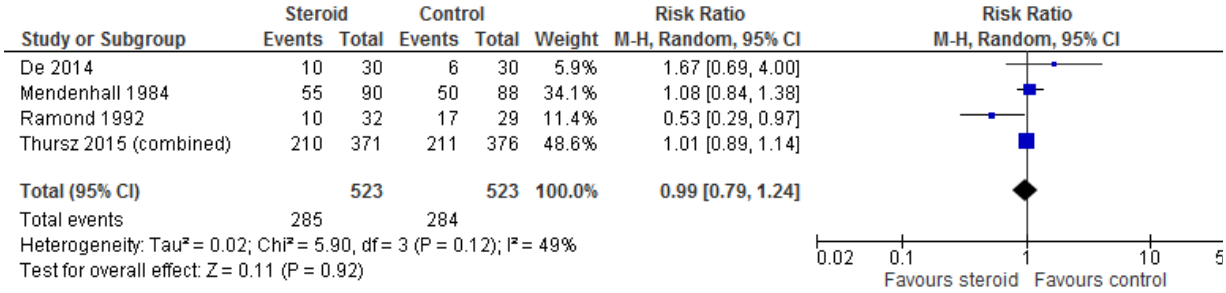


Figure 10: All-cause mortality – within 1 year

Subgroup (i): Severe = DF≥32 and/or hepatic encephalopathy at baseline (or otherwise defined 'severe' AH)

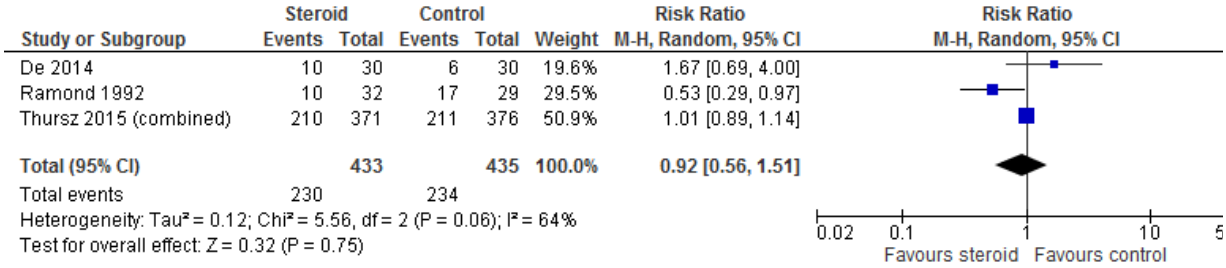


Figure 11: Liver-related mortality – within 28 days

All participants and levels of severity

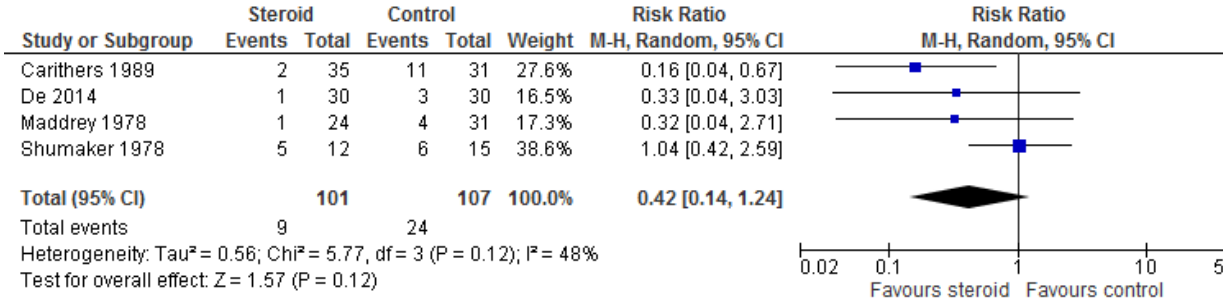


Figure 12: Liver-related mortality – within 28 days

Subgroup (i): Severe = DF≥32 and/or hepatic encephalopathy at baseline (or otherwise defined 'severe' AH)

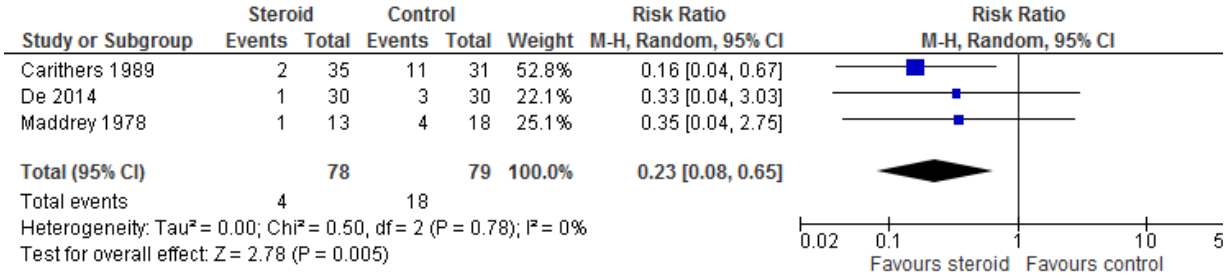


Figure 13: Liver-related mortality – within 90 days

All participants and levels of severity

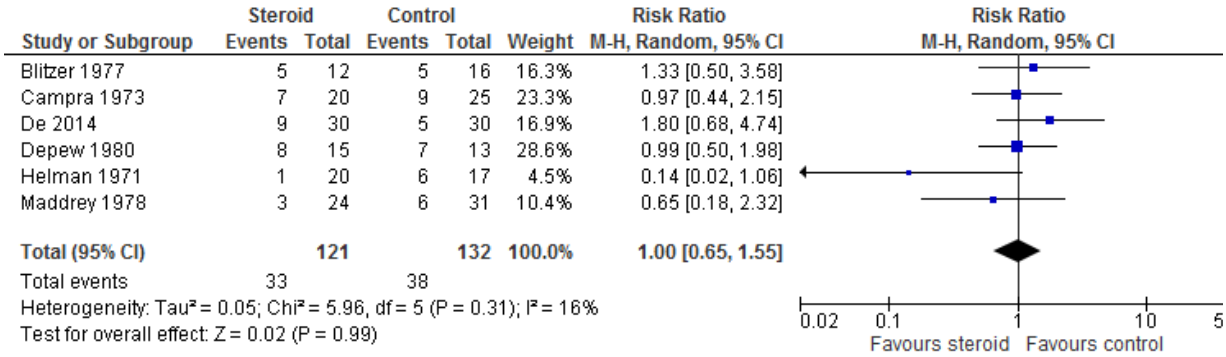


Figure 14: Liver-related mortality – within 90 days

Subgroup (i): Severe = DF≥32 and/or hepatic encephalopathy at baseline (or otherwise defined 'severe' AH)

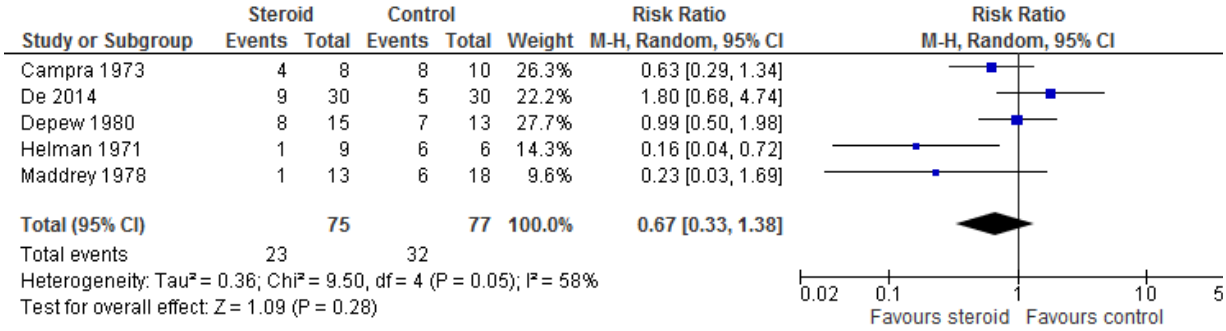
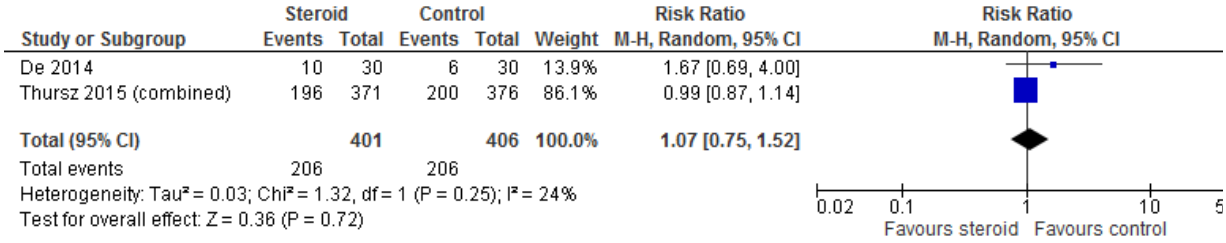


Figure 15: Liver-related mortality – within 1 year

Subgroup (ii): Severe = DF≥32



Note: both studies were in populations with severe AH = DF≥32

Figure 16: Serious infections – within 28 days

Subgroup (i): Severe = DF≥32 and/or hepatic encephalopathy at baseline (or otherwise defined 'severe' AH)

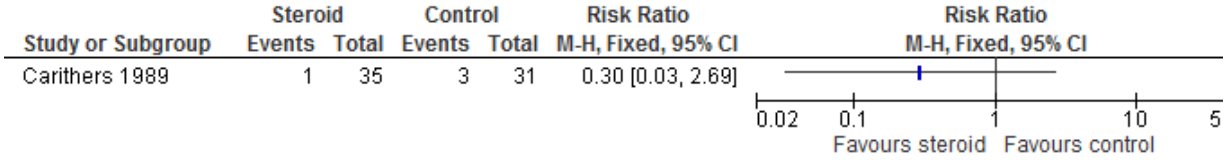


Figure 17: Serious infections – within 90 days

All participants and levels of severity

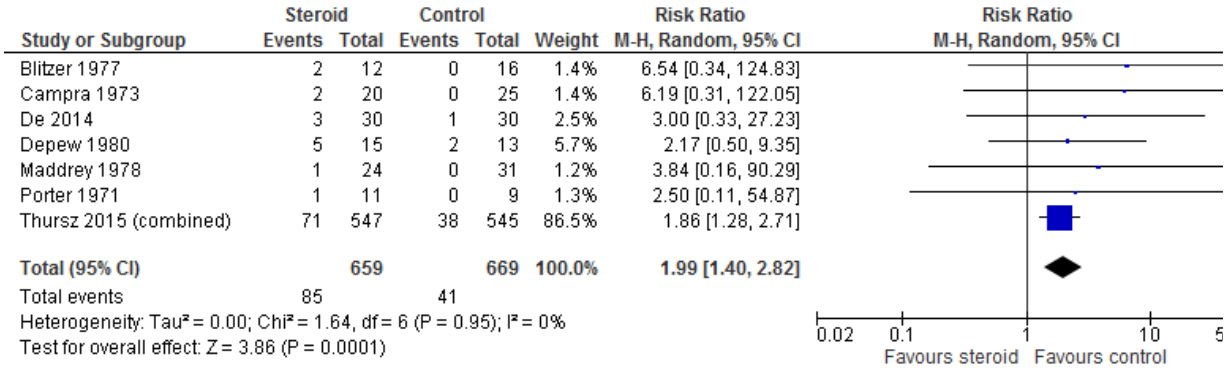


Figure 18: Serious infections – within 90 days

Subgroup (i): Severe = DF≥32 and/or hepatic encephalopathy at baseline (or otherwise defined 'severe' AH)

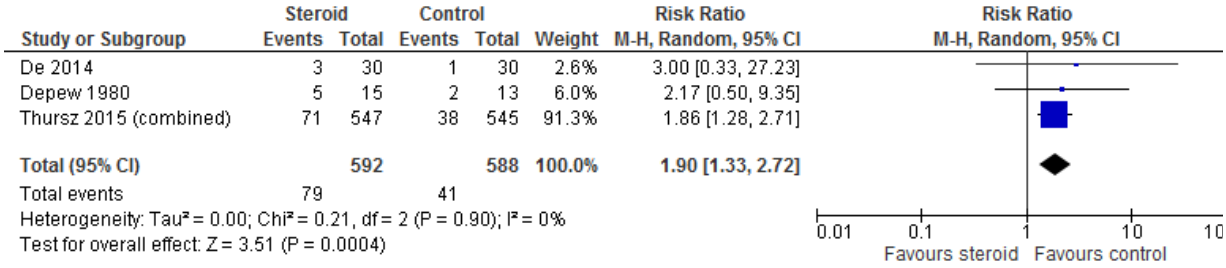


Figure 19: Serious infections – within 1 year

Subgroup (ii): Severe = DF≥32

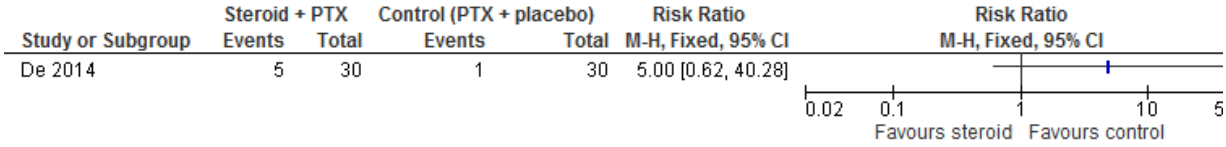


Figure 20: Serious adverse events (including infections)

All participants and levels of severity

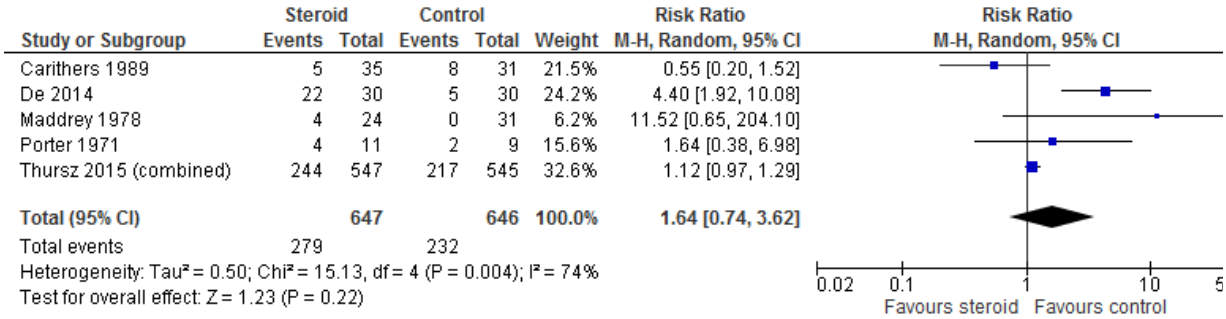


Figure 21: Serious adverse events (including infections)

Subgroup (i): Severe = DF≥32 and/or hepatic encephalopathy at baseline (or otherwise defined 'severe' AH)

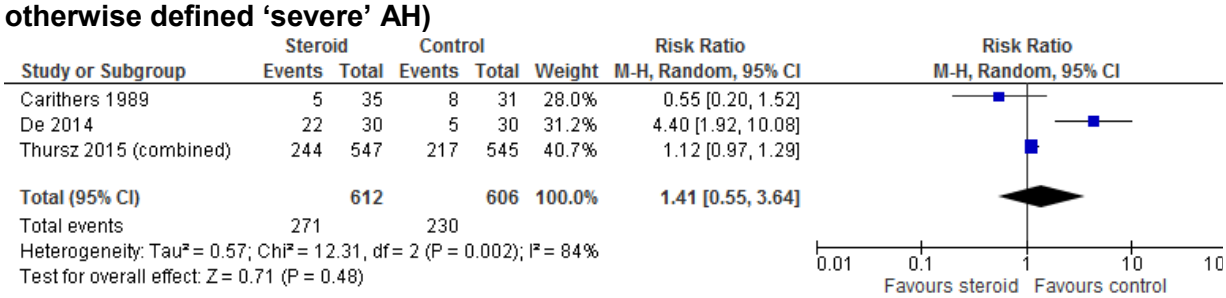
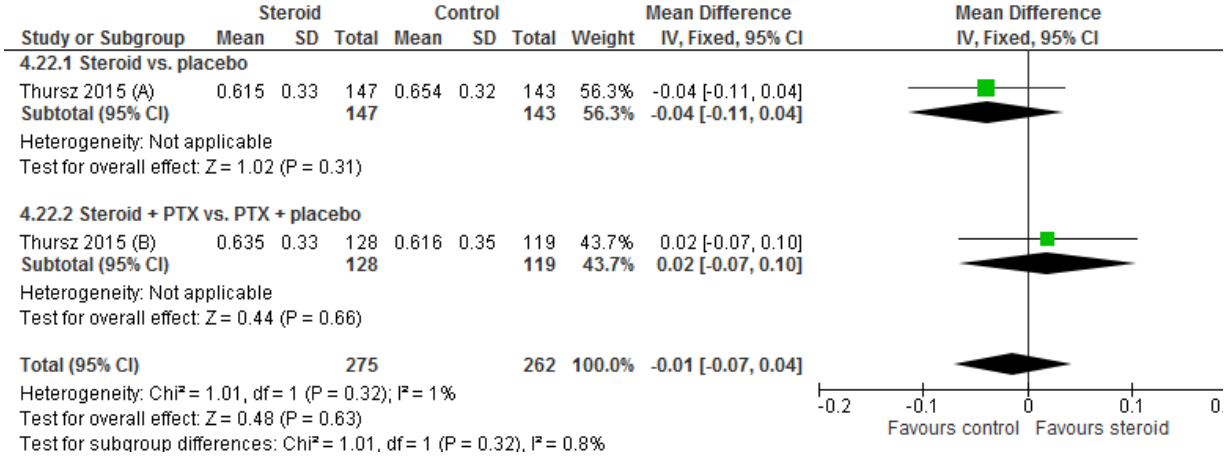


Figure 22: Quality of life (EQ-5D utility value[a]) – at discharge

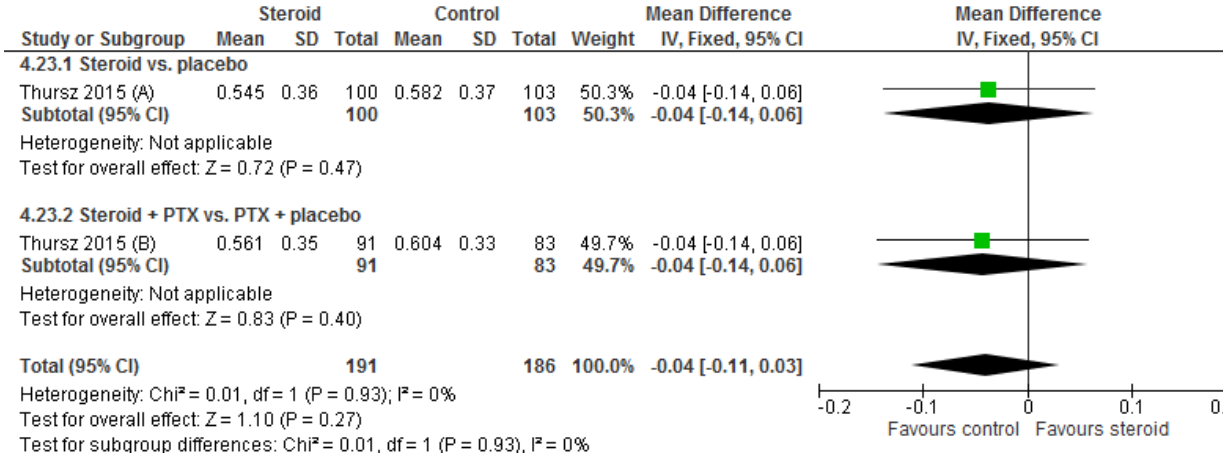
Data from STOPAH trial (treatment comparison A and B) - test for subgroup difference: p=0.32



[a] *Higher score = better quality of life*

Figure 23: Quality of life (EQ-5D utility value[a]) – at 90 days

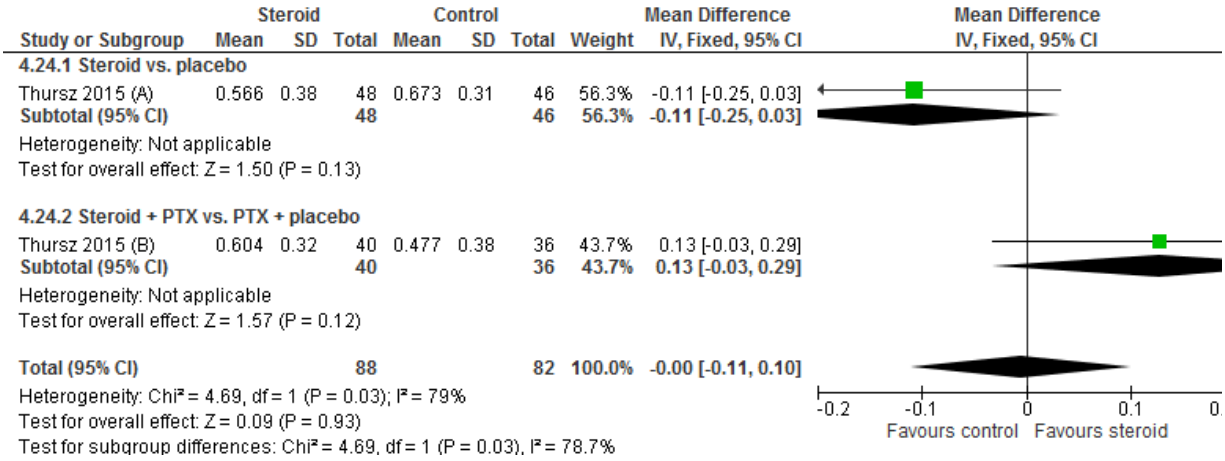
Data from STOPAH trial (treatment comparison A and B) - test for subgroup difference: p=0.93



[a] *Higher score = better quality of life*

Figure 24: Quality of life (EQ-5D utility value[a]) – at 1 year

Data from STOPAH trial (treatment comparison A and B) - test for subgroup difference: p=0.03



[a] *Higher score = better quality of life*

Appendix J: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 6. The search strategy is shown in Table 7. The same strategy was translated for the other databases listed.

Table 6: Economic search summary

Databases	Date searched	Version/files	No. retrieved	RefMan data
MEDLINE (Ovid)	13/09/2016	Ovid MEDLINE(R) 1946 to August Week 5 2016	52	1-52
MEDLINE In-Process (Ovid)	13/09/2016	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations September 13, 2016	9	53-61
Embase (Ovid)	13/09/2016	Embase 1974 to 2016 Week 37	269	62-330
Health Technology Assessment (HTA Database)	13/09/2016	Health Technology Assessment Database : Issue 3 of 4, July 2016	0	-
NHS Economic Evaluation Database (NHS EED) (legacy database)	13/09/2016	NHS Economic Evaluation Database : Issue 2 of 4, April 2015	0	-
PubMed	13/09/2016	-	61	331-391

Table 7: Economic search strategy

Database: Ovid MEDLINE(R) 1946 to August Week 5 2016
1 Hepatitis, Alcoholic/ (1950)
2 Hepatic Encephalopathy/ (9543)
3 ((severe* or serious* or acute*) adj4 hepat*).tw. (27041)
4 ((hepat* or portal systemic or portosystemic) adj4 (encephalopath* or coma* or stupor*)).tw. (8183)
5 Hepatorenal Syndrome/ (1168)
6 (hepatorenal adj4 (syndrome* or insuffic* or disease* or fail*)).tw. (1880)
7 Hematemesis/ (2254)
8 ((upper GI or upper gastro* or varice* or varix) adj4 (bleed* or hemorrhag* or blood loss or hematochez*)).tw. (12847)
9 or/1-8 (54854)
10 exp Ethanol/ (99830)

Database: Ovid MEDLINE(R) 1946 to August Week 5 2016

11 exp Alcoholic Beverages/ (16686)

12 exp Alcohol-Related Disorders/ (104389)

13 exp Alcohol Drinking/ (58982)

14 Alcoholic Neuropathy/ (118)

15 (alcohol* or ethanol* or beer* or wine* or spirit*).tw. (346946)

16 (dipsomania* or drunkenness).tw. (905)

17 ((binge* or hazard* or harmful* or problem* or unhealth* or unsaf* or peril* or risk* or damag* or destruct* or ruinous* or disadvantag* or detriment* or trouble*) adj4 drink*).tw. (13058)

18 or/10-17 (413075)

19 exp Hepatitis/ (147698)

20 hepat*.tw. (552369)

21 (liver* adj4 (inflam* or swell* or distend* or protrud*)).tw. (7464)

22 or/19-21 (578728)

23 18 and 22 (29325)

24 9 or 23 (79634)

25 exp Adrenal Cortex Hormones/ (367758)

26 (corticosteroid* or corticoid* or adrenocorticosteroid* or hydroxycorticosteroid* or ketosteroid*).tw. (89776)

27 (adrenal cort* adj4 (hormone* or steroid*)).tw. (1900)

28 ((cortic* or adrenocort*) adj4 (steroid* or hormone*)).tw. (21232)

29 ((adrenal or adreno) adj4 steroid*).tw. (5560)

30 (glucocorticoid* or glucorticoid* or glycocorticoid* or glucocorticoidsteroid* or glucocorticosteroid*).tw. (57597)

31 exp Prednisolone/ (47595)

32 prednisolone*.tw. (20916)

33 (Delta-Phoricol or Deltacortril or Deltastab or Pevanti or Precortisyl or Pred Forte or Predenema or Predfoam or Prednesol or Predsol or Sintisone).tw. (52)

Database: Ovid MEDLINE(R) 1946 to August Week 5 2016

34 (Ak-Pred or Articulose-50 or AsmalPred Plus or Delta-Cortef or Econopred or Flo-Pred or Hydeltra-TBA or Hydeltrasol or Inflamase or Key-Pred-SP or Key-Pred or Millipred or Omnipred or Orapred or Pediapred or Pred Mild or Pred-Phosphate or Pred or Predaject or Predalone or Predate or Predcor or Prednisol or Predonine or Prelone or Veripred).tw. (2664)

35 (Predmix or Solupred or Decortin H or Prednisolut or Ultracortenol).tw. (54)

36 (methylprednisolone* or medrone).tw. (12506)

37 (A-Methapred or Adlone or D-Med or depMedalone or Depo-Medrol or Depo-Predate or Depoject or Depopred or Duralone or M-Prednisol or Medralone or Medrol Acetate or Medrol or Solu-Medrol or solu-medrone or betnelan or betnesol or calcort or depomedrone or adcortyl or kenalog or Depo-medrone).tw. (585)

38 exp Dexamethasone/ (47278)

39 dexamethasone*.tw. (46000)

40 (Decadron or Dexafree or Dexsol or Dropodex or Martapan or Maxidex or Oradexon or Ozurdex).tw. (323)

41 (Aeroseb-Dex or Ak-Dex or Alba Dex or Baldex or Baycadron or Dalalone or Decaderm in Estergel or Decaject or Decaspray or Dexacort or Dexameth or Dexasone or Dexone or DexPak or Hexadrol or Solurex or Zema).tw. (32)

42 (hydrocortisone* or efcortesol or cortef or cortisol or cortisone* or epicortisol or solu-cortef).tw. (75269)

43 (Anflam or Colifoam or Corlan or Cortenema or Cortopin or Cortropin or Dermacort or Dioderm or Efcortelan Soluble or Efcortelan or Exe-Cort or Hc45 or Hydrocortistab or Hydrocortisyl or Hydrocortone or Lanacort or Locoid or Mildison or Plenadren or Timocort).tw. (66)

44 (A-Hydrocort or Acticort or Aeroseb-HC or Ala-Cort or Anucort-HC or Anuprep HC or Aquanil HC or Bactine or CaldeCort or Carmol HC or Cetacort or Colocort or Cort-Dome or CortaGel or Cortaid or Cortef or Corticaine or Corticool or Cortifair or Cortifoam or Cortizone or Cortril or Delcort or Dermacort or Dermarest or Dri-Cort or Dermasorb HC or Dermol HC or Dermolate or EarSol-HC or GRx HiCort or Hemril-HC or Hi-Cor or Hycort or Hydrocortone or HydroSkin or HydroTex or Hytone or Lacticare-HC or Massengill Medicated or Noble Formula HC or NuCort or Nutracort or Orabase HCA or Pandel or Procort or Proctocort or Recort Plus or Rectacort-HC or S-T Cort or Scalacort DK or Synacort or Tegrin-HC or Texacort or U-Cort or Westcort or Xerese).tw. (89)

45 exp Budesonide/ (3976)

46 (budesonide* or budelin or pulmicort or horacort or rhinocort).tw. (4141)

47 (Budenofalk or Cortiment or Entocort or Preferid or Uceris).tw. (49)

48 Prednisone/ (37027)

49 prednisone*.tw. (22347)

50 (Dehydrocortisone or delta-Cortisone or Prednison Hexal or Sone or Sterapred or Ultracorten or Winpred or Cortan or Cortancyl or Panafcort or Cutason or Decortin or Dacortin or Encortone or

Database: Ovid MEDLINE(R) 1946 to August Week 5 2016

Encorton or Enkortolon or Kortancyl or Panasol or Predni Tablinen or Prednidib or Predniment or Prednison acsis or Prednison Galen or Pronisone or Rectodelt).tw. (372)

51 (Decortisyl or Econosone or Lodotra).tw. (0)

52 (Deltasone or Liquid Pred or Meticorten or Orasone or Panasol-S or Prednicen-M or Rayos or Sterapred).tw. (62)

53 exp Triamcinolone/ (8718)

54 triamcinolone*.tw. (6001)

55 (Adcortyl or Kenalog or Ledercort or Lederspan or Nasacort or Volon).tw. (237)

56 (AllerNaze or Amcort or Aristocort or Aristospan or Articulose LA or Atolone or Azmacort or Cinalone 40 or Cinonide 40 or Delta-Tritex or Dermasorb TA or Flutex or Kenacort or Kenaject or Kenonel or Oralone Dental or pediaderm TA or Tac or Tri-Kort or Triacet or Triam-A or Triam or Triamcinair or Triamolone or Triamonide or Trianex or Triderm or Triesence or Trilog or Trilone or Tristoject or Trivaris or Trymex).tw. (7370)

57 exp Betamethasone/ (6696)

58 Betamethasone*.tw. (3944)

59 (Audavate or Betacap or Betesil or Betnelan or Betnesol or Betnovate RD or Betnovate or Bettamousse or Bextasol or Diprosone or Vista-Methasone).tw. (84)

60 (Alphatrex or B-S-P or Beta-Val or Betatrex or Cel-U-Jec or Celestone or Diprolene or Luxiq or Maxivate or Psorion or Selestoject or Sernivo or Teladar or Uticort or Valisone).tw. (112)

61 Beclomethasone/ (2907)

62 beclomethasone*.tw. (2567)

63 (Beclometasone or Asmabec Clickhaler or Ascocortonyl or Beclamet or Beclo Asma or Beclo AZU or Beclocort or Beclomet or Bemedrex Easyhaler or Beclorhinol or Becloturmant or Sanasthmax or Beclovent or Beconase or Becloforte or Becodisk* or Becotide or Propaderm or Sanasthmyl or Bronchocort or Junik or Qvar or Aerobec or Beclazone or Ecobec or Filair or Nasobec or Prolair or Respocort or Ventolair or Vancenase or Vanceril or Aldecin or Viarin or Apo-Beclomethasone).tw. (331)

64 (Beceze or Beclo Aqua or Beclogen or Clenil or Clipper or Hayfever Relief or Nasal Spray for Hayfever or Nasal-Bec or Pollenase Nasal or Pulvinal or Qnasl).tw. (106)

65 Pyridoxine/ (7511)

66 Pyrrolidonecarboxylic Acid/ (2663)

67 (Pyridox* or Rodex or Metadoxine).tw. (12929)

68 (pyrrolidone adj4 carboxylate).tw. (62)

Database: Ovid MEDLINE(R) 1946 to August Week 5 2016

69 ((Pyrrolidonecarboxylic or Pidolic or Pyroglutamic or Pidolate) adj4 (acid* or magnesium)).tw. (661)

70 Pyroglutamate.tw. (518)

71 ("5" adj4 (oxop* or ketoproline)).tw. (621)

72 Acetylcysteine/ (11454)

73 (acetylcystein* or N-Acetyl-L-cystein* or N Acetyl L cystein*).tw. (12624)

74 (Fabrol or Parvolex).tw. (10)

75 (Acetadote or Cetylev or Mucomyst or Mucosil).tw. (35)

76 or/25-75 (512955)

77 24 and 76 (2926)

78 Animals/ not Humans/ (4280821)

79 77 not 78 (2499)

80 limit 79 to english language (1855)

81 Economics/ (26791)

82 exp "Costs and Cost Analysis"/ (202339)

83 Economics, Dental/ (1889)

84 exp Economics, Hospital/ (21835)

85 exp Economics, Medical/ (13956)

86 Economics, Nursing/ (3943)

87 Economics, Pharmaceutical/ (2645)

88 Budgets/ (10585)

89 exp Models, Economic/ (12066)

90 Markov Chains/ (11577)

91 Monte Carlo Method/ (23178)

92 Decision Trees/ (9692)

93 econom$.tw. (182080)

Database: Ovid MEDLINE(R) 1946 to August Week 5 2016

94 cba.tw. (9207)

95 cea.tw. (17976)

96 cua.tw. (848)

97 markov$.tw. (13861)

98 (monte adj carlo).tw. (24105)

99 (decision adj3 (tree$ or analys$)).tw. (9770)

100 (cost or costs or costing$ or costly or costed).tw. (356748)

101 (price$ or pricing$).tw. (26380)

102 budget$.tw. (19439)

103 expenditure$.tw. (39764)

104 (value adj3 (money or monetary)).tw. (1569)

105 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3021)

106 or/81-105 (744614)

107 "Quality of Life"/ (142921)

108 quality of life.tw. (167413)

109 "Value of Life"/ (5520)

110 Quality-Adjusted Life Years/ (8821)

111 quality adjusted life.tw. (7558)

112 (qaly$ or qald$ or qale$ or qtime$).tw. (6174)

113 disability adjusted life.tw. (1646)

114 daly$.tw. (1559)

115 Health Status Indicators/ (21838)

116 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (17967)

117 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1098)

118 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3415)

Database: Ovid MEDLINE(R) 1946 to August Week 5 2016

119 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)

120 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (348)

121 (euroqol or euro qol or eq5d or eq 5d).tw. (5216)

122 (qol or hql or hqol or hrqol).tw. (30546)

123 (hye or hyes).tw. (54)

124 health$ year$ equivalent$.tw. (38)

125 utilit$.tw. (131640)

126 (hui or hui1 or hui2 or hui3).tw. (1011)

127 disutili$.tw. (265)

128 rosser.tw. (72)

129 quality of wellbeing.tw. (8)

130 quality of well-being.tw. (354)

131 qwb.tw. (187)

132 willingness to pay.tw. (2834)

133 standard gamble$.tw. (700)

134 time trade off.tw. (845)

135 time tradeoff.tw. (216)

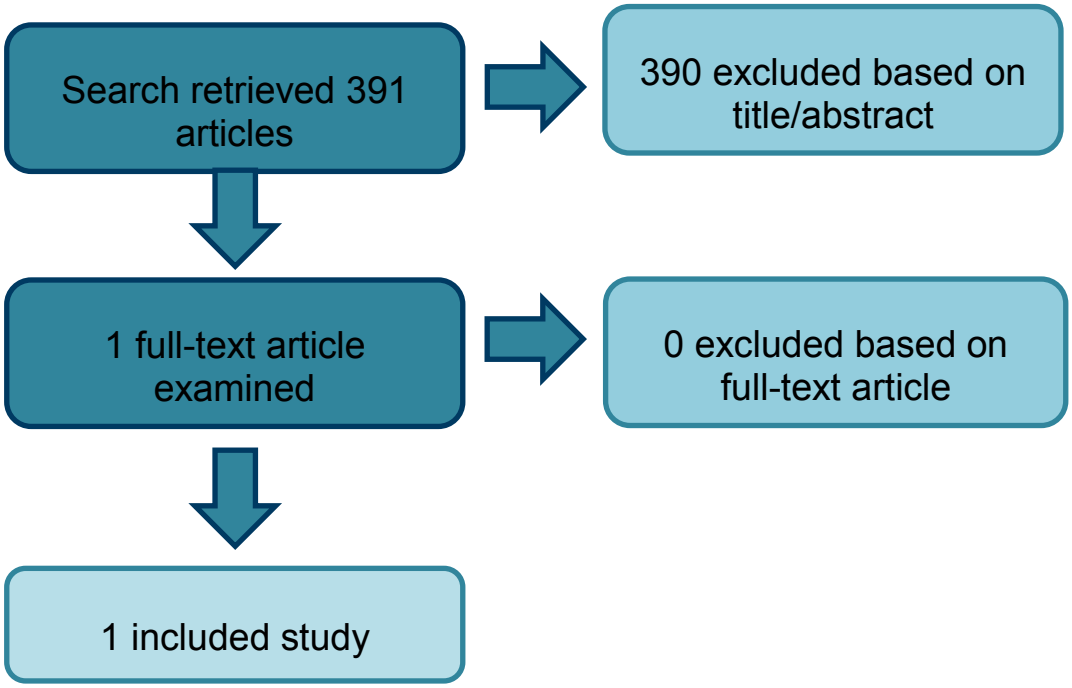
136 tto.tw. (688)

137 or/107-136 (376229)

138 106 or 137 (1069089)

139 80 and 138 (52)

Appendix K: Economic review flowchart



Appendix L:Full economic evidence tables

These are the full evidence tables for all included economic studies.

Table 8: Full economic evidence tables

Bibliographic reference	**Thursz, M., Forrest, E., Roderick, P., Day, C., Austin, A., O'Grady, J., Ryder, S., Allison, M., Gleeson, D., McCune, A. and Patch, D., 2015. The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2× 2 factorial randomised controlled trial. Health Technol Assess, 19, pp.1-104.**
Overview	

Interventions	Prednisolone Pentoxifyllline (PTX) Prednisolone and PTX
Comparators	Placebo
Base-line cohort characteristics	Patients with a clinical diagnosis of alcoholic hepatitis with a Maddrey's discriminant function value of ≥32
Type of Analysis	Cost effectiveness (28 day time horizon) Cost utility (1 year and 10 year time horizons)
Structure	In trial analysis (28 day time horizon) Markov model (1 year and 10 year time horizons)
Cycle length	1 day
Time horizon	28 days 1 year 10 years
Perspective	NHS
Country	UK
Currency unit	GBP
Cost year	Assumed 2015
Discounting	3.5%
Other comments	-

Bibliographic reference	**Thursz, M., Forrest, E., Roderick, P., Day, C., Austin, A., O'Grady, J., Ryder, S., Allison, M., Gleeson, D., McCune, A. and Patch, D., 2015. The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2× 2 factorial randomised controlled trial. Health Technol Assess, 19, pp.1-104.**

Results

28 day horizon

Intervention	Cost	Effect (survival)	Incremental cost	Incremental effect	ICER (incremental cost per additional survivor)
Prednisolone	£3,618	0.857	-	-	-
Prednisolone and PTX	£3,827	0.865	£659	0.008	£26,125
PTX	£4,194	0.806	£367	-0.059	Dominated
Placebo	£4,869	0.833	£675	0.027	Dominated

1 year horizon

Intervention	Cost	Effect (survival)	Incremental cost	Incremental effect	ICER (incremental cost per QALY)
PTX	£21,223	0.2000	-	-	-
Prednisolone	£21,653	0.2621	£430	0.0621	£6,924
Prednisolone and PTX	£21,992	0.2604	£339	-0.0017	Dominated
Placebo	£26,082	0.2604	£4,429	0.0000	Dominated

10 year horizon

Intervention	Cost	Effect (survival)	Incremental cost	Incremental effect	ICER (cost per additional survivor)
Prednisolone	£42,899	0.4068	-	-	-
Prednisolone and PTX	£43,275	0.5263	£376	0.1195	£3,146
PTX	£45,517	0.5420	£2,242	0.0157	£142,803
Placebo	£54,052	0.5418	£8,535	-0.0002	Dominated

Data sources

Base-line data	Data were sourced from the clinical trial conducted alongside the economic evaluation
Effectiveness data	Data were sourced from the clinical trial conducted alongside the economic evaluation
Cost data	Healthcare resource usage data were sourced from the clinical trial conducted alongside the economic evaluation. Unit costs were sourced from routine NHS sources: British National Formulary/NHS Reference Costs/NHS Tariffs/PSSRU

Bibliographic reference	**Thursz, M., Forrest, E., Roderick, P., Day, C., Austin, A., O'Grady, J., Ryder, S., Allison, M., Gleeson, D., McCune, A. and Patch, D., 2015. The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2× 2 factorial randomised controlled trial. Health Technol Assess, 19, pp.1-104.**
	Utility data: Utility scores at discharge and 90 days were sourced from the clinical trial conducted alongside the economic evaluation. Baseline utility score was assumed to be -0.402 (source not specified).
Uncertainty	**One-way sensitivity analysis**: 28 day horizon: Deterministic sensitivity analyses were carried out in which the most costly 10% of patients were removed from each treatment arm, and in which patients whose status at 28 days was unknown were excluded. Neither scenario had an appreciable effect on incremental cost effectiveness results. 1 year and 10 year horizons: A deterministic sensitivity analysis was carried out in which the assumption was made that all additional hospital admissions after the initial 28 days were in an intensive care unit and multiple imputations were used to estimate missing utility values at discharge and 28 days. This scenario resulted in a considerably higher ICER for prednisolone (£85,427/QALY) compared to PTX, although prednisolone still dominated placebo.
	Probabilistic sensitivity analysis: 28 day horizon: Bootstrapping of estimates of mean costs and mean probability of death across the four treatment arms was used to conduct probabilistic sensitivity analysis. The cost effectiveness of prednisolone was shown to be robust at a 28 day horizon. 1 year and 10 year horizons: Monte Carlo simulation was used to conduct probabilistic sensitivity analyses. Results indicated that, at a threshold of £20,000/QALY, prednisolone was the treatment with the highest probability of being cost effective at both horizons. However, there was considerable uncertainty surrounding these results.
Applicability	**Directly applicable**

Bibliographic reference	**Thursz, M., Forrest, E., Roderick, P., Day, C., Austin, A., O'Grady, J., Ryder, S., Allison, M., Gleeson, D., McCune, A. and Patch, D., 2015. The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2× 2 factorial randomised controlled trial. Health Technol Assess, 19, pp.1-104.**
Limitations	**Potentially serious limitations** • The model-based approach employs a simplistic approach to Markov modelling: living patients are associated with a fixed utility score, daily cost, and daily probability of death, which does not vary according to time spent in the model. This does not fully reflect reality, as patients have a considerably higher mortality risk and healthcare resource usage for the first 28 days.
Conflicts	Mark Thursz has received fees for advisory boards and speaker engagements from Gilead, BMS, Abbvi, MSD, Jenssen and Abbott Laboratories. Paul Roderick has received grant support from Pfizer and is a member of the Health Services and Delivery Research Board. Michael Allison has received fees for advisory board engagements from Norgine and Luke Vale is a member of the Clinical Trials Board.

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years