<table>
<tr><th colspan="9">In patients with acute alcoholic hepatitis, what is the safety and efficacy of corticosteroids v placebo?</th></tr>
<tr><th>Reference</th><th>Study type
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Carithers RL, Jr., Herlong HF, Diehl AM et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Annals of Internal Medicine. 1989; 110(9):685-690. Ref ID: 111</td>
<td>RCT
Double blind
Multicentre
Blocked randomisation
Code held by independent source
Power analysis
No ITT analysis (2/66 drop-outs)

1++</td>
<td>N=66

Completers: N=55 (89%)

Drop-outs: N=2</td>
<td>Patients with alcoholic hepatitis with either spontaneous hepatic encephalopathy or a discriminant function greater than 32

<table>
<tr><th>Characteristic</th><th>Methylpred.</th><th>Placebo</th></tr>
<tr><td>No</td><td>35</td><td>31</td></tr>
<tr><td>Age</td><td>43</td><td>44</td></tr>
<tr><td>Days before study entry</td><td>4.0</td><td>4.5</td></tr>
<tr><td>Men: women</td><td>20:15</td><td>21:10</td></tr>
<tr><td>Ascites</td><td>71%</td><td>65%</td></tr>
<tr><td>Encephalopathy</td><td>14/35 40%</td><td>19/32 61%</td></tr>
<tr><td>PTT</td><td>18</td><td>18</td></tr>
<tr><td>AST µkat/L</td><td>2.6</td><td>2.1</td></tr>
<tr><td>Creatinine µmol/L</td><td>135.6</td><td>132.9</td></tr>
<tr><td>Discriminant function</td><td>46.4</td><td>46.7</td></tr>
</table>
There was no significant differences between the groups at baseline

Exclusion criteria: Negative hepatitis B surface antigen within the first 3 days of hospitalisation, no previous history of viral hepatitis, GI haemorrhage requiring transfusion, insulin-dependent diabetes, active infection requiring treatment, pre-existing renal disease with serum creatinine greater than 175 µmol</td>
<td>Methylprednisolone

Tablets or i.v

32 mg for 28 days

16 mg for 7 days

8 mg for 7 days

Discontinued drug therapy if severe infection, GI bleeding or steroid-related complication suspected</td>
<td>Placebo</td>
<td>28 days</td>
<td>Treatment failure defined as: Treatment complications eg., lack of fluid intake, hallucinations lasting for more than 2 days after admission, occurrence of relapse

Treatment success defined as when at the time of evaluation, the patient was able to continue treatment on the psychiatric service, was not hallucinating and did not subsequently have a</td>
<td>National Institute for Alcohol Abuse and Alcoholism</td>
</tr>
</table>

							relapse	
Effect **Steroid vs placebo** *Mortality – total (28 days)* 2/35 (6%) vs 11/31 (35%) (p=0.006) (mean difference 29%; 95%CI approx12 to 70%) *Mortality - liver related (28 days)* 0/35 vs 5/31 (no p value reported) hepatic failure *Hepatic renal impairment* Not reported *Encephalopathy* Not reported *GI bleeds (variceal and non-variceal not stated) (28 days)* All were reported as a cause of death 2/35 vs 3/31 (no p value) *Infection (28 days)* All were reported as a cause of death 0/35 vs 3/31 placebo group *Discontinuations:* N=3 steroid: acute psychosis, acute pancreatitis, sepsis N=2 placebo: upper GI bleeding **Patients with spontaneous hepatic encephalopathy** *Mortality- total (28 days)* 1/14 (7%) vs 9/19 (47%) (p=0.021) (mean difference 40%; 95%CI approx 14 to 66%)								
Ramond MJ, Poynard T, Rueff B et al. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *New England Journal of Medicine.* 1992; 326(8):507-512. Ref ID: 1354	RCT Double blind Multicentre Blocked randomisation Power analysis ITT analysis 1++	N=61 Completed treatment: N=57 (93%) Lost to follow-up: N=1	All the patients included in the study had biopsy-proved alcoholic hepatitis (characterised by hyaline necrosis and infiltration of polymorphonuclear leukocytes) and spontaneous hepatic encephalopathy or a discriminatn-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.	Prednisolone Tablets or i.v 40 mg for 28 days Drug therapy was interrupted by the attending physician if there was severe bacterial infection	Placebo	2 months	Primary endpoint: death within 2 months	Not stated

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>Characteristic</td><td>Prednisolone.</td><td>Placebo</td></tr>
<tr><td>No</td><td>32</td><td>29</td></tr>
<tr><td>Age</td><td>48</td><td>48</td></tr>
<tr><td>Days before study entry</td><td>14</td><td>17</td></tr>
<tr><td>Men: women</td><td>10:22</td><td>9:20</td></tr>
<tr><td>Ascites</td><td>24 (75%)</td><td>25 (86%)</td></tr>
<tr><td>Encephalopathy</td><td>9 (28%)</td><td>10 (34%)</td></tr>
<tr><td>PTT (% of normal)</td><td>38.6</td><td>37.4</td></tr>
<tr><td>AST (no of times upper limit of normal)</td><td>3.7</td><td>3.3</td></tr>
<tr><td>Serum creatinine µmol/L</td><td>83.3</td><td>103.1</td></tr>
<tr><td>Serum bilirubin µmol/L</td><td>213</td><td>284</td></tr>
<tr><td>Discriminant function</td><td>51</td><td>60</td></tr>
</table>
There was no significant differences between the groups at baseline

Exclusion criteria: Gastrointestinal bleeding or bacterial infection unless they could be effectively treated within 48 hours, neoplastic disease, presence of hepatitis B surface antigen, presence of HIV antibodies and anticoagulation therapy.
</td>
<td>or gastrointestinal bleeding or if a corticosteroid-related complication was suspected. The remaining study drug tablets were replaced with placebo.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td colspan="8">Effect
Steroid vs placebo
Mortality – total (66 days)
4/32 (13%) vs 16/29 (55%) (p=0.001)

Survival rates
1 month: 88 ± 5% vs 62 ± 9%
2 months: 88 ± 5% vs 45 ± 8%</td>
</tr>
</table>

6 months: 84± 6% vs 45 ± 9% (p=0.002)

Mortality - liver related
Not reported although hepatocellular failure was severe in most patients.

Hepatic renal impairment
Not reported

Encephalopathy
Survival was significantly better in the steroid treated patients whether encephalopathy was present or absent (p=0.0017). In patients with no encephalopathy 2/23 steroid patients and 9/19 placebo patients had died two months after study entry.

GI bleeds
All were reported as a cause of death 1/32 vs 5/29 (no p value)

Infection
All were reported as a cause of death 2/32 vs 8/29 (no p value)

Discontinuations:
N=2 steroid: psychological disturbance, bacterial meningitis
N=2 placebo: bacterial infection and gastrointestinal bleeding in one patient the other patient left hospital and was lost to follow-up

<table>
<tr>
<td>Bories P, Guedj JY, Mirouze D et al. Treatment of acute alcoholic hepatitis with prednisolone. Presse Medicale. 1987; 16(16):769-772. Ref ID: 1993</td>
<td>RCT
• Unclear allocation concealment
• Inadequate blinding
• No ITT analysis
• No power calculation

(taken from Cochrane – paper in French)</td>
<td>N=45</td>
<td>Patients with alcoholic hepatitis

<table>
<tr><th>Characteristic</th><th>Methylpred.</th><th>Placebo</th></tr>
<tr><td>No</td><td>24</td><td>21</td></tr>
<tr><td>Age</td><td>41</td><td>49</td></tr>
<tr><td>Days before study entry</td><td></td><td></td></tr>
<tr><td>Men: women</td><td>16:8</td><td>11:10</td></tr>
<tr><td>Ascites</td><td>12/24 (50%)</td><td>12/21 (57%)</td></tr>
<tr><td>Encephalopathy</td><td>4/24 (17%)</td><td>4/21 (19%)</td></tr>
<tr><td>Hepatomegalie</td><td>13/24 (54%)</td><td>14/21 (67%)</td></tr>
<tr><td>PTT %</td><td>70.8</td><td>67.5</td></tr>
<tr><td>AST/ALT Mui/ML</td><td>78</td><td>78</td></tr>
</table>
</td>
<td>Methylprednisolone

40 mg

1500 kg calories and 50 g protein per day

Duration of treatment: one month</td>
<td>Control

No intervention</td>
<td>3 months</td>
<td>Mortality – total (one month, 90 days)
Mortality – liver related (one month, 90 days)
GI bleeding
Infection</td>
<td>None reported</td>
</tr>
</table>

	1+		Albumin g/l: 31.1 / 29.3 Hemaglobin g/100 ml: 11.5 / 11.2 Hepatitis only: 4/24 (17%) / 3/21 (14%) Hepatitis with firbrosis: 6/24 (25%) / 7/21 (33%) Hepatitis with cirrhosis: 14/24 (58%) / 11/21 (52%) Child-Pugh A: 4/24 / 2/21 B: 19/24 / 17/21 C: 1/24 / 2/21					
Effect **Steroid vs placebo** *Mortality – total (one month)* 1/24 vs 2/21 (no p value reported) *Mortality – liver-related (one month)* 0/24 vs 2/21 (no p value reported) *Mortality – total (90 days)* 4/24 fvs 5/21 (no p value reported) *Mortality – liver related (90 days)* 0/24 vs 2/21 (no p value reported) *Complications* Gastro-intestinal bleeding None reported Infection None reported									
Blitzer BL, Mutchnick MG, Joshi PH et al. Adrenocorticosteroid therapy in alcoholic hepatitis. A	RCT Double blind No power analysis No ITT analysis (5/33 drop-	N=33 Completers: N=28 (85%) Drop-outs:	Patients with alcoholic hepatitis who met the following criteria after at least 5 days in hospital were included in the study: recent history of heavy alcohol consumption, hepatomegaly based on physical examination, total serum bilirubin greater than 5mg/100 ml and at least two of the	Prednisolone 10mg qid for 14 days 5mg qid for 4 days	Placebo	Cumulative survival calculated until day 63	Acute mortality at end of treatment (26 days)	US Public Health Service training grants

<table>
<tr>
<td>prospective, double-blind randomized study. American Journal of Digestive Diseases. 1977; 22(6):477-484. Ref ID: 164</td>
<td>outs)

1+</td>
<td>N=5 (15%) all from the prednisolone group</td>
<td>following abnormalities: 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.

<table>
<tr><th>Characteristic</th><th>Prednisolone</th><th>Placebo</th></tr>
<tr><td>No</td><td>12</td><td>16</td></tr>
<tr><td>Age</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 was no significant differences between the groups at baseline with the exception of serum bilirubin (p<0.05).

Exclusion criteria: Patients treated with adrenocorticosteroids in the six months prior to admission or who showed evidence of psychotic behaviour precluding their cooperation.</td>
<td>2.5mg qid for 4 days

2.5mg bid for 4 days</td>
<td></td>
<td></td>
<td>Overall survival</td>
<td></td>
</tr>
<tr>
<td colspan="8">Effect
Steroid vs placebo
Mortality – total (26 days)
2/12 (17%) vs 2/16 (13%) (NS but no p value reported)

Mortality – total (during the hospital admission- final death day 54)
6/12 (50%) vs 5/16 (31%) (NS but no p value reported)

Mortality - liver related (during the hospital admission- final death day 54)</td>
</tr>
</table>

<table>
<tr><td colspan="9">0/12 vs 3/16 (no p value reported) hepatorenal syndrome or hepatocellular carcinoma

Hepatic renal impairment
Not reported

Encephalopathy
Mortality in the encephalopathy patients was not related to type of therapy (figures not reported)

GI bleeds
All were reported as a cause of death 1/12 vs 2/16 (no p value)

Infection
4/12 (33%) developed fungal infections vs 0/16 (no p value).

Discontinuations:
N=5 steroid: N=3 left the hospital against medical advice, N=2 GI haemorrhage
N=0 placebo</td></tr>
<tr><td>Campra JL, Hamlin EM, Jr., Kirshbaum RJ et al. Prednisone therapy of acute alcoholic hepatitis. Report of a controlled trial. Annals of Internal Medicine. 1973; 79(5):625-631. Ref ID: 1363</td><td>RCT
Not double blind
(no placebo)
No ITT analysis
No power analysis
1+</td><td>N=50 randomised

N=5 excluded from analysis</td><td>Patients had a clinical diagnosis of severe acute alcoholic liver disease, were randomised within 10 days of hospitalisation and 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). 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>Characteristic</td><td>Prednisolone</td><td>Control</td></tr><tr><td>No</td><td>20</td><td>25</td></tr><tr><td>Age</td><td>43</td><td>43</td></tr><tr><td>Days before study entry</td><td>8.4</td><td>7.0</td></tr></table></td><td>Prednisolone

0.5 mg/kg body weight for 3 weeks

0.25 mg/kg body weight for 3 weeks</td><td>Control (no placebo)</td><td>6 weeks</td><td>Primary outcome: mortality at 6 weeks</td><td>Not reported</td></tr>
</table>

			<table><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. Exclusion criteria: Prior history of liver disease, contraindication to corticosteroid therapy and any other known illnesses.					

Effect

Steroid vs control

Mortality – total (6 weeks)

7/20 (35%) vs 9/25 (36%) (NS- no p value reported).

Mortality - liver related

All deaths resulted from progressive hepatic failure, either alone or in association with other terminal events.

Hepatic renal impairment

Death was preceded by renal failure in 4/7 patients in the prednisolone group and 4/9 in the control group.

Encephalopathy

4/8 patients in the prednisolone group with encephalopathy pre-treatment died vs 8/10 in the control group ($p<0.2$).

GI bleeds

No difference in the incidence of gastrointestinal erosions, ulcerations, or bleeding was noted in the prednisone group when compared with control patients. Death was preceded by gastrointestinal bleeding in 3/7 patients in the prednisolone group and 5/9 in the control group.

Infection

Not reported

<table>
<tr><td colspan="9">Discontinuations/ withdrawals:
N=4 steroid: gastric ulcer, jaundice proved to be caused by hepatitis B antigen-positive hepatitis superimposed on mild alcoholic liver disease and two patients with fatty liver without recognisable cell necrosis
N=1 control: fatty liver without recognisable cell necrosis</td></tr>
<tr><td>Depew W, Boyer T, Omata M et al. Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. Gastroenterology. 1980; 78: 524-529. Ref IS:152</td><td>RCT
Double blind
Stratified randomisation
No power analysis
ITT analysis

1+</td><td>N=28

No drop-outs/ withdrawals</td><td>Alcohol abusers with a clinical diagnosis of severe acute alcoholic hepatitis manifested by hepatomegaly, leukocytosis and a serum bilirubin greater than 5mg/dl. All had encephalopathy occurring in the absence of gastrointestical 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).

<table><tr><td>Characteristic</td><td>Prednisolone</td><td>Placebo</td></tr><tr><td>No</td><td>15</td><td>13</td></tr><tr><td>Age</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/mm^3 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>Croatinine mg/dl</td><td>2.3</td><td>3</td></tr></table>Groups were similar at randomisation.

Exclusion criteria: Severe diabetes, active TB and serious bacterial infection.</td><td>Prednisolone

40 mg daily by mouth for 28 days followed by tapered withdrawal over the next 14 days</td><td>Placebo</td><td>Study duration assumed to be duration of hospital-isation. (Mean duration was 66 days for the steroid group and 56 days for placebo).</td><td>Primary outcome: mortality at end of study</td><td>Not stated</td></tr>
<tr><td colspan="9">Effect
Steroid vs placebo</td></tr>
</table>

Mortality – total (during study duration –approx 8 weeks)
8/15 (53%) vs 7/13 (54%) NS (no p-value)

Mortality - liver related (during study duration –approx 8 weeks)
All of those who died had hepatic failure accompanied by varying degrees of renal failure

Hepatic renal impairment
4 patients in the steroid group and 2 in the placebo group developed renal failure after randomisation (serum creatinine>2.5mg/dl).

GI bleeds (variceal and non-variceal not stated)
4 episodes of major gastrointestinal bleeding in the steroid group and 2 in the placebo group.

Infection
Urinary tract infections were found in 7 instances in the steroid group and 6 instances in the placebo group. 2 episodes of septicaemia occurred in the steroid group.

Discontinuations:
No discontinuations were reported

Helman RA, Temko MH, Nye SW et al. Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. *Annals of Internal Medicine.* 1971; 74(3):311-321. Ref ID: 1365	RCT Double blind No power analysis ITT analysis 1+	N=37 No drop outs	Diagnosis of alcoholic hepatitis was confirmed in all patients by biopsy before inclusion in the study. Patients were classified into three groups according to the clinical severity of their disease. Group I: severely ill and manifesting precoma 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. Severity group / Prednisolone / Placebo Group I: 9 / 6 Group II: 6 / 4 Group III: 5 / 7 Total: 20 / 17 The average age was 47.8 years. There were 12 (32%) men and 25 (68%) women. The differences in age, sex and treatment selection	Prednisolone 40mg daily for 4 weeks	Placebo	4 months	Mortality at end of study	Supported in part by grants from the US public health service

were not different between severity groups. 73% had ascites. (NB few patient characteristics are reported by treatment arm).

Characteristic	Group I	Group II	Group III
WBC x $10^3/mm^8$	12.8	11.4	10.7
Bilirubin mg/100ml	13.1	13.3	5.7
Prothrombin time	15.8	14.6	13.6

Exclusion criteria: Patients were excluded if a biopsy could not be obtained within the first week of hospitalisation, if gastrointestinal bleeding requiring transfusion occurred during this period or if the purified protein derivative (PPD) test was positive.

Effect

Steroid vs placebo

Mortality in Group I(4 months)

1/9 (11%) vs 6/6 (100%) ($p<0.001$) in group I (deaths occurred from 3 days to 3 months after study entry). There were no deaths in the other two groups.

Mortality - liver related

Cause of death was attributable to hepatorenal failure in four, hepatic failure with lower gastrointestinal bleeding in one, hepatic failure with cardiovascular collapse in one and bleeding esophageal varices with hepatic encephalopathy in one (causes of death not reported separately for steroid vs placebo groups).

Hepatic renal impairment

Not reported

Encephalopathy

Not reported

GI bleeds

There was no evidence of gastrointestinal ulceration or bleeding during the study period.

<table>
<tr><td colspan="8">Infection
There was no evidence of infection due to prednisolone during the study period

Discontinuations:
None reported</td></tr>
<tr>
<td>Lesesne HR, Bozymski EM, Fallon HJ. Treatment of alcoholic hepatitis with encephalopathy. Comparison of prednisolone with caloric supplements. Gastroenterology. 1978; 74(2:Pt 1):t-73. Ref ID: 161</td>
<td>RCT
No blinding
No placebo
No power analysis
No ITT analysis (3/17 drop-outs)

1+</td>
<td>N=14 included in the analysis

N=3 selected not to participate (2 given supportive treatment died and one given prednisolone died. They were not included in the analysis)</td>
<td>Patients with a historical, clinical and biochemical evidence of alcoholic hepatitis and who were in or developed spontaneous stage II encephalopathy. Liver biopsy was not required for study inclusion (later liver biopsy of 5/7 patients in the calorie group and 6/7 in the steroid group confirmed alcoholic hepatitis).

<table>
<tr><td>Characteristic</td><td>Prednisolone</td><td>Placebo</td></tr>
<tr><td>No</td><td>7</td><td>7</td></tr>
<tr><td>Age</td><td>54</td><td>45</td></tr>
<tr><td>Days before study entry</td><td>5.7</td><td>6.6</td></tr>
<tr><td>Men: women</td><td>6:1</td><td>4:3</td></tr>
<tr><td>Ascites</td><td>86%</td><td>83%</td></tr>
<tr><td>PTT(sec >control)</td><td>5.4</td><td>7.3</td></tr>
<tr><td>Bilirubin mg/dl</td><td>25.8</td><td>28.7</td></tr>
<tr><td>Creatinine mg/dl</td><td>2.1</td><td>1.9</td></tr>
<tr><td>Leukocyte count ($10/^3mm^3$)</td><td>16.0</td><td>15.1</td></tr>
</table>
There was no significant differences between the groups at baseline

Exclusion criteria: If the encephalopathy was not “spontaneous” or cleared during the initial 48 hour period of standard hepatic coma therapy.</td>
<td>Prednisolone

40mg daily for 30 days followed by a 2-week tapering.

These patients were permitted to eat ad libitum or if unable to eat were given a maximum of 600 calories daily as intravenous glucose</td>
<td>Calorie group (no placebo)

Caloric supplements of at least 1600 calories per day.</td>
<td>Survivors remained in the hospital for 30 to 60 days.</td>
<td>Survival as defined as a patient’s ability to leave the hospital and return home.</td>
<td>Partially supported by grants from the US public health service</td>
</tr>
<tr><td colspan="8">Effect</td></tr>
</table>

Steroid vs placebo

Mortality – total (all deaths in the range 3-16 days after study admission)
2/7 (29%) vs 7/7 (100%) (p<0.01)

Mortality - liver related
All patients died in hepatic failure

Hepatic renal impairment
Not reported

GI bleeds
In the calorie group one patient developed gastrointestinal bleeding

Infection (28 days)
One patient in the calorie group had aspiration pneumonia and another had Klebsiella bacteremia documented at autopsy. In the prednisolone group one patient developed pneumococcal pneumonia whilst on 5mg of prednisolone.

Maddrey WC, Boitnott JK, Bedine MS et al. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology.* 1978; 75(2):193-199. Ref ID: 1362	RCT Double blind Randomisation within 3 groups based on severity No power analysis No ITT analysis (2 randomised patients not included in the analysis) 1+	N=55 Completers: N=55 Drop-outs: N=0 patient withdrawals	Patients were evaluated for the study within 5 days of hospital admission. They had a history of long-standing and recent alcoholism. A percutaneous liver biopsy was performed unless precluded by coagulation abnormalities.	Prednisolone 5mg tablets were given in a single dose of 8 pills each morning for 28 to 32 days.	Placebo	28 to 30 days of treatment plus 5 days	Primary outcome: mortality at 28 to 30 days of treatment plus 5 days	Treatment provided by Upjohn Co.

Characteristic	Prednisolone	Placebo
No	24	31
Age	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	15.5	15.8
Serum creatinine mg/dl	1.2	1.6
WBC ($x10^3/mm^3$)	13.7	9.9
Clinical group A	7	8
Clinical group B	4	5

			<table><tr><td>Clinical group C</td><td>13</td><td>18</td></tr></table>There were no significant differences between the groups at baseline for most characteristics however the prednisolone treated patients did have a higher white blood cell count (p<0.01).. 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 B 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. Exclusion criteria: Patients with active gastrointestinal haemorrhage, pancreatitis, history of peptic ulcer disease, active infection, presence of hepatitis B antigen or history of previous viral hepatitis.					

Effect

Steroid vs placebo

Mortality – total (28 to 32 days- end of treatment plus 5 days)

1/24 (4%) vs 6/31 (19%) (NS p=0.10)

All deaths occurred in the group c (severely ill) patients. 1/13 (8%) vs 6/18(33%) (NS p=0.10)

Mortality - liver related (28 to 32 days plus 5 days)

All deaths were due to hepatic failure with terminal coma and hepatorenal syndrome

Hepatic renal impairment

Not reported

Encephalopathy

All patients who died had hepatic encephalopathy with asterixis upon admission to the study. Of patients with hepatic encephalopathy, 1/5 (20%) vs 6/10 (60%) died in each group (NS p=0.18).

GI bleeds
None reported

Infection
No patient developed an infection during the study

Discontinuations- patients removed from the study and the analysis:
N=1 steroid: bleeding from the esophageal varices before receiving the study drug
N=1 placebo: an episode of upper gastrointestinal haemorrgage presumably from esophageal varices after receiving prednisolone for 9 days the study drug was stopped.

<table>
<tr>
<td>Mendenhall CL, Anderson S, Garcia PP et al. Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. New England Journal of Medicine. 1984; 311(23):1464-1470. Ref ID: 1357</td>
<td>RCT
Double blind
Multicentre
Power analysis
ITT analysis

1+</td>
<td>N=178
(An Oxandrolone arm is not reported here)

Treatment completers:
N=170

Treatment drop-outs:
N=8

Lost to follow-up:
N=24</td>
<td>Men with moderate or severe alcoholic hepatitis based on conventional clinical and laboratory changes characteristic of the disease. Histologic confirmation was not required. Severity was estimated by the degree of jaundice (bilirubin) and coagulopathy (prothrombin time). (Precise definition for grouping patients by severity not given),
<table>
<tr><th>Characteristic</th><th>Prednisolone</th><th>Placebo</th></tr>
<tr><td>No</td><td>90</td><td>88</td></tr>
<tr><td>Age</td><td>51.5</td><td>50.4</td></tr>
<tr><td>Days before study entry</td><td>8.5</td><td>8.1</td></tr>
<tr><td>Men: women</td><td>90:0</td><td>88:0</td></tr>
<tr><td>Ascites</td><td>93%</td><td>86%</td></tr>
<tr><td>Encephalopathy</td><td>70%</td><td>67%</td></tr>
<tr><td>PTT (sec)</td><td>4.1</td><td>4.0</td></tr>
<tr><td>White-cell count ($x10^3/mm^3$)</td><td>11.4</td><td>11.9</td></tr>
<tr><td>AST (µU/liter)</td><td>110.8</td><td>113.8</td></tr>
<tr><td>Bilirubin (mmol/l)</td><td>275.3</td><td>263.3</td></tr>
<tr><td>Creatinine (mg/dl)</td><td>1.5</td><td>1.6</td></tr>
<tr><td>Disease severity (no)
Moderate</td><td>
46</td><td>
45</td></tr>
</table>
</td>
<td>Prednisolone

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</td>
<td>Placebo</td>
<td>4.4 years

Median follow-up:

Placebo:
180 days

Prednis-olone:
320 days</td>
<td>Acute mortality

Overall survival</td>
<td>The Cooperative Studies Program of the Veterans Admin-istration Medical Research Services</td>
</tr>
</table>

			Severe 44 43 There was no significant differences between the groups at baseline. Exclusion criteria: Concomitant conditions that would make interpretation of therapeutic efficacy difficult, if they had conditions that contraindicated corticosteroid therapy or if they had taken corticosteroids within the preceding three months.					

Effect
Steroid vs placebo
ALL PATIENTS
Mortality – total (30 days)
There was no significant difference between the two groups. (Patient numbers and p values not reported, just survival curves shown. Also no patient numbers/p values reported by treatment and severity classification).

FROM MATHURIN et al. 2002
15/91 vs 17/88

Mortality –total (at study end)
There were 50/88 (57%) deaths in the placebo group and 55/90 (51%) in the prednisolone group. From the 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).

Mortality – liver related
All deaths for which a cause could be determined were attributable either directly or indirectly to liver disease.

Hepatic renal impairment
Not reported

Encephalopathy
In the placebo group 75% had encephalopathy present at study entry but this was 21% at 12 months (N=24). In the prednisolone group 75% had encephalopathy present at study entry but this was 18% at 12 months (N=28). (Pre-treatment and follow-up values based on the same patients – no p values).

GI bleeds
Not reported

Infection

<table>
<tr><td colspan="9">Not reported

FROM MATHURIN et al. 2002

DF ≥ 32
Steroid vs placebo
Mortality – total (30 days)
12/52 vs 14/44</td></tr>
<tr>
<td>Porter HP, Simon FR, Pope CE et al. Corticosteroid therapy in severe alcoholic hepatitis. A double-blind drug trial. New England Journal of Medicine. 1971; 284(24):1350-1355. Ref ID: 1364</td>
<td>RCT
Double blind
No power analysis (but described as a pilot study)
No ITT analysis (3/23 were not included in the analysis as they died within 36 hrs of the start of therapy)

1+</td>
<td>N=20</td>
<td>Absolute criteria for admission to the study were as follows: a history of recent, heavy alcohol ingestion; a serum total bilirubin concentration of 5mg per 100ml or more, and 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. For study admission all three absolute criteria were required. 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; and a total bilirubin over 20mg per 100ml. 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; esophageal varices on barium swallow x-ray study or endoscopy; spider angiomas; fluid retention (edema or ascites); palmar erythema; and a prothrombin time prolonged 3 or 4 more seconds over control.

<table>
<tr><td>Characteristic</td><td>Methylpred.</td><td>Placebo</td></tr>
</table>
</td>
<td>Methylprednisolone

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. 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</td>
<td>Placebo</td>
<td>40 days</td>
<td>Primary outcome: survival to discharge from hospital</td>
<td>Medication supplied courtesy of Upjohn Co.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>No</td><td>11</td><td>9</td></tr>
<tr><td>Age</td><td>45</td><td>50</td></tr>
<tr><td>Days before study entry</td><td>14</td><td>11</td></tr>
<tr><td>Men (%)</td><td>64%</td><td>67%</td></tr>
<tr><td>Ascites</td><td>82%</td><td>100%</td></tr>
<tr><td>Encephalopathy</td><td>7/11 64%</td><td>8/9 89%</td></tr>
<tr><td>Serum total bilirubin (mg/ 100 ml)</td><td>24.6</td><td>24.3</td></tr>
<tr><td>White cell count (x 10^3)</td><td>16.8</td><td>20.0</td></tr>
</table>
There were no significant differences between the groups at baseline.

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 criteria: Active gastrointestinal bleeding, pancreatitis, radiologic evidence of peptic-ulcer disease, active TB and potentially life-threatening bacterial infections.
</td>
<td>4 days of therapy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td colspan="8">Effect
Steroid vs placebo
Mortality – total (40 days)
6/11 (55%) vs 7/9 (78%) (NS – p value not reported).

Mortality - liver related
Not reported

Hepatic renal impairment
Not reported</td>
</tr>
</table>

Encephalopathy Not reported *GI bleeds* 4/11 (36%) vs 2/9 (22%) demonstrated upper gastrointestinal erosion, ulceration or bleeding (NS – p value not reported). *Infection* None reported *Discontinuations:* None reported								
Shumaker JB, Resnick RH, Galambos JT et al. A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. *American Journal of Gastroenterology.* 1978; 69(4):443-449. Ref ID: 1361	RCT Double blind Code held by independent source ITT analysis 1+	N=27 Withdrawal: N=1 after 8 days but included in the analysis	Patients with a clinical diagnosis of alcoholic hepatitis with 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. Additionally, a patient had to have a minimum of two major criteria or one major or two minor to be placed in the study. Major criteria: were a liver biopsy showing alcoholic hepatitis, hepatic encephalopathy, azotemia unexplained by another process, creatinine >1.5mg.%, hyperbilirubinemia and 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, splenomegaly or liver stigmas. 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” (DA). Characteristics in BF patients | Methylpred. | Placebo	Methylprednisolone 80mg for 4 to 7 days; the medication was then tapered on a flexible schedule with cessation of therapy planned for 4 weeks	Placebo	4 weeks (mean duration of patients on steroids was 8.5 days compared to 16.4 days for those receiving placebo).	Primary outcome: survival at study end	Upjohn Co supplied and prepared the medications and placebo.

			<table><tr><td>No</td><td>4</td><td>6</td></tr><tr><td>Age</td><td>44</td><td>46</td></tr><tr><td>% male</td><td>75%</td><td>50%</td></tr><tr><td>Bilirubin (mg.%)</td><td>9</td><td>16</td></tr><tr><td>PPT</td><td>2.1</td><td>3.3</td></tr><tr><td>WBC (x10^3/cu. mm)</td><td>15.2</td><td>18.5</td></tr></table> <table><tr><td>Characteristics in BD patients</td><td>Methylpred.</td><td>Placebo</td></tr><tr><td>No</td><td>8</td><td>9</td></tr><tr><td>Age</td><td>47</td><td>43</td></tr><tr><td>% male</td><td>4.0</td><td>4.5</td></tr><tr><td>Bilirubin (mg.%)</td><td>29.1</td><td>20.3</td></tr><tr><td>PPT</td><td>5.6</td><td>5.8</td></tr><tr><td>WBC (x10^3/cu. mm)</td><td>20</td><td>20.9</td></tr></table> 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). Exclusion criteria: Patients were not considered for the study if their SGOT was >500 µ/ml, if they manifested active gastrointestinal bleeding, pancreatitis, x-ray evidence of peptic ulcer disease, active TB, acute infection or severe psychiatric disorder.				
Effect **Steroid vs placebo** *Mortality – total (4 weeks)* 6/12 (50%) vs 7/15 (47%) (p>0.05) *Mortality - liver related (4 weeks)* 2/12 vs 0/15 (no p value reported) hepatic failure as cause of death								

Hepatic renal impairment
Not reported

Encephalopathy
6/8 vs 6/9 (no p value) in the biopsy disallowed patients

GI bleeds
4/8 vs 5/9 (no p value) in the biopsy disallowed patients

Infection
2/8 vs 3/9 (no p value) in the biopsy disallowed patients had sepsis. This was the cause of death in 2 patients in the placebo group.

Discontinuations:
In the BD group only 3 patients remained in the protocol for longer than 21 days (1/8 in the steroid group and 2/9 in the control group).

Theodossi A, Eddleston AL, Williams R. Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. *Gut.* 1982; 23(1):75-79. Ref ID: 1359	RCT No blinding (no placebo) No power or ITT analysis 1-	N=60 N=55 included in final analysis	Patients with a history of alcohol intake of about 80g or more daily for at least 5 years, a serum bilirubin concentration greater than 80 µmol/L, a serum AST level at least twice the limit of normal and a PPT prolonged by at least 9 seconds. Characteristic / Methylpred. / Control No: 27 / 28 Men: women: 19:8 / 12:16 Ascites: 93% / 71% Encephalopathy: 74% / 50% PTT: 10 / 11 AST IU/L: 177 / 149 Creatinine µmol/L: 100 / 115 White cell count: 10.7 / 15.2 There was no significant differences between the groups at baseline Exclusion criteria: Patients with hepatoma and those with other diseases such as recent myocardial infarction, an accompanying	Methylprednisolone i.v.1g daily for 3 days	Control (no placebo)	Duration unclear	Primary outcome: survival during the study	Not stated

			cerebrovascular accident including evidence of subdural haematoma and active tuberculosis.					

Effect
Steroid vs placebo
Mortality – total
63% of the steroid group and 57% of the control group died during the study (NS – no p value).

Mortality - liver related
Not reported

Hepatic renal impairment
Not reported

Encephalopathy
Of the patients with encephalopathy, 94% of those in the steroid group and 69% of those in the control group died (NS – no p value).

GI bleeds (variceal and non-variceal not stated)
All were reported as a cause of death. Massive upper gastrointestinal bleeding in 41% of the corticosteroid group and 21% of the control group, mostly variceal in origin (NS – no p value).

Infection
Seven steroid patients and six control patients had septicaemia

Discontinuations:
Not stated

,