ACUTE LIVER FAILURE WITH ENCEPHALOPATHY
Supporting information

This guideline has been prepared with reference to the following:

NICE. Cirrhosis in over 16s: assessment and management. 2023. London. NICE

https://www.nice.org.uk/guidance/ng50

Lee WM, Larson, A.M & Stravitz, T.R. The management of acute liver failure: Update 2011: AASLD Position Paper. Hepatology 2012;55:965-7

https://www.aasld.org/practice-guidelines/management-acute-liver-failure

Immediate treatment

Correcting hypoxia, hypokalaemia, hypoglycaemia and hypotension affects the clinical outcome?
Generally accepted measures for the treatment of acute hepatic encephalopathy include correction and avoidance of any factor that could potentially aggravate pre-existing encephalopathy, such as hypoglycaemia, hypoxia, haemorrhage, sepsis, drug toxicity, and electrolyte and acid base disturbance (Caraceni, 1995).
Tissue hypoxia contributes to multiple-organ failure and is associated with a very poor prognosis: non-surviving patients have been shown to present with lower systemic vascular resistance indices, lower oxygen extraction ratios, and higher blood lactate levels than surviving patients (Bihari, 1986; Bihari, 1985).

Bihari DJ, Gimson AE, Williams R. Cardiovascular, pulmonary and renal complications of fulminant hepatic failure. Semin Liver Dis 1986;6:119-28

Bihari D, Gimson AE, Waterson M, et al. Tissue hypoxia during fulminant hepatic failure. Crit Care Med 1985;13:1034-9

Caraceni P, van Thiel DH. Acute liver failure. Lancet 1995;345:163-9

Evidence Level: V

Lactulose (except in fulminant liver failure), intra-rectally, orally or via NG tube, influences the clinical outcome?
A 2016 systematic review found that non-absorbable disaccharides (such as Lactulose and lactitol) are associated with a beneficial effect on clinically relevant outcomes when compared with placebo (mortality [RR 0.59, 95% CI 0.40 to 0.87], hepatic encephalopathy [RR 0.58, 95% CI 0.50 to 0.69], adverse events [RR 0.47, 95% CI 0.36 to 0.60]) (Gluud, 2016).
A 2014 guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (Vilstrup, 2014) reviewed the evidence as follows:
“Lactulose is generally used as initial treatment for OHE (Overt Hepatic Encephalopathy).

Gluud LL, Vilstrup H, Morgan MY. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database Syst Rev. 2016
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003044.pub4/full

Vilstrup H, Amodio P, Bajaj J et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715-35
http://onlinelibrary.wiley.com/wol1/doi/10.1002/hep.27210/full

Evidence Level: I

Routine use of fluconazole and prophylactic antibiotics influences the clinical outcome?
Patients with acute liver failure are prone to infections due to impaired host defence mechanisms (Plevris, 1998). A prospective study of 50 consecutive patients with acute liver failure has recorded bacteriologically confirmed infection in 80% (Rolando, 1990) and fungal infection in 32% (Rolando, 1991). A randomised trial of fluconazole in liver transplant patients (Winston, 1999) found decreased

fungal colonisation rates as compared to placebo (42% decrease v 20% increase). Another trial comparing fluconazole to nystatin (Lumbreras, 1996) found candida colonisation in 25% v 53% of patients respectively. Although fluconazole is associated with fewer deaths from fungal infection, it does not improve overall survival (Winston, 1999).
The development of resistant organisms may be a problem with long-term prophylactic therapy, but this is not considered to be a risk with short-term prophylaxis in acute liver disease (Fisher, 1998).
A review of the literature (Festi, 2006) has suggested that rifaximin has the highest benefit-risk ratio in the overall treatment of hepatic encephalopathy.
Both neomycin and metronidazole are active against aerobic gut flora and thus reduce the endogenous production of ammonia (Blei, 2001; Morgan, 1982). Prophylactic (compared to clinically indicated) parenteral antibiotics are effective at reducing the risk of infection by up to 30% in patients with acute liver failure but do not influence mortality (Rolando, 1996).

Bernal W, Wendon J. Acute liver failure: clinical features and management. Europ J Gastroenterol Hepatol 1999;11:977-84

Blei AT, Cordoba J. Hepatic encephalopathy. Am J Gastroenterol 2001;96:1968-76
http://s3.gi.org/physicians/guidelines/HepaticEncephalopathy.pdf

Festi D, Vestito A, Mazzella G, et al. Management of hepatic encephalopathy: focus on antibiotic therapy. Digestion 2006;73:94-101

Fisher NC, Cooper MA, Hastings JG, et al. Fungal colonisation and fluconazole therapy in liver disease. Liver 1998;18:320-5

Lumbreras C, Cuervas-Mons V, Jara P, et al. Randomized trial of fluconazole versus nystatin for the prophylaxis of candida infection following liver transplantation. J Infect Dis 1996;174:583-8
http://jid.oxfordjournals.org/content/174/3/583.long

Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. Gut 1982;23:1-7
http://gut.bmj.com/content/23/1/1.long

Plevris JN, Schina M, Hayes PC. Review article: the management of acute liver failure. Aliment Pharmacol Ther 1998;12:405-18
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2009.04175.x/full

Rolando N, Wade JJ, Stangou A, et al. Prospective study comparing the efficacy of prophylactic parenteral antimicrobials, with or without enteral decontamination, in patients with acute liver failure. Liver Transplant Surg 1996;2:8-13
http://onlinelibrary.wiley.com/doi/10.1002/lt.500020103/pdf

Rolando N, Harvey F, Brahm J, et al. Fungal infection: a common, unrecognised complication of acute liver failure. J Hepatol 1991;12:1-9

Rolando N, Harvey F, Brahm J, et al. Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients. Hepatology 1990;11:50-3

Winston DJ, Pakrasi A, Busuttil RW. Prophylactic fluconazole in liver transplant recipients: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999;131:729-37

Evidence Level II

Pabrinex IV (in the presence of encephalopathy) influences the clinical outcome?
Biochemical deficiency of thiamine has been detected in 71% of patients with fulminant liver failure (Rossouw, 1978). In another study (Labadarios, 1977), 9 out of 24 patients with acute hepatocellular necrosis leading to fulminant liver failure showed thiamine deficiency early in the course of their illness. This was corrected effectively by twice daily IV thiamine hydrochloride (100 mg b.d.). This regime is also indicated in a review (Messner, 1990).

Labadarios D, Rossouw JE, McConnell JB, et al. Thiamine deficiency in fulminant hepatic failure and effects of supplementation. Int J Vitam Nutr Res 1977;47:17-22

Messner M, Brissot P. Traditional management of liver disorders. Drugs 1990;40(Suppl 3):45-57

Rossouw JE, Labadarios D, Davis M, et al. Water-soluble vitamins in severe liver disease. S Afr Med J 1978;54:183-6

Evidence Level: V

Sedatives (benzodiazepines, phenothiazines, opioids) should be avoided?
Observational studies (Bakti, 1987; Branch, 1976) have established that patients with liver failure are highly vulnerable to sedatives, with therapeutic doses precipitating coma or near-coma and having a prolonged effect (Hammond, 1998).
Endogenous benzodiazepine-like substances have been identified in the cerebrospinal fluid of patients with hepatic encephalopathy. Benzodiazepines should not therefore be used in the management of agitation in these patients, due to the potential for confounding effects on encephalopathy (Gill, 2001)

Bakti G, Fisch HU, Karlaganis G, et al. Mechanism of the excessive sedative response of cirrhotics to benzodiazepines: model experiments with triazolam. Hepatology 1987;7:629-38

Branch RA, Morgan MH, James J, et al. Intravenous administration of diazepam in patients with chronic liver disease. Gut 1976;17:975-83
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1411230/pdf/gut00493-0057.pdf

Gill RQ, Sterling RK. Acute liver failure. J Clin Gastroenterol 2001;33:191-8

Hammond JB, Ahmad F. Hepatic encephalopathy and role of antibenzodiazepines. Am J Ther 1998;5:33-6

Evidence Level: IV

Subsequent management

Asymptomatic ascites need not be treated urgently?
Ascites is not generally a life-threatening condition (Habeeb, 1997). Treatment is largely to prevent complications such as spontaneous bacterial peritonitis (McGuire, 1998).

Habeeb KS, Herrera JL. Management of ascites: paracentesis as a guide. Postgrad Med 1997;101(1):191-200

McGuire BM, Bloomer JR. Complications of cirrhosis: why they occur and what to do about them. Postgrad Med 1998;103(2):209-224

Evidence Level: V

Spironolactone up to 400 mg daily is the preferred treatment for ascites causing symptoms (and furosemide additionally if no response)?
Spironolactone, an aldosterone antagonist, is the drug of choice for ascites when glomerular filtration rate is not reduced (Ljubicic, 1998). A randomised comparative study (Perez-Ayuso, 1983) treated 21 patients with furosemide and 19 with spironolactone. Eleven of 21 responded in the first group, compared to 18 of 19 in the second. The addition of a loop diuretic, such as furosemide potentiates the natiuretic effects of spironolactone (Gentilini, 1989). As the onset of diuresis in patients treated with spironolactone alone takes approximately 2 weeks (Sungaila, 1992; Fogel, 1981), giving spironolactone and furosemide together may also be considered (Runyon, 1994).

Fogel MR, Sawhney VK, Neal EA, et al. Diuresis in the ascitic patient: a randomized controlled trial of three regimens. J Clin Gastroenterol 1981;3(suppl 1):73-80

Gentilini P, Laffi G. Renal functional impairment and sodium retention in liver cirrhosis. Digestion 1989;43:1-32

Ljubicic N, Kujundzic M, Banic M, et al. Predictive factors influencing the therapeutic response to diuretic treatment of ascites in nonazotemic cirrhotic patients. Scand J Gastroenterol 1998;33:441-7

Perez-Ayuso RM, Arroyo V, Planas R, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Gastroenterology 1983;84:961-8

Runyon BA. Care of patients with ascites. N Engl J Med1994;330:337-42

Sungaila I, Bartle WR, Walker SE, et al. Spironolactone pharmacokinetics and pharmacodynamics in patients with cirrhotic ascites. Gastroenterology 1992;102:1680-5

Evidence Level: II

Weight reduction should not exceed 1 kg/day?
This advice is based on a study (Shear, 1970) showing that ascitic fluid absorption during pharmacologic diuresis is relatively slow and that rates of mobilisation of fluid from ascitic and nonascitic compartments are different. The authors suggested that weight loss should be limited to 200-300 g/day in patients with no oedema and to 1 kg/day in patients with oedema, with the aim of avoiding adverse effects of too-rapid diuresis (e.g. hyponatraemia, hyperkalaemia or hypochloraemia). A later study of 14 patients with chronic liver disease (Pockros, 1986) found that patients with oedema as well as ascites could tolerate weight loss of >2 kg/day without adverse effects.
Subsequent reviews of the subject have either supported the original advice given by Shear (McGuire, 1998) or the later findings of Pockros (Habeeb, 1997).

Habeeb KS, Herrera JL. Management of ascites: paracentesis as a guide. Postgrad Med 1997;101(1):191-200

McGuire BM, Bloomer JR. Complications of cirrhosis: why they occur and what to do about them. Postgrad Med 1998;103(2):209-24

Pockros PJ, Reynolds TB. Rapid diuresis in patients with ascites from chronic liver disease: the importance of peripheral edema. Gastroenterology 1986;90:1827-33

Shear L, Ching S, Gabuzda GJ. Compartmentalization of ascites and edema in patients with hepatic cirrhosis. N Engl J Med 1970;282:1391-6

Evidence Level: IV

Replace drained ascitic fluid with IV albumin?
A randomised comparative study (Gines, 1988) has shown that the use of albumin as an accompaniment to large-volume paracentesis is associated with a reduction in renal and electrolyte complications. 105 patients with tense ascites were divided into 2 groups: 52 were treated with paracentesis (4-6 L/day until disappearance of ascites) plus intravenous albumin (40 g after each tap) and 53 with paracentesis without albumin. 11 patients from the non-albumin group developed renal impairment or severe hyponatraemia, compared with 1 from the albumin group. No difference in mortality or serious morbidity was observed however, and some authors have suggested that, in view of the high cost of albumin, plasma expansion may not be necessary if <= 5 L of fluid is removed (Peltekian, 1997; McGuire, 1998).

Gines P, Tito L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94:1493-1502

McGuire BM, Bloomer JR. Complications of cirrhosis: why they occur and what to do about them. Postgrad Med 1998;103(2):209-24

Peltekian KM, Wong F, Liu PP, et al. Cardiovascular, renal, and neurohumoral responses to single large-volume paracentesis in patients with cirrhosis and diuretic-resistant ascites. Am J Gastroenterol 1997;92:394-9

Evidence Level: III

Mannitol (IV infusion 20%) is appropriate for cerebral oedema?
Osmotherapy with mannitol (1g/kg body weight in a 20% IV infusion) is the mainstay of treatment of intracranial hypertension in acute liver failure (Bernal, 1999; Neuberger, 1999). A randomised controlled trial (Canalese, 1982) compared mannitol (in the dose mentioned above) with dexamethasone in 44 patients whose intracranial pressure rose above 30 mm Hg for more than 5 mins, or (in the absence of ICP monitoring) in whom clinical signs of cerebral oedema appeared. Mannitol treatment increased overall survival from 6% to 47% (and resolved 83% of episodes of cerebral oedema), whereas dexamethasone treatment had no effect.
Caution must be exercised in patients who have or who are developing renal failure (Gill, 2001).

Bernal W, Wendon J. Acute liver failure: clinical features and management. Europ J Gastroenterol Hepatol 1999;11:977-84

Canalese J, Gimson AE, Davis C, et al. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. Gut 1982;23:625-9

http://gut.bmj.com/content/23/7/625.long

Gill RQ, Sterling RK. Acute liver failure. J Clin Gastroenterol 2001;33:191-8

Neuberger JM. Acute liver failure. Europ J Gastroenterol Hepatol 1999;11:943-7

Evidence Level: II

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