Hepatic encephalopathy in adults: Treatment

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INTRODUCTION

Hepatic encephalopathy or portal-systemic encephalopathy represents a reversible impairment of neuropsychiatric function associated with impaired hepatic function. Despite the frequency of the condition, we lack a clear understanding of its pathogenesis. Nevertheless, decades of experience have suggested that an increase in ammonia concentration is implicated and that there may be a role for inhibitory neurotransmission through gamma-aminobutyric acid (GABA) receptors in the central nervous system and changes in central neurotransmitters and circulating amino acids. (See "Hepatic encephalopathy: Pathogenesis".)

Available therapies for hepatic encephalopathy are based on these hypotheses (table 1). Some treatments are based on clinical observations, some on extrapolation of experimental data obtained in animal models of hepatic encephalopathy, and a smaller number on randomized trials. However, there are a number of problems that interfere with the interpretation of data from these studies:

- A common problem is the variety of clinical conditions that are summarized under the term "hepatic encephalopathy." The clinical features of hepatic encephalopathy include a wide range of neuropsychiatric symptoms ranging from minor, not readily discernible signs of altered brain function (minimal hepatic encephalopathy), to overt psychiatric and/or neurologic symptoms, to deep coma. As a result, the methods to quantify treatment effects and endpoints are highly variable. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis".)

- It is not known if data regarding treatment in patients with overt hepatic encephalopathy can be extrapolated to minimal hepatic encephalopathy and vice versa. However, many studies included patients both with overt and minimal hepatic encephalopathy.

- Another important variable is the treatment of control groups. Very few studies use a placebo; in most cases, the new drug was compared with "standard treatment" (which by itself may be highly effective) or specifically to lactulose.

- The sample size of most published studies was small.

This topic will review the management of hepatic encephalopathy in patients with chronic liver disease. The pathogenesis, clinical manifestations, and diagnosis of hepatic encephalopathy and the approach to patients with hepatic encephalopathy in the setting of acute liver failure are discussed elsewhere. (See "Hepatic encephalopathy: Pathogenesis" and "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis" and "Acute liver failure in adults: Management and prognosis", section on 'Hepatic encephalopathy'.)

The management of hepatic encephalopathy has also been addressed in a 2014 joint guideline from the American Association for the Study of Liver Diseases and the European Association for the Study of Liver Diseases. The discussion that follows is consistent with this guideline [1].

MANAGEMENT OVERVIEW

Overt hepatic encephalopathy — Patients with overt hepatic encephalopathy have clinically apparent impairments in cognitive and neuromuscular function. Treatment includes determining the appropriate setting for care, correcting any predisposing conditions, and lowering blood ammonia levels with medications such as lactulose, lactitol, or rifaximin. Restricting dietary protein is not recommended for the majority of patients.

The severity of overt hepatic encephalopathy is graded from I to IV based on the clinical manifestations (table 2 and figure 1). (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Clinical manifestations'.):

- Grade I: Changes in behavior, mild confusion, slurred speech, disordered sleep
- Grade II: Lethargy, moderate confusion
- Grade III: Marked confusion (stupor), incoherent speech, sleeping but arousable
- Grade IV: Coma, unresponsive to pain

Treatment will vary depending on the severity of a patient's hepatic encephalopathy. An elevated serum ammonia level in the absence of clinical signs of hepatic encephalopathy is not

an indication for treatment. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Ammonia'.)

Patient triage — Patients with mild hepatic encephalopathy (grade I) may be managed as outpatients, provided that caregivers are available to look for signs of worsening hepatic encephalopathy and to bring the patient to the hospital if needed. Whether to admit a patient with grade II encephalopathy to the hospital will depend on the degree of lethargy and confusion. If there is any concern that a patient may not be able to adhere to treatment or if caregivers are not available who can monitor the patient, the patient should be admitted to the hospital for care. Patients with more severe hepatic encephalopathy (grades III to IV) require hospital admission for treatment, typically to an intensive care unit. In addition, consideration should be given to intubating such patients for airway protection. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Categorization and grading'.)

General supportive care — General supportive care for patients with hepatic encephalopathy includes providing appropriate nutritional support, avoiding dehydration and electrolyte abnormalities, and providing a safe environment. Precautions to prevent falls should be instituted for patients who are disoriented.

Patients hospitalized with hepatic encephalopathy may be agitated. Agitation often resolves with treatment of the hepatic encephalopathy; however, patients may represent a hazard to themselves and their caregivers until treatment takes effect. Management may include judicious use of restraints, which may be a safer option than pharmacologic treatment, since patients with advanced liver disease and hepatic encephalopathy may be particularly vulnerable to oversedation with medications. Should medications be required, haloperidol is a safer option than benzodiazepines based mainly on clinical experience and some limited data [2]. Patients with advanced cirrhosis may be particularly sensitive to benzodiazepines because of an increased concentration of benzodiazepine receptor ligands in the brain. (See 'Flumazenil' below.)

Nutritional support — Nutritional support should include maintaining an energy intake of 35 to 40 kcal/kg/day, with a protein intake of 1.2 to 1.5 g/kg/day. Patients with cirrhosis are often malnourished and protein restrictions are associated with increased mortality, so patients with hepatic encephalopathy should generally not have their protein intake restricted [3-5]. Patients with mild to moderate hepatic encephalopathy can typically take nutrition orally. Patients with severe hepatic encephalopathy usually do not receive oral nutrition. As soon as they improve, a standard diet can be given. Patients should be instructed to eat small meals throughout the day with a late-night snack of complex carbohydrates because fasting results in the production of

glucose from amino acids, with resultant ammonia production [6]. (See "Evaluating nutritional status in adults with cirrhosis".)

In patients whose symptoms worsen with protein intake, substitution of proteins from fish, milk, or meat with vegetable proteins may improve nitrogen balance and mental status [7]. Another alternative for patients intolerant to protein is the addition of branched-chain amino acids (BCAA) to a low protein diet. BCAA supplementation is indicated only in severely protein-intolerant patients. As a general rule, only patients who have had a transjugular intrahepatic portosystemic shunt or surgical portosystemic shunt have hepatic encephalopathy severe enough to warrant use of vegetable protein or protein restriction with BCAA supplementation. (See 'Branched-chain amino acids' below.)

Acute therapy — The initial management of acute hepatic encephalopathy in patients with chronic liver disease involves two steps:

- Identification and correction of precipitating causes
- Measures to lower the blood ammonia concentration

Correction of precipitating causes — The first step in the treatment of hepatic encephalopathy is the identification and correction of precipitating causes. Treatment of precipitating causes combined with standard therapy is typically associated with a prompt improvement in mental status and hepatic encephalopathy.

Careful evaluation should be performed to determine if any of the following are present (table 3) (see "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Evaluation for precipitating causes'):

- Gastrointestinal bleeding
- Infection (including spontaneous bacterial peritonitis and urinary tract infections)
- Hypokalemia and/or metabolic alkalosis
- Renal failure
- Hypovolemia
- Hypoxia
- Sedative or benzodiazepine use
- Hypoglycemia
- Constipation
- Rarely, hepatocellular carcinoma and/or vascular occlusion (hepatic vein or portal vein thrombosis)

When possible, these precipitating causes should be treated.

Lower blood ammonia — The second step in the treatment of hepatic encephalopathy is initiation of measures to lower blood ammonia concentrations (whether or not the values are frankly elevated) with medications such as lactulose, lactitol, or rifaximin.

It is important to note that an elevated serum ammonia level in the absence of clinical signs of hepatic encephalopathy is not an indication for ammonia-lowering therapy. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Ammonia'.)

Correction of hypokalemia is also an essential component of therapy since hypokalemia increases renal ammonia production. However, dietary protein restriction is generally not recommended. (See 'Commonly used treatments' below and 'Nutritional support' above.)

Drug therapy is the mainstay of treatment to lower the blood ammonia concentration. Our approach to drug therapy is as follows (algorithm 1):

- We suggest initiating drug therapy for acute hepatic encephalopathy with lactulose or lactitol. Lactulose and lactitol act through a variety of mechanisms that lead to decreased absorption of ammonia from the gastrointestinal tract. The dose of lactulose (30 to 45 mL [20 to 30 grams] orally two to four times per day) should be titrated to achieve two to three soft stools per day. An equivalent dose of lactitol is approximately 30 to 60 grams (powder), diluted according to the label (eg, in 100 mL of water), given orally in two to four divided doses per day. Lactulose or lactitol enemas can be given if the patient cannot take a nonabsorbable disaccharide orally. We do not administer therapy by nasogastric tube because of the risk of aspiration. (See 'Lactulose and lactitol' below.)

  Ornithine-aspartate, which stimulates the metabolism of ammonia, is an alternative for the treatment of hepatic encephalopathy, but it is not available in the United States. (See 'L-ornithine-L-aspartate' below.)

- For patients without improvement in mental status within 48 hours or who cannot take lactulose or lactitol, we suggest treatment with rifaximin. The dose of rifaximin is 550 mg orally two times daily or 400 mg orally three times daily. Data comparing dosing regimens are lacking, and we have not observed any differences in efficacy based on dose. The safety and tolerability of rifaximin has been demonstrated for up to 24 months [8].

  As a general rule, antibiotics are added to, rather than substituted for, lactulose or lactitol. (See 'Oral antibiotics' below.)

  If a condition that precipitated hepatic encephalopathy (eg, hypokalemia) has resolved and there has been no hepatic encephalopathy recurrence in three months, the rifaximin

can be discontinued [9-11].

Neomycin has been used as a second-line therapy in patients who have not responded to disaccharides, but it has not been shown to be efficacious in randomized trials and can be associated with ototoxicity and nephrotoxicity. We reserve neomycin for patients who are unable to take or cannot get insurance coverage for rifaximin. Various doses have been used, but we generally use 1 gram twice daily or 500 mg three times a day. Other antibiotics that can be used include vancomycin and metronidazole.

Other alternatives for patients who are refractory to conventional therapy include L-ornithine-L aspartate and branched-chain amino acids. (See 'L-ornithine-L-aspartate' below and 'Branched-chain amino acids' below.)

Chronic therapy — In patients with recurrent encephalopathy, we suggest continual administration of lactulose or lactitol. The dose of lactulose (30 to 45 mL [20 to 30 grams] orally two to four times per day) or lactitol (30 to 60 grams [powder] diluted according to the label [eg, in 100 mL water], given orally in two to four divided doses per day) should be titrated to achieve two to three soft stools per day. If needed (eg, if hepatic encephalopathy is not adequately treated or recurs despite lactulose or lactitol), rifaximin can be added to the regimen. (See 'Lactulose and lactitol' below and 'Oral antibiotics' below.)

As with the acute treatment of hepatic encephalopathy, patients receiving chronic therapy should generally not have their protein intake restricted. (See 'Nutritional support' above.)

If the precipitating factors that were responsible for the recurrent hepatic encephalopathy are controlled, prophylactic therapy may be discontinued. It should only be given if necessary.

Medication adherence — Adherence to the lactulose regimen is typically very low. In our experience, many patients do not adhere to therapy without support from a caregiver. Hepatic encephalopathy related to medication nonadherence is a common indication for hospitalization among patients with cirrhosis [12]. Although lactulose is the first-line agent for treating hepatic encephalopathy, polyethylene glycol (PEG) solution is a reasonable alternative, with the goal of two to three soft bowel movements per day. This author has found that adherence to therapy is better with PEG solution than with lactulose. (See 'Polyethylene glycol' below.)

Minimal hepatic encephalopathy — Compared with patients who have cirrhosis but do not have minimal hepatic encephalopathy, patients with minimal hepatic encephalopathy appear be at increased risk for developing overt hepatic encephalopathy, requiring hospitalization, requiring liver transplantation, or dying [13]. However, data are limited on the value of treatment in these patients [14].

Patients with minimal hepatic encephalopathy may benefit from treatment with lactulose or lactitol, but the decision to treat should be individualized based on the results of psychometric testing and the degree to which the encephalopathy has an impact on quality of life [1]. We typically reserve treatment with lactulose or lactitol for patients with minimal hepatic encephalopathy who have impaired quality of life attributable to the minimal hepatic encephalopathy.

An elevated serum ammonia level in the absence of clinical signs of hepatic encephalopathy is not an indication for treatment. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Diagnosis' and 'Use in minimal hepatic encephalopathy' below.)

Nutritional support — Patients with cirrhosis and minimal hepatic encephalopathy are advised to implement oral nutritional therapy. In a trial that compared a daily diet of 30 to 35 kcal/kg and 1.0 to 1.5 g vegetable protein/kg with no dietary intervention in 120 patients with minimal hepatic encephalopathy, the rate of reversal of minimal hepatic encephalopathy was greater in those receiving nutritional therapy (71 versus 23 percent) [15]. In addition, overt hepatic encephalopathy developed in fewer patients in the nutritional therapy group (10 versus 22 percent). Minimal hepatic encephalopathy was diagnosed using the psychometric hepatic encephalopathy score, which is discussed separately.

SPECIFIC TREATMENTS

Commonly used treatments — Commonly used treatments for hepatic encephalopathy aim to reduce ammonia production and absorption. This is accomplished by correcting hypokalemia, giving synthetic disaccharides (such as lactulose) and/or antibiotics, and favoring colonization with non-urease-producing bacteria.

The gastrointestinal tract is the primary source of ammonia, which enters the circulation via the portal vein. Ammonia is produced by enterocytes from glutamine and by colonic bacterial catabolism of nitrogenous sources, such as ingested protein and secreted urea. A healthy liver clears almost all of the portal vein ammonia, converting it into glutamine and preventing its entry into the systemic circulation. Elevations of ammonia are detected in 60 to 80 percent of patients with hepatic encephalopathy, and therapy aimed at reduction of the circulating ammonia level usually results in improvement in mental status and resolution of encephalopathy. However, an elevated serum ammonia level in the absence of clinical signs of hepatic encephalopathy is not an indication for treatment. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Ammonia' and "Hepatic encephalopathy: Pathogenesis".)

Correct hypokalemia — Correction of hypokalemia, if present, is an essential component of therapy for hepatic encephalopathy, since hypokalemia increases renal ammonia production. The often concurrent metabolic alkalosis may contribute to hepatic encephalopathy by promoting ammonia entry into the brain by favoring the conversion of ammonium (NH_4+), a charged particle that cannot cross the blood-brain barrier, into ammonia (NH_3), a neutral particle that can [16]. (See "Hypokalemia-induced kidney dysfunction", section on 'Increased ammonia production'.)

Lactulose and lactitol — Lactulose and lactitol are synthetic disaccharides that are a mainstay of therapy of overt hepatic encephalopathy, albeit there is limited evidence from well-designed randomized trials showing their efficacy. The available data suggest that approximately 70 to 80 percent of patients with hepatic encephalopathy improve on lactulose treatment [17-19]. Lactulose is widely available, but lactitol is not available in some countries, including the United States.

The dose of medication should be titrated to achieve two to three soft stools per day. (See 'Acute therapy' above and 'Chronic therapy' above.)

Treatment is usually well tolerated, and the principal side effects include abdominal cramping, diarrhea, and flatulence. Lactulose and lactitol may also be given as enemas in patients who are unable to take them orally (refer to Lexicomp drug database for disaccharide enema dosing and administration).

Mechanism of action — Treatment with lactulose or lactitol is based on the absence of a specific disaccharidase on the microvillus membrane of enterocytes in the human small bowel, thereby permitting entry of the disaccharides into the colon. In the colon, lactulose (beta-galactosidofructose) and lactitol (beta-galactosidosorbitol) are catabolized by the bacterial flora, resulting in an acidic pH. The reduction in pH favors the formation of the nonabsorbable NH_4+ from NH_3, trapping NH_4+ in the colon and thus reducing plasma ammonia concentrations.

Other effects that may contribute to the clinical effectiveness of lactulose and lactitol include [17]:

- Increased incorporation of ammonia by bacteria for synthesis of nitrogenous compounds.
- Modification of colonic flora, resulting in displacement of urease-producing bacteria with non-urease-producing *Lactobacillus* [20].
- Cathartic effects of a hyperosmolar load in the colon that improves gastrointestinal transit, allowing less time for ammonia absorption.
- Increased fecal nitrogen excretion (up to fourfold) due to the increase in stool volume [21].

- Reduced formation of potentially toxic short-chain fatty acids (eg, propionate, butyrate, valerate) [22].

Efficacy — A systematic review found that the use of lactulose or lactitol was more effective than placebo in improving hepatic encephalopathy (relative risk of no improvement 0.6, 95% CI 0.5 to 0.8) but did not improve survival [23]. However, the benefit on encephalopathy no longer reached statistical significance when the analysis was confined to studies with the highest methodologic quality. The authors also found that antibiotics appeared to be more effective than lactulose or lactitol. (See 'Oral antibiotics' below.)

At least two meta-analyses suggest that lactitol is at least as effective as lactulose, is more palatable, and may have fewer side effects [24-26]. In patients with lactase deficiency, non-digested lactose has most of the same effects as the synthetic disaccharides and is much less expensive [27].

Lactulose has also been studied for the prevention of recurrent hepatic encephalopathy. In a randomized trial with 140 patients who had recovered from hepatic encephalopathy, patients assigned to lactulose (30 to 60 mL in two to three divided doses so that patients passed two to three soft stools per day) had significantly fewer episodes of recurrent overt hepatic encephalopathy than patients who received placebo during 14 months of follow-up (20 versus 47 percent) [28]. However, there were no significant differences in deaths or rates of readmission for causes other than hepatic encephalopathy.

Disaccharide enemas are also effective for removing ammoniagenic substrates from the colon. A randomized trial that included 20 patients with hepatic encephalopathy suggested that 1 to 3 L of a 20 percent lactose or lactitol solution given as an enema was more effective than tap water enemas [29]. A possible explanation for this finding is that colonic acidification rather than bowel cleansing was the therapeutic mechanism.

It is unclear whether the route of administration of nonabsorbable disaccharides affects their efficacy. However, the convenience of oral administration generally makes it the preferred route.

Use in minimal hepatic encephalopathy — Most trials of disaccharides included patients with overt hepatic encephalopathy. However, the use of nonabsorbable disaccharides may also benefit patients with minimal hepatic encephalopathy [14,30]. One trial that showed this included 61 patients with minimal hepatic encephalopathy [31]. Treatment with lactulose was associated with improvement in health-related quality of life and cognitive function. However, other trials have failed to show a benefit of treating patients with minimal hepatic

encephalopathy. As a result, whether treatment should be routine in patients with minimal hepatic encephalopathy is unclear. (See 'Minimal hepatic encephalopathy' above.)

Oral antibiotics — Nonabsorbable antibiotics are also effective for treating acute or preventing recurrent hepatic encephalopathy. Rifaximin is used most often. (See 'Overt hepatic encephalopathy' above.)

For treating acute hepatic encephalopathy or to prevent recurrent episodes, antibiotics are typically added to (rather than substituted for) lactulose or lactitol. However, all antibiotics cause alterations in gut flora and some are substantially more costly than nonabsorbable disaccharides. As a result, they may be best suited for patients who cannot tolerate or do not respond sufficiently to disaccharides.

A meta-analysis of five randomized trials of rifaximin for hepatic encephalopathy found that it had similar efficacy to nonabsorbable disaccharides for acute and chronic hepatic encephalopathy, but was perhaps somewhat better tolerated [32]. A randomized trial published after the meta-analysis found that during six months of follow-up, rifaximin was more effective than a placebo in preventing recurrent episodes of hepatic encephalopathy in patients with cirrhosis who had a documented history of recurrent hepatic encephalopathy and were in remission at the start of the trial [9]. Eighty-two patients in the placebo group of the phase 3 trial joined a 24-month open-label maintenance (OLM) study [33]. Thirty-nine of the patients (48 percent) had experienced an episode of hepatic encephalopathy during the original randomized trial compared with 14 patients (17 percent) during the OLM study. Other randomized trials found that rifaximin improved quality of life [34,35] and performance on a simulated driving test in patients with minimal hepatic encephalopathy [36].

Another randomized trial compared the combination of rifaximin and lactulose with lactulose alone in 120 patients hospitalized with overt hepatic encephalopathy [37]. Patients were followed until they were discharged from the hospital or died. Patients who received rifaximin and lactulose were more likely than those who received lactulose alone to have complete resolution of their hepatic encephalopathy (76 versus 44 percent) and lower mortality (24 versus 49 percent). A meta-analysis of 19 trials showed that rifaximin has a beneficial effect on hepatic encephalopathy and may reduce mortality [38].

Rifaximin plays a role in gut barrier repair, and this function may ameliorate bacterial translocation and systemic endotoxemia in patients with cirrhosis [39].

Neomycin had been used for many years to treat hepatic encephalopathy, but studies reached variable conclusions regarding its efficacy, and there is concern over its association with ototoxicity and nephrotoxicity if used long-term. An early study found neomycin to be as

effective as lactulose in 33 patients [18], and a subsequent randomized trial that compared neomycin with rifaximin in 49 patients with cirrhosis found that both treatments were similarly effective at reducing the neuropsychiatric signs of hepatic encephalopathy and blood ammonia levels [40]. On the other hand, a randomized trial of 39 patients comparing neomycin at a dose of 6 g per day with placebo reported no difference in outcomes between the two treatment groups [41].

Other antibiotics, such as metronidazole and oral vancomycin, were effective for treating hepatic encephalopathy in limited clinical trials and are not associated with the same toxicities as neomycin [42,43]. However, metronidazole is associated with neurotoxicity and there are concerns about bacterial resistance in patients receiving vancomycin. As a result, neither is used commonly.

L-ornithine-L-aspartate — Oral L-ornithine-L-aspartate (LOLA) is frequently given to patients with hepatic encephalopathy outside of the United States [44]. Treatment with L-ornithine-L-aspartate has shown benefit compared with placebo, although trials comparing LOLA with standard therapy (ie, lactulose or lactitol) are needed [44-47]. LOLA improves health-related quality and is well tolerated [48].

In a meta-analysis of four trials, patients with overt hepatic encephalopathy who received L-ornithine-L-aspartate were more likely to improve clinically compared with those receiving placebo (OR 3.71, 95% CI 1.98-6.98) [46].

In trial of 40 patients who underwent transjugular intrahepatic portosystemic shunt placement, prophylactic use of LOLA infusion was safe and effective in reducing post-prandial increases in venous ammonia concentration [49]. (See "Transjugular intrahepatic portosystemic shunts: Postprocedure care and complications", section on 'Issues related to portosystemic shunting'.)

L-ornithine-L-aspartate does not appear to be effective for patients with hepatic encephalopathy in the setting of acute liver failure [50]. (See "Acute liver failure in adults: Management and prognosis", section on 'Hepatic encephalopathy'.)

L-ornithine-L-aspartate lowers plasma ammonia concentrations by enhancing the metabolism of ammonia to glutamine. Ammonia is removed from the body by formation of urea in periportal hepatocytes and/or by synthesis of glutamine from glutamate in perivenous hepatocytes. In patients with cirrhosis, the activities of carbamyl phosphate synthetase and of glutamine synthetase (the key enzymes for urea and glutamine synthesis) are impaired and the glutaminase flux is increased in a compensatory fashion, resulting in hyperammonemia. Ornithine serves both as an activator of carbamyl phosphate synthetase and ornithine-carbamyl transferase in periportal hepatocytes and as a substrate for ureagenesis. Ornithine

(via alpha-ketoglutarate) and aspartate increase ammonia removal by these cells via stimulation of glutamine synthesis.

Branched-chain amino acids — It has been suggested that increases in the ratio of plasma aromatic amino acids (AAA) to branched-chain amino acids (BCAA) as a consequence of hepatic insufficiency could contribute to encephalopathy. The altered ratio could then increase brain levels of aromatic amino acid precursors for monoamine neurotransmitters and contribute to altered neuronal excitability. As a result, a number of studies have evaluated the effects of the provision of BCAA, given either intravenously or orally. The efficacy of BCAAs was examined in a meta-analysis of 16 trials with 827 participants with hepatic encephalopathy [51]. Patients in the control groups received placebo/no intervention (2 trials), dietary interventions (10 trials), lactulose (2 trials), or neomycin (2 trials). Treatment with BCAAs did not result in a benefit with regard to mortality (relative risk [RR] 0.8, 95% CI 0.7-1.1), but it did have a beneficial effect on hepatic encephalopathy (defined as improvement in the manifestations of hepatic encephalopathy; RR 0.7, 95% CI 0.6-0.9).

- **BCAA infusions** – Several randomized trials have evaluated the use of parenteral nutrition with modified amino acid solutions with a high content of BCAA and a low content of AAA [52,53]. A meta-analysis suggested that mental recovery was consistently more rapid in patients who received BCAA [53]. Three studies suggested lower mortality in BCAA-treated patients, while two others suggested that BCAA-treatment increased mortality. The studies included in this meta-analysis differed with respect to the amino acid solutions used, the study protocols, patient selection, and the duration of treatment, and therefore cannot be compared directly. In addition, all studies were of relatively short duration. We do not presently consider infusions of modified amino acid solutions or BCAA as standard treatment of patients with hepatic encephalopathy.

- **Oral BCAA supplements** – The benefit of oral BCAA is unclear. Significant improvement in chronic hepatic encephalopathy has been described in some trials. As an example, a randomized trial with 64 patients found that a low-protein diet supplemented with oral BCAA was more likely to improve mental performance at three months than supplementation with casein (80 versus 35 percent) [54]. In addition, some patients who did not improve on casein rapidly improved when switched to BCAA. Another trial evaluated 37 hospitalized patients with cirrhosis who were protein-intolerant [55]. The addition of BCAA to the diet enabled the daily protein intake to be increased to up to 80 g without worsening cerebral function; by comparison, many control patients (receiving casein as a protein source) deteriorated after increasing dietary protein intake. No benefit of BCAA supplementation was observed in protein-tolerant patients. A subsequent

randomized trial of 116 patients who had a prior episode of hepatic encephalopathy found no benefit of BCAA on recurrent encephalopathy, although supplementation appeared to improve minimal hepatic encephalopathy and muscle mass [56]. Based on these results, we believe that dietary BCAA supplementation is indicated only in severely protein-intolerant patients. (See 'Nutritional support' above.)

Modification of colonic flora (prebiotics and probiotics) — Probiotics are formulations of microorganisms that have beneficial properties for the host (see "Probiotics for gastrointestinal diseases", section on 'Mechanisms of benefit'). Prebiotics are substances that promote the growth of such organisms. Prebiotic and probiotic therapy appear to lower blood ammonia concentrations, possibly by favoring colonization with acid-resistant, non-urease producing bacteria [57]. The most commonly used prebiotic for the treatment of hepatic encephalopathy is lactulose, though it also acts by altering the colonic pH, improving gastrointestinal transit and increasing fecal nitrogen excretion. Fermentable fiber is another prebiotic that may promote the growth of beneficial bacteria. (See 'Mechanism of action' above.)

Most commercial probiotic products have been derived from food sources, especially cultured milk products. The list of such microorganisms continues to grow and includes strains of lactic acid bacilli (eg, *Lactobacillus* and *Bifidobacterium*), a nonpathogenic strain of *Escherichia coli* (eg, *E. coli* Nissle 1917), *Clostridium butyricum, Streptococcus salivarius*, and Saccharomyces boulardii (a nonpathogenic strain of yeast). The most efficacious species for hepatic encephalopathy appear to be *Lactobacilli* and *Bifidobacteria* [44].

Alteration of gut flora (either with prebiotics or with probiotics) has been associated with improvement in hepatic encephalopathy. A meta-analysis of 21 trials that included 1420 participants showed improved recovery compared with placebo or no treatment, but failed to show a benefit in clinically significant outcomes when probiotics were compared with lactulose [58]. However, probiotic groups had reduced plasma ammonia concentrations compared with the placebo/no intervention groups, but not when compared with lactulose groups. Additional studies are needed before probiotics can routinely be recommended for the treatment or prevention of hepatic encephalopathy.

Probiotics may prevent recurrent encephalopathy. Prevention of recurrent hepatic encephalopathy was investigated in an unblinded randomized trial. Two hundred and thirty-five patients who had recovered from hepatic encephalopathy were assigned to receive lactulose, VSL#3 (containing four species of lactobacilli and three of bifidobacteria and *Streptococcus thermophilus*) or no therapy [59]. Recurrent hepatic encephalopathy occurred in fewer patients who received lactulose or probiotics compared with no treatment (27 and 34 percent,

respectively, versus 57 percent). The difference in recurrence rates between those who received lactulose and those who received probiotics was not statistically significant.

Treatments that require more study — Several additional treatments for hepatic encephalopathy appear to be effective, but additional trials are needed before they can be routinely recommended.

Polyethylene glycol — Polyethylene glycol (PEG) solution is a cathartic that may help treat hepatic encephalopathy by increasing excretion of ammonia in the stool. PEG was compared with lactulose in a trial that included patients with cirrhosis who were admitted to the hospital with hepatic encephalopathy [60]. Patients were randomly assigned to receive four liters of PEG over four hours or lactulose (three or more doses of 20 to 30 g over 24 hours). After 24 hours, patients who received PEG had more improvement in their hepatic encephalopathy scoring algorithm (HESA) score compared with those who received lactulose (from a mean of 2.3 to 0.9 compared with 2.3 to 1.6). In addition, the median time to resolution of the hepatic encephalopathy was shorter with PEG (one versus two days).

PEG solution may be used for long-term therapy.

Acarbose — Acarbose (an inhibitor of alpha glycosidase that is approved for treatment of diabetes mellitus) inhibits the upper gastrointestinal enzymes (alpha-glucosidases) that convert carbohydrates into monosaccharides. It also promotes the proliferation of intestinal saccharolytic bacterial flora, while reducing proteolytic flora that produce mercaptans, benzodiazepine-like substances, and ammonia. This reduction in proteolytic flora theoretically could improve hepatic encephalopathy. This hypothesis appeared to be confirmed by a randomized crossover trial involving 107 patients with cirrhosis, diabetes mellitus, and grade I-II hepatic encephalopathy [61]. Treatment was associated with a significant reduction in blood ammonia levels and improvement in encephalopathy. (See "Alpha-glucosidase inhibitors for treatment of diabetes mellitus".)

Sodium benzoate — Sodium benzoate reduces ammonia levels by reacting with glycine to form hippurate, which is renally excreted. For each mole of benzoate used, one mole of waste nitrogen is excreted into the urine.

A randomized trial of 74 patients with acute hepatic encephalopathy found that treatment with sodium benzoate (5 gm twice daily) resulted in similar improvements in encephalopathy as lactulose [62]. The cost of lactulose was 30 times that of sodium benzoate. While this study is encouraging, we would not recommend sodium benzoate as first-line therapy until the results are confirmed in additional randomized trials, given the much broader experience with lactulose.

Flumazenil — While some patients with hepatic encephalopathy have short-term benefit from the benzodiazepine receptor antagonist flumazenil, it cannot be recommended as routine therapy. Flumazenil may be helpful, however, in patients who have received benzodiazepines. (See "Benzodiazepine poisoning and withdrawal".)

In a meta-analysis of nine trials including 824 patients with hepatic encephalopathy, more patients treated with flumazenil improved compared with patients given placebo (RR of failure to improve 0.75, 95% CI 0.71-0.80); however, follow-up duration was less than one day in most trials [63]. Although patients may respond to flumazenil within a few minutes after intravenous administration, the effect is transient and the majority of patients deteriorate within two to four hours [64-68]. In a meta-analysis of 11 trials including 842 patients, flumazenil had no effect on all-cause mortality [63].

The gamma-aminobutyric acid (GABA)-receptor complex appears to be a contributor to neuronal inhibition in hepatic encephalopathy. This complex, in the postsynaptic membrane, is the principal inhibitory network in the central nervous system. It consists of a GABA-binding site, a chloride channel, and barbiturate and benzodiazepine receptor sites. GABAergic transmission may interact with ammonia in the pathogenesis of hepatic encephalopathy [69]. Increases in transmission could be caused by increases in ligands for any of the three receptors. Since there is evidence for an increase in benzodiazepine receptor ligands in patients with hepatic encephalopathy, the effects of benzodiazepine receptor antagonists, such as flumazenil, have been studied [70,71]. (See "Hepatic encephalopathy: Pathogenesis".)

Zinc — Zinc has been suggested as having potential value in some patients with chronic or recurrent hepatic encephalopathy, but little evidence exists to document its effectiveness.

Zinc deficiency is common in patients with cirrhosis and in those with hepatic encephalopathy [72]. Zinc is contained in vesicles in the presynaptic terminals of some classes of neurons, the majority of which are a subclass of the glutamatergic neurons [73]. Stimulated zinc release may modulate ion channel function and neurotransmission [74]. Zinc may also enhance the hepatic conversion of amino acids into urea [75].

Little information is available on the clinical effects of zinc supplementation in overt hepatic encephalopathy. A patient has been described who exhibited a relationship between zinc deficiency and severe recurrent hepatic encephalopathy [76]. The study included a period in which zinc deficiency was artificially induced by oral histidine. An episode of overt encephalopathy occurred that was identical to earlier episodes and responded to oral zinc. Long-term zinc supplementation significantly improved severe recurrent hepatic encephalopathy that had been refractory to protein restriction, lactulose, and neomycin.

However, this anecdotal report has not been confirmed in larger studies. As an example, short-term zinc supplementation had no clinically significant effect in 15 patients with chronic hepatic encephalopathy studied in a randomized crossover trial [77]. As a result, we do not recommend zinc supplementation for treatment of hepatic encephalopathy.

Melatonin — One of the most frequently described symptoms of subclinical forms of hepatic encephalopathy is sleep disturbances or, more generally, alterations in the sleep/wake cycle. The alterations in the sleep/wake cycle may be disabling for some patients. Unsatisfactory sleep is also characteristic of patients with cirrhosis who do not have encephalopathy (48 percent of patients in one study [78]).

The abnormalities in sleep may be due in part to alterations in the 24-hour rhythm of the hormone melatonin, which is considered to be the output signal of the biological "clock." In one series of patients with cirrhosis, the onset of the rise in plasma concentrations of melatonin and occurrence of the melatonin peak during the night were delayed by hours [79]. Furthermore, plasma melatonin levels in patients with cirrhosis were significantly higher during daylight hours, a time when melatonin is normally very low or absent. (See "Pharmacotherapy for insomnia in adults", section on 'Melatonin'.)

These findings support the hypothesis that an alteration of circadian rhythmicity of melatonin is responsible for the disruption in the sleep/wake cycle frequently seen in cirrhosis. Melatonin can influence its own rhythm when administered at defined time points during the day, shifting the curve forward or backward [80]. Some authorities have tried orally administered melatonin in patients with cirrhosis who have an altered sleep/wake cycle. However, our clinical experience with this drug has not revealed a benefit in patients with cirrhosis. (See "Pharmacotherapy for insomnia in adults", section on 'Melatonin'.)

Ornithine phenylacetate — Ornithine phenylacetate is an ammonia scavenger that is being studied for treating hepatic encephalopathy [81-83]. In a trial including 231 hospitalized patients with cirrhosis and hepatic encephalopathy, there was no significant difference in time to clinical improvement for patients given ornithine phenylacetate plus standard care (eg, lactulose with or without rifaximin) versus standard care alone [81]. Treatment-related adverse events were not significantly different between the groups.

Experimental treatments — A number of experimental approaches are being evaluated in animal models for the treatment of hepatic encephalopathy. Few have received any testing in clinical trials.

- **L-Carnitine** – Carnitine is a metabolite in the degradation pathway of the essential amino acid lysine and is synthesized by oxidation of E-amino-trimethyl-lysine. It serves as a

carrier for short chain fatty acids across the mitochondrial membrane. Data in portacaval-shunted rats suggest that L-carnitine is protective against ammonia neurotoxicity [84,85].

The available clinical data are insufficient to assess the role of L-carnitine in human disease. In patients with cirrhosis who were subjected to a rectal ammonia overload test, intravenous L-carnitine supplementation improved psychometric tests significantly after 30 minutes, whereas circulating ammonia levels were not influenced [86]. However, the increase in plasma ammonia after rectal ammonia overload was significantly lower in treated patients with evidence of portal hypertension than in patients without evidence of portal hypertension.

Treatment with acetyl-L-carnitine supplementation has been tested in small trials of patients with hepatic encephalopathy [87]. One trial included 67 patients with minimal hepatic encephalopathy who were assigned to receive acetyl-L-carnitine supplementation or placebo [88]. Patients treated with acetyl-L-carnitine supplementation had more improvement in energy levels, general functioning, and well-being than those who received placebo.

- **Glutamatergic antagonists** – There is good evidence that the glutamatergic neurotransmitter system is involved in the pathogenesis of hepatic encephalopathy. The N-methyl-D-aspartate (NMDA) receptor is one of three known central glutamate receptors. NMDA overactivity has been observed in two different experimental rat models of encephalopathy. The administration of the NMDA receptor antagonist memantine resulted in a significant improvement in clinical grading and less slowing of electroencephalogram activity, smaller increases in cerebral spinal fluid glutamate concentrations, and lower intracranial pressure and brain water content than in untreated control rats [89]. (See "Hepatic encephalopathy: Pathogenesis", section on 'Glutamatergic neurotransmission'.)

- **Serotonin antagonists** – Accumulated neurochemical data in different animal models of fulminant hepatic failure and in humans with hepatic encephalopathy suggest that serotoninergic tone is increased in the brain in hepatic encephalopathy. The nonselective serotonin receptor antagonist methysergide had no effect in control rats, but it increased motor activity in rats with stage II to III hepatic encephalopathy in a dose-dependent manner; by contrast, the 5-HT2 receptor antagonist seganserin had no effect [90]. (See "Hepatic encephalopathy: Pathogenesis", section on 'Serotonin'.)

- **Opioid antagonists** – Plasma levels of methionine (Met)-enkephalin and beta-endorphin are elevated in patients and in experimental animals suffering from liver failure.

Administration of (+/-)-naltrexone, but not (+)-naloxone, significantly increased the motor activity of rats with stage III hepatic encephalopathy [91].

- **Embolization of large spontaneous portosystemic shunts** – Large spontaneous portosystemic shunts may contribute to hepatic encephalopathy [92,93]. In a retrospective study of 37 patients with large spontaneous portosystemic shunts who were treated with embolization, 22 (59 percent) were free of hepatic encephalopathy within 100 days of the procedure, and 18 (49 percent) remained hepatic encephalopathy-free over a mean follow-up of 697 days [92]. There did not appear to be an increase in de novo development or worsening of varices, portal hypertensive gastropathy, or ascites.

PROGNOSIS AFTER RECOVERY

Patients with overt hepatic encephalopathy may have persistent and cumulative neurologic deficits despite an apparent normalization of mental status after treatment [94,95]. In a study that summarized the results of two cohorts of patients with cirrhosis, for example, overt hepatic encephalopathy was associated with persistent deficits in working memory, response inhibition, and learning when assessed by psychometric testing [94]. The number of episodes of overt hepatic encephalopathy correlated with the severity of residual impairment.

CAPACITY TO DRIVE

Issues related to driving in patients with hepatic encephalopathy are discussed separately. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Capacity to drive'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cirrhosis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hepatic encephalopathy (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Overt hepatic encephalopathy**
  - **General principles** – Patients with overt hepatic encephalopathy have clinically apparent impairments in cognitive and neuromuscular function. Treatment includes determining the appropriate setting for care, correcting any precipitating conditions (table 3), and lowering ammonia production and absorption with medications such as lactulose, lactitol, or rifaximin (algorithm 1). Restricting dietary protein is not recommended for the majority of patients. (See 'Overt hepatic encephalopathy' above.)

    Patients with mild hepatic encephalopathy (grade I) may be managed as outpatients, provided caregivers are available to look for signs of worsening hepatic encephalopathy and to bring the patient to the hospital if needed. Whether to admit a patient with grade II encephalopathy to the hospital will depend on the degree of lethargy and confusion. If there is any concern that a patient may not be able to adhere to treatment or if caregivers are not available who can monitor the patient, the patient should be admitted to the hospital for care. Patients with more severe hepatic encephalopathy (grades III to IV) require hospital admission for treatment. (See 'Patient triage' above and "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Categorization and grading'.)

  - **Supportive measures** – General supportive care for patients with hepatic encephalopathy includes avoiding dehydration and electrolyte abnormalities, providing nutritional support, and providing a safe environment. Patients should **not** have their protein intake restricted unless they are severely protein-intolerant. Patients should be instructed to eat small meals throughout the day with a late-night snack of complex

carbohydrates. Precautions to prevent falls should be instituted for patients who are disoriented. (See 'General supportive care' above and 'Nutritional support' above.)

- **Drug therapy** – For patients with acute, overt hepatic encephalopathy, we suggest initial treatment with lactulose or lactitol (where available) rather than a nonabsorbable antibiotic (**Grade 2B**). This recommendation is based primarily on cost; for patients for whom cost is not an important consideration, initial treatment with rifaximin is a reasonable alternative. The dose of lactulose (30 to 45 mL [20 to 30 grams] orally two to four times per day) should be titrated to achieve two to three soft stools per day. An equivalent dose of lactitol is approximately 30 to 60 grams (powder), diluted according to the label (eg, in 100 mL of water), given orally in two to four divided doses per day. Lactulose or lactitol enemas can be given if the patient cannot take a nonabsorbable disaccharide orally. (See 'Lactulose and lactitol' above and 'Oral antibiotics' above.)

  For patients who have not improved within 48 hours of starting lactulose or lactitol or who cannot take lactulose or lactitol, we suggest rifaximin rather than an alternative nonabsorbable oral antibiotic (**Grade 2C**). The dose of rifaximin is 400 mg orally three times daily or 550 mg orally two times daily. As a general rule, antibiotics are added to, rather than substituted for, lactulose or lactitol. (See 'Oral antibiotics' above.)

  In patients with recurrent encephalopathy, we suggest daily administration of lactulose or lactitol rather than waiting for episodes of overt hepatic encephalopathy to develop to initiate treatment (**Grade 2B**). Rifaximin can be added to lactulose or lactitol if needed. Polyethylene glycol (PEG) solution is an alternative to using lactulose for patients who do not tolerate or will not use lactulose. (See 'Chronic therapy' above.)

- **Minimal hepatic encephalopathy**

  - Patients with minimal hepatic encephalopathy have signs and symptoms that are not clinically apparent, but can be detected with psychometric testing. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis", section on 'Clinical manifestations'.)

  - Whether to treat patients with minimal hepatic encephalopathy is unclear. For patients with minimal hepatic encephalopathy that is impacting quality of life, we suggest treating with lactulose or lactitol rather than not treating (**Grade 2C**). We do not give treatment to patients with minimal hepatic encephalopathy who do not have impaired quality of life attributable to the minimal hepatic encephalopathy. (See 'Minimal hepatic encephalopathy' above.)

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GRAPHICS

Efficacy of treatments of hepatic encephalopathy

Rationale	Controlled studies	
	vs lactulose	vs placebo
Ammonia hypothesis		
Decrease in ammoniagenic substrates		
Enemas with lactulose		+
Restriction of dietary protein intake		?
Inhibition of ammonia production		
Antibiotics		
Neomycin, paromomycin, metronidazole	=	ND
Rifaximin	=	+
Vancomycin	=/+	ND
Disaccharides		
Lactulose		?
Lactitol	=	ND
Lactose in lactase deficiency		+
Modification of colonic flora		
Lactobacillus SF 68	=	ND
Correction of hypokalemia	ND	ND
Metabolic ammonia removal		
Ornithine-aspartate		+
Benzoate	=	ND
False neurotransmitter hypothesis		
Branched chain amino acid supplementation		
Modified amino acid solutions (FO80 type)	=	±
"COMA" solutions	ND	ND
Dietary BCAA supplementation		+
Increased dopamine		
L-DOPA, bromocriptine		-

GABA hypothesis		
Flumazenil		+
Other		
Zinc		±

+: superior to control; =: equal to lactulose; -: no effect; ±: conflicting results; ND: not done.

Graphic 64629 Version 3.0

Grading system for hepatic encephalopathy

Grade	Mental status	Asterixis	EEG
I	Euphoria/depression	Yes/no	Usually normal
	Mild confusion		
	Slurred speech		
	Disordered sleep		
II	Lethargy	Yes	Abnormal
	Moderate confusion		
III	Marked confusion	Yes	Abnormal
	Incoherent		
	Sleeping but arousable		
IV	Coma	No	Abnormal

EEG: electroencephalogram.

Graphic 62922 Version 2.0

Clinical features of hepatic encephalopathy in adults

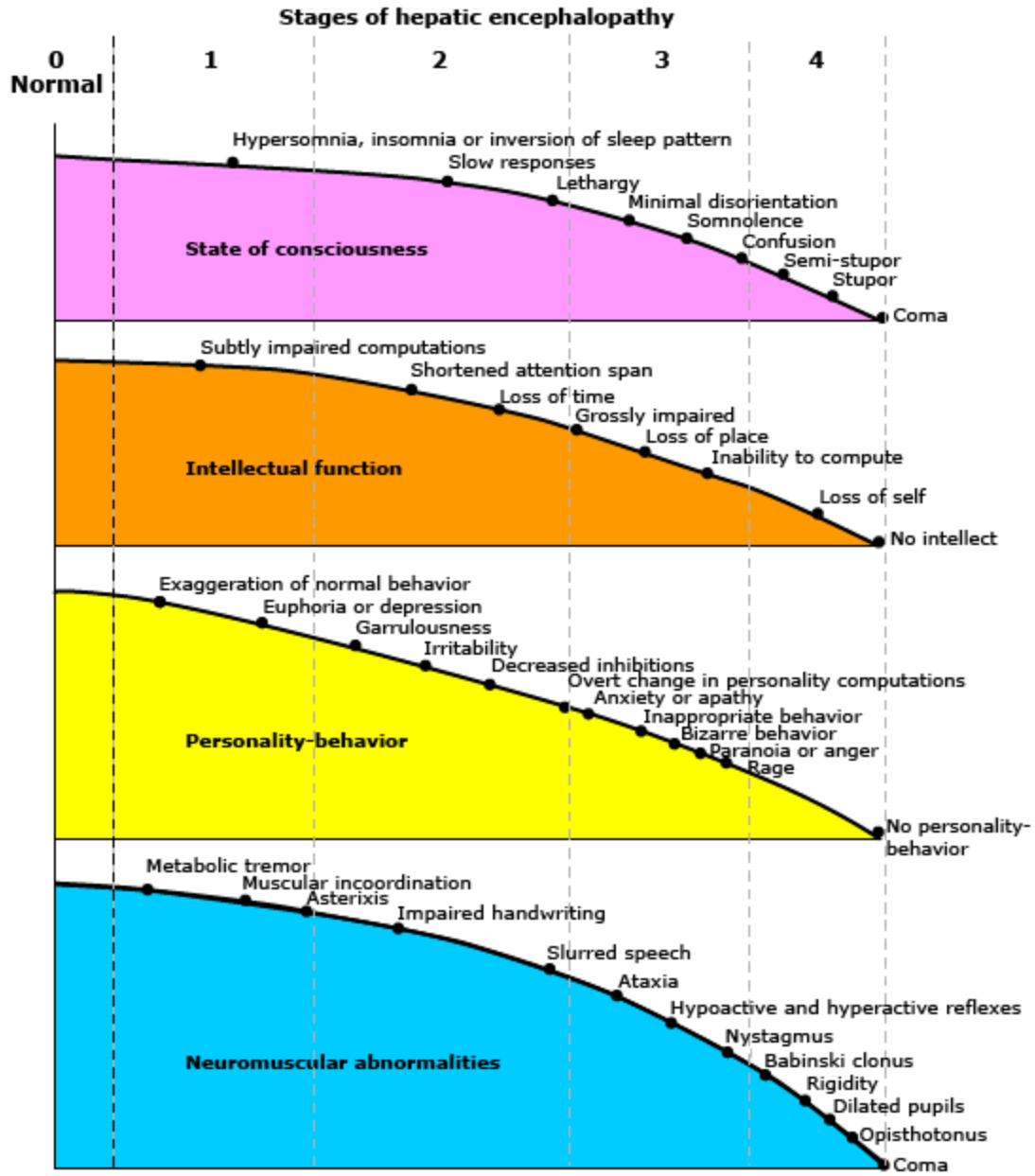


Diagram depicting the grade of hepatic encephalopathy in adults and the clinical features associated with advancing stages.

Data from: Conn HO, Lieberthal MM. The hepatic coma syndromes and lactulose. Lippincott Williams & Wilkins, Baltimore 1979.

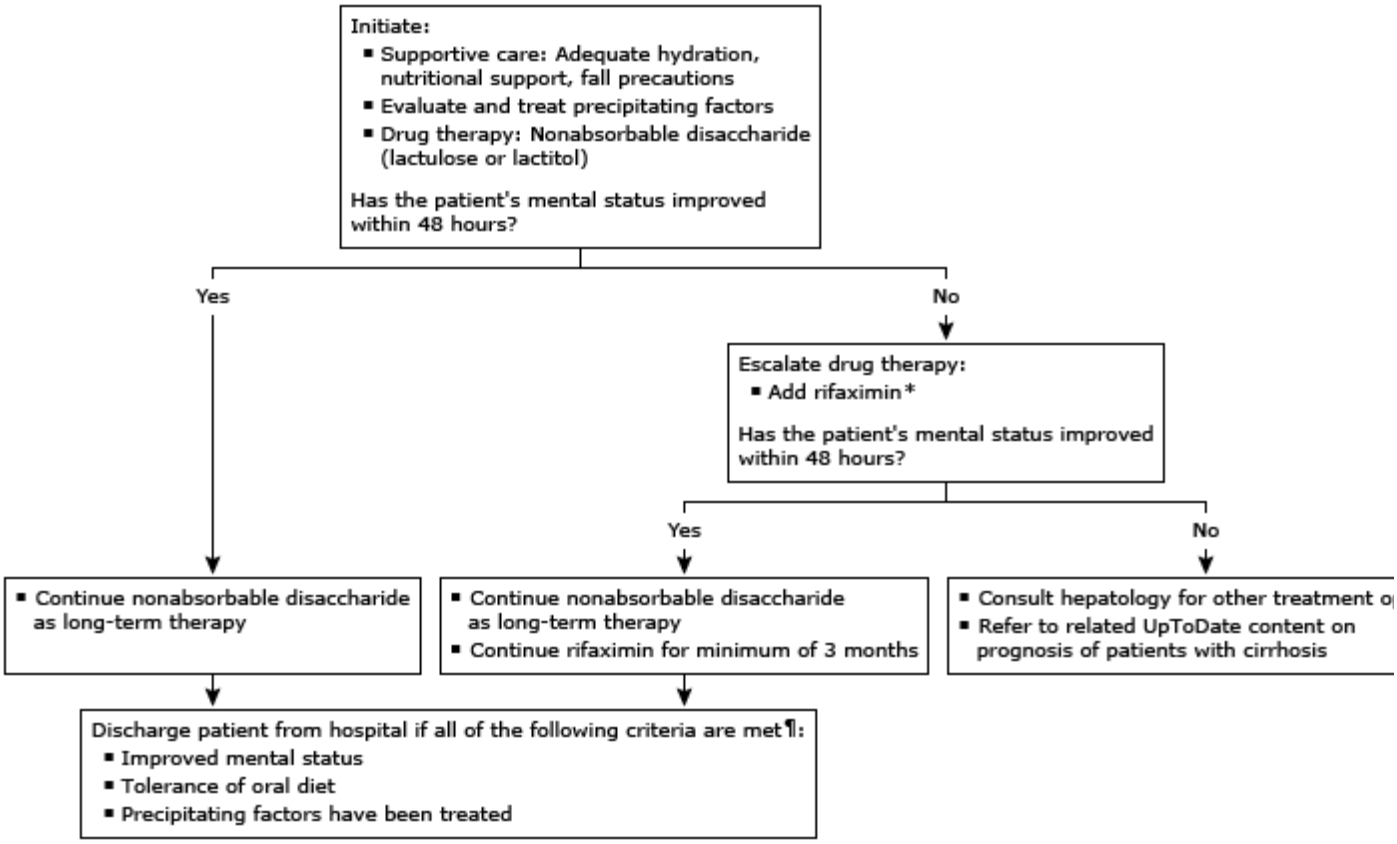
Graphic 70740 Version 6.0

Precipitants of hepatic encephalopathy in patients with cirrhosis

Drugs
Benzodiazepines
Nonbenzodiazepine hypnotics (eg, zolpidem)
Narcotics
Alcohol
Increased ammonia production, absorption or entry into the brain
Excess dietary intake of protein
Gastrointestinal bleeding
Infection
Electrolyte disturbances such as hypokalemia
Constipation
Metabolic alkalosis
Dehydration
Vomiting
Diarrhea
Hemorrhage
Diuretics
Large volume paracentesis
Portosystemic shunting
Radiographic or surgically placed shunts
Spontaneous shunts
Vascular occlusion
Hepatic vein thrombosis
Portal vein thrombosis
Primary hepatocellular carcinoma

Graphic 50440 Version 4.0

Inpatient management for adult patients with acute hepatic encephalopathy



Refer to UpToDate content on the management of hepatic encephalopathy for additional details.

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* For patients who are being treated with systemic antibiotics, rifaximin is not added to the treatment regim

¶ At the time of discharge, patients and their caregivers are provided with written instructions for dosing an

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Graphic 131713 Version 2.0

Contributor Disclosures

Bruce A Runyon, MD, FAASLD No relevant financial relationship(s) with ineligible companies to disclose. **Bruce A Runyon, MD, FAASLD** No relevant financial relationship(s) with ineligible companies to disclose. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

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