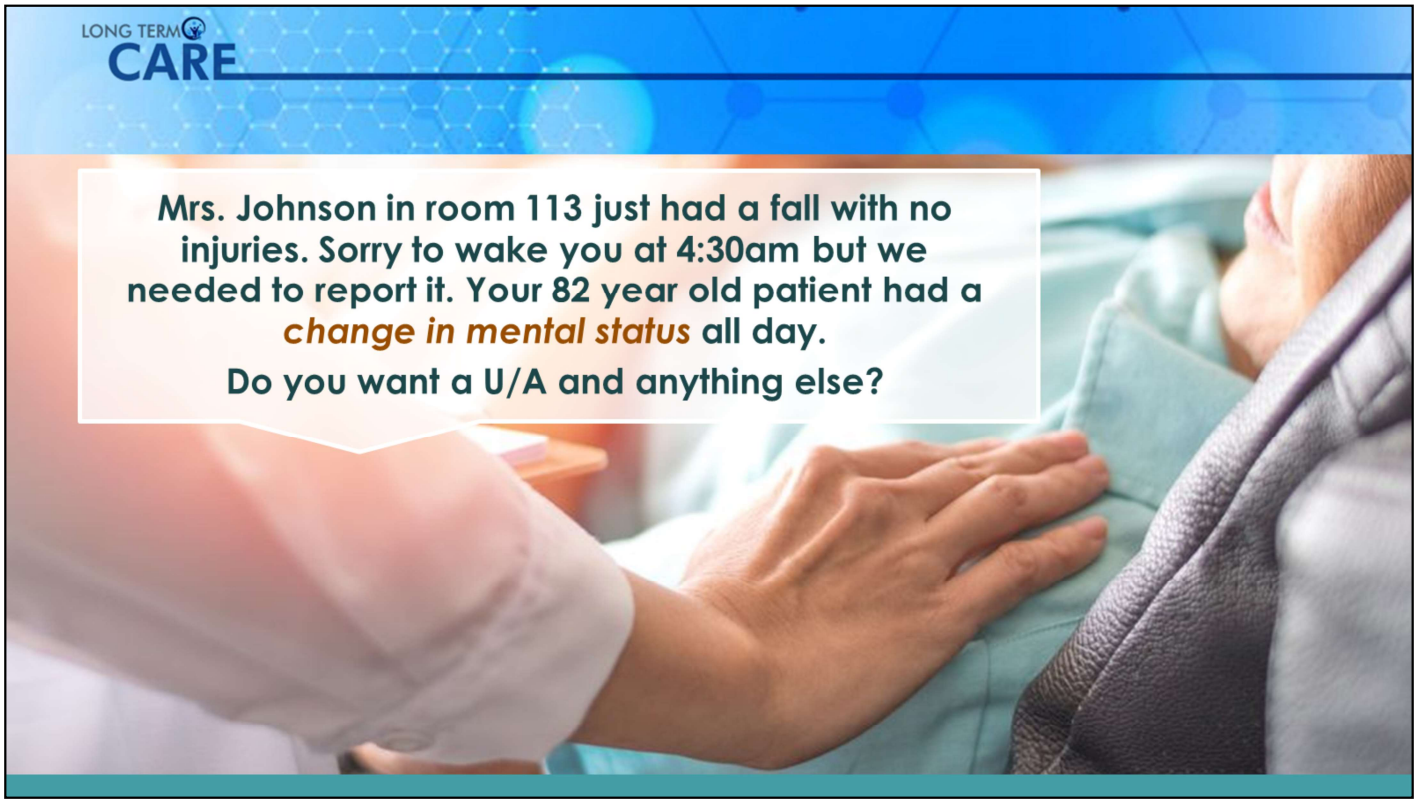
LONG TERM CARE

PART 1

Change in Mental Status
Hepatic Encephalopathy (HE)

Management Overview

This is Part 1 of our 2 part series on Changes in Mental Status – Hepatic Encephalopathy. This part covers the Management Overview from a review of problem, diagnosis and treatment. Part 2 goes into detail on the treatments for HE as well as the roles and responsibilities for each member of the Interdisciplinary Team.



Facilitator Notes:

How often does this scenario happen ?…in most SNFs this is a weekly occurrence at least, if not more often.

And how often are we missing the real issue ?

Let's take the next few minutes to review one possible explanation for a change in mental status…Hepatic Encephalopathy.

LONG TERM CARE

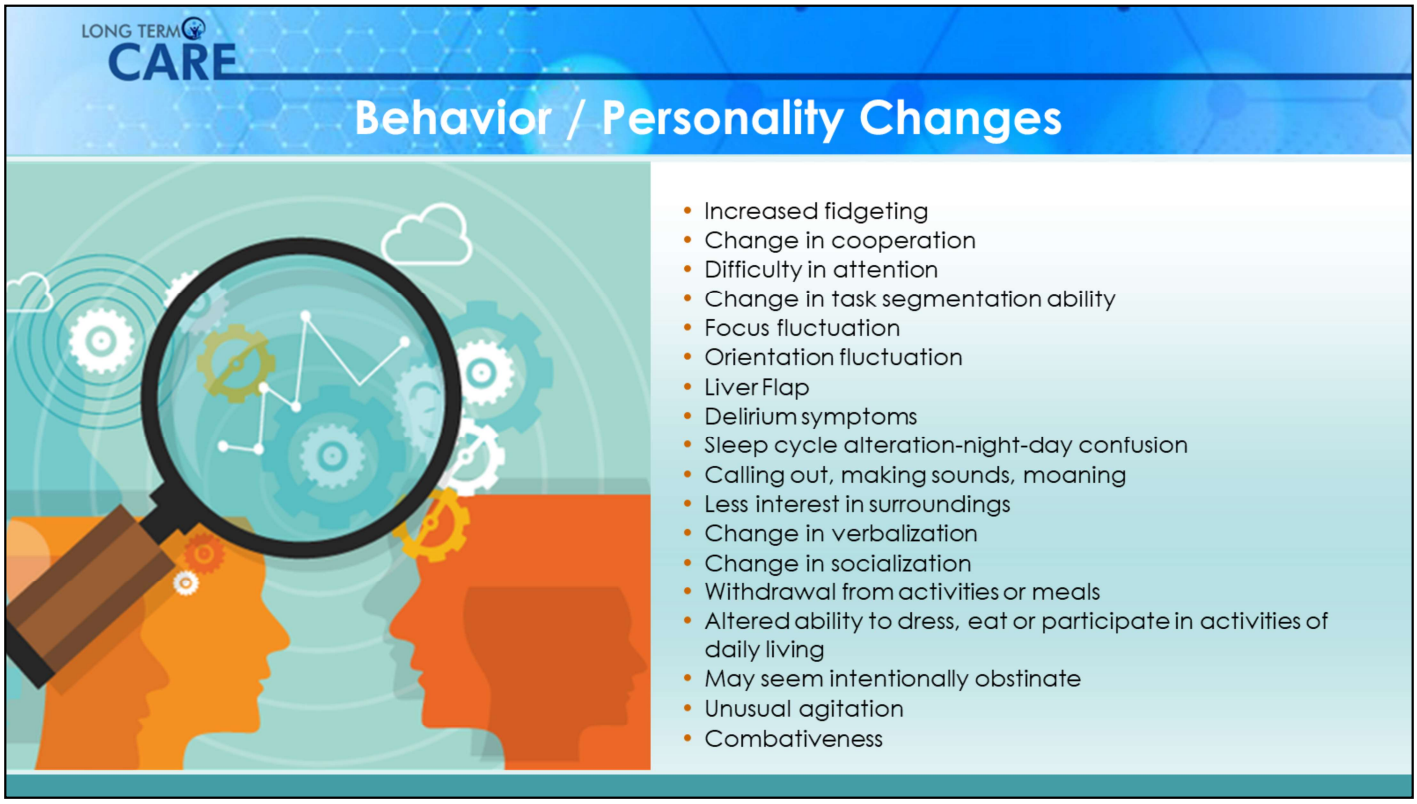
Causes of Altered Mental Status in Adults

- Fever or infection
- Poisoning or overdose
- Blood sugar/endocrine problems
- Head injury
- Inadequate oxygenation or ventilation
- Conditions leading to decreased blood flow or oxygen to the brain
- Cardiac or diabetic emergencies
- Shock
- Stroke
- Behavioral Illness
- Seizures

Facilitator Notes:

An infection e.g. UTI, is only one of the possible causes of changes in mental status, but there are of course many others to consider.

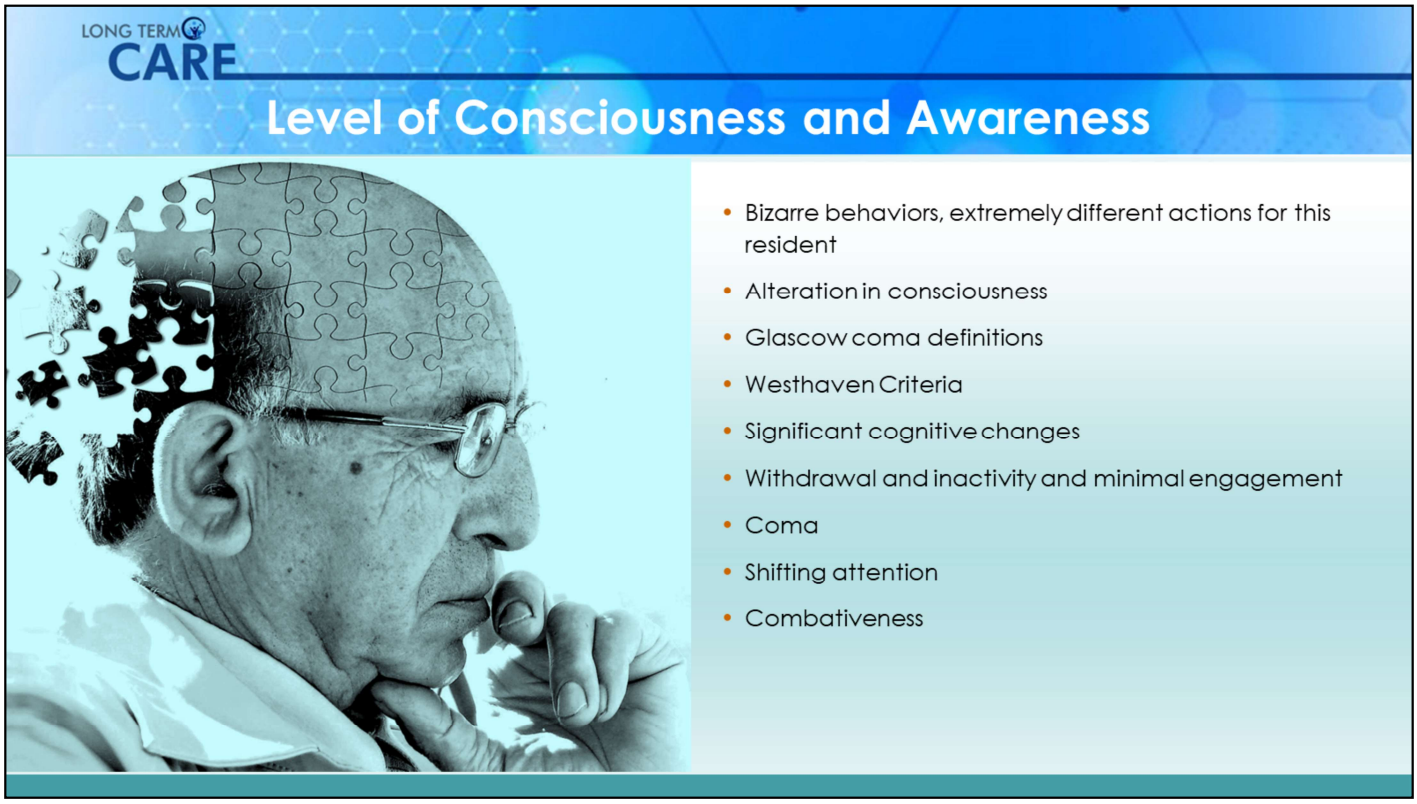
One of the causes of changes in mental status is the buildup of toxic levels of serum ammonia in patients with chronic liver failure, which underlies hepatic encephalopathy (HE).



Facilitator Notes:

The behavior and personality changes that can occur with HE include more than a 'change in mental status'. They can include any of the following 20 signs and symptoms highlighted on this slide.

These observations by nursing staff are much more beneficial to early recognition of HE than an early morning phone call to a provider of a 'change in mental status'.



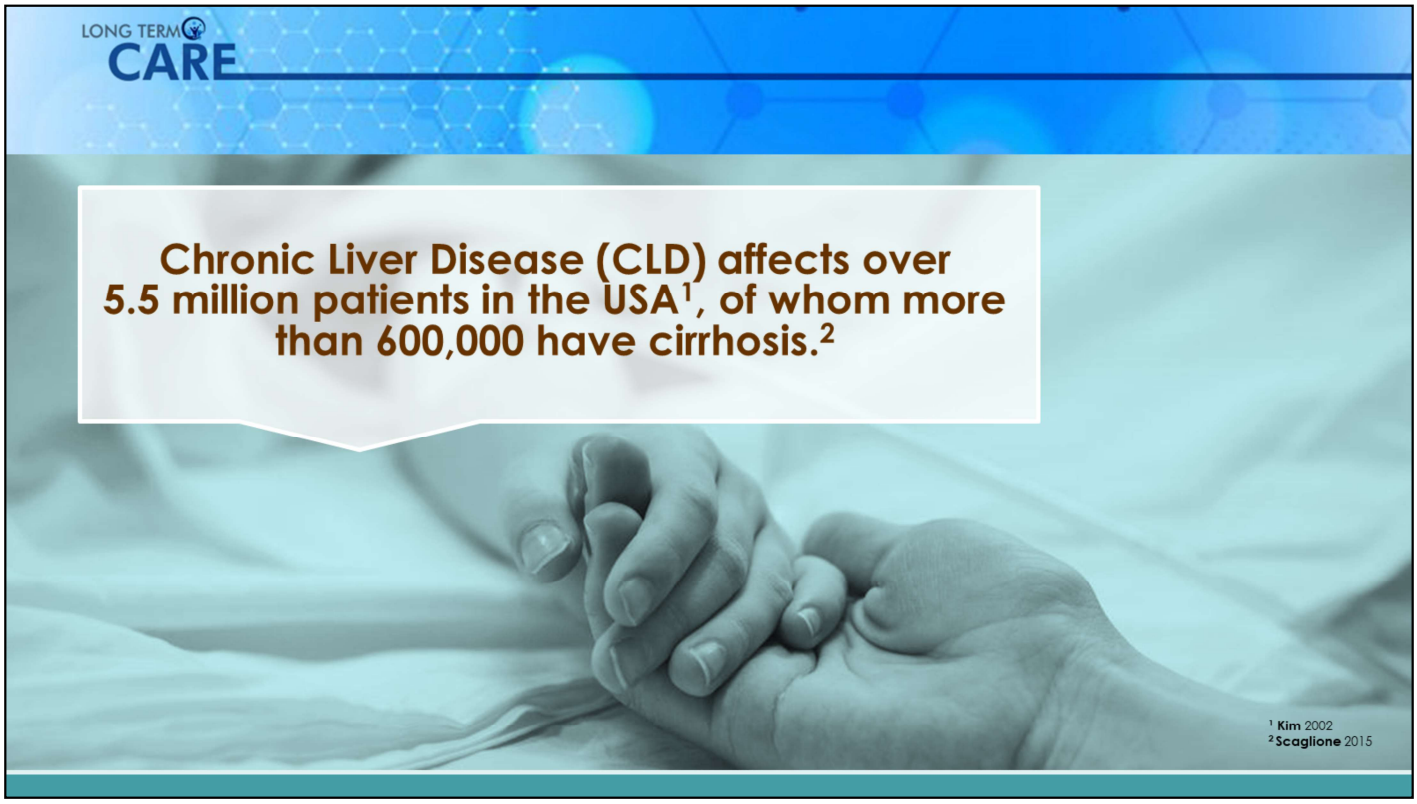
Facilitator Notes:

The more specific we can be regarding 'change in mental status', with more descriptions when we deliver our SBAR – Situation, Background, Assessment and Recommendation or Request, the better will be the prospect of hitting the mark on the true cause.

As such, recognizing the level of consciousness and awareness is important. This could be done through the use of one of the standard criteria or definitions such as Glascow or Westhaven. The more detail the better.

Facilitator Notes:

So how big a problem is HE that we should keep this on our radars? – Let's take a quick look at the numbers to appreciate why we should care about HE for our LTC patients.



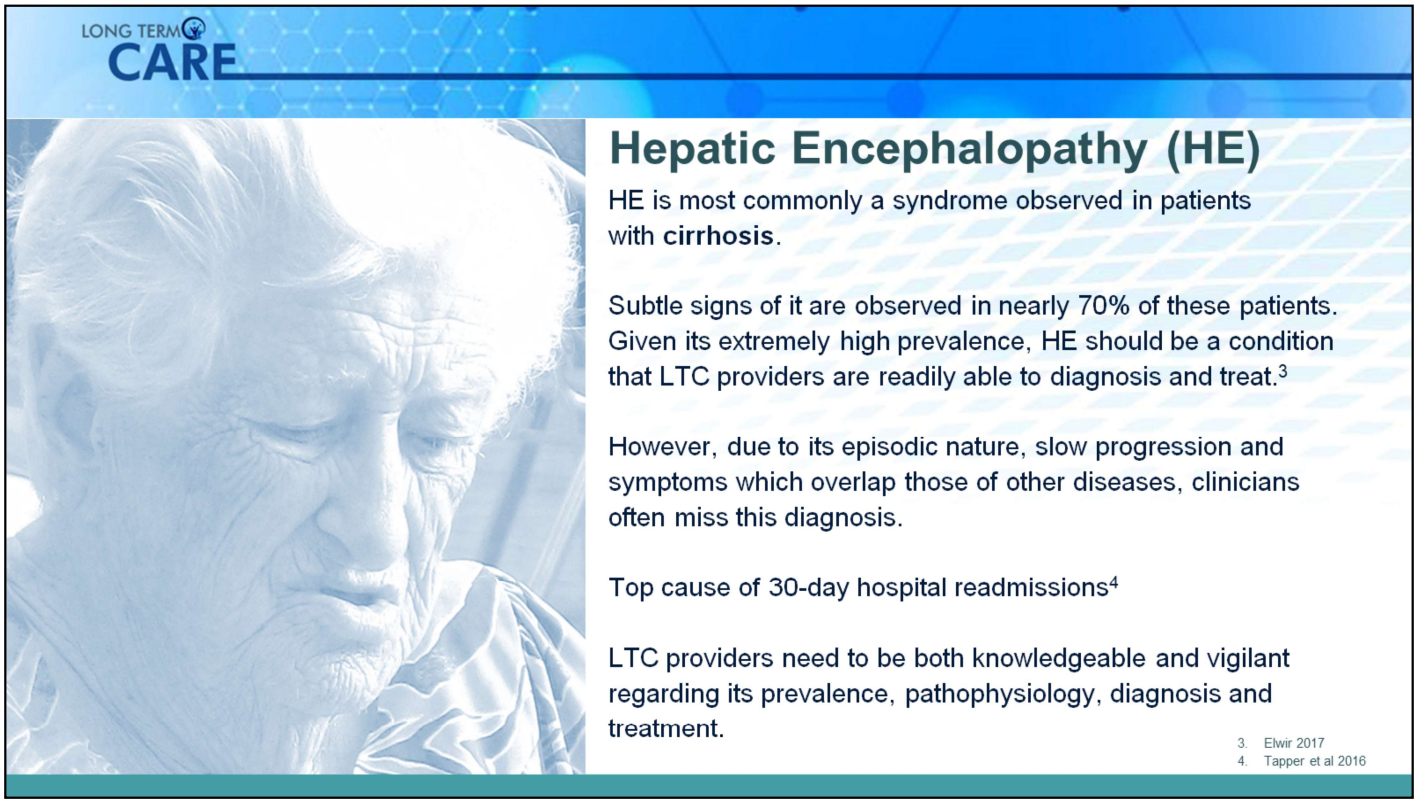
Facilitator Notes:

Hepatic Encephalopathy is a term that means brain disease, damage, or malfunction that comes from issues with one's Liver.

This comes from chronic liver disease which is especially prevalent in the US, including the serious progression of this disease to cirrhosis.

Cirrhosis is a late-stage of scarring (fibrosis) of the liver caused by many forms of liver diseases and conditions, such as hepatitis and chronic alcoholism.

With so many affected, many of these patients end up in our nursing homes.



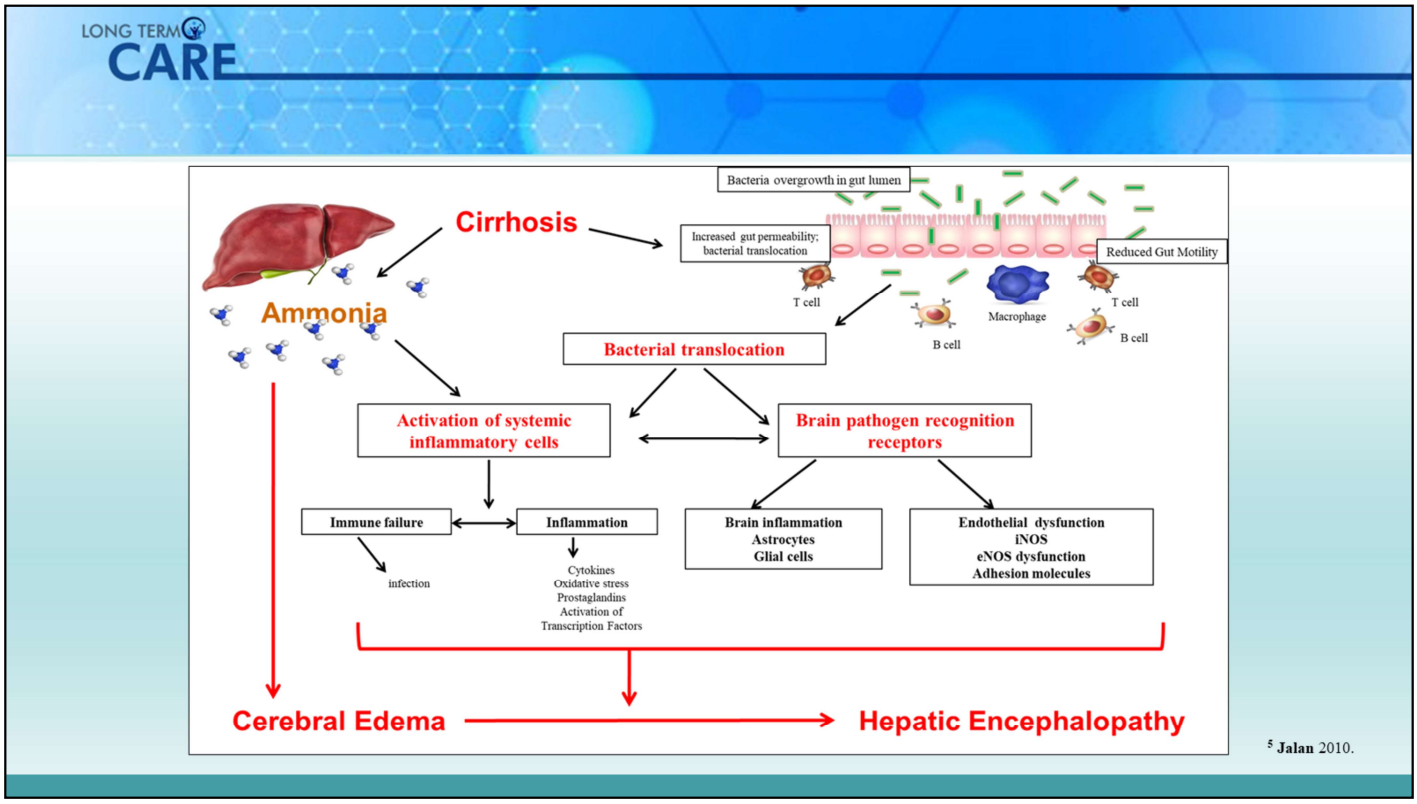
Facilitator Notes:

A couple key points to remember about HE are as follows;

- HE is most commonly a syndrome observed in patients with **cirrhosis**.
- Subtle signs of it are observed in nearly 70% of these patients
- Due to its episodic nature, slow progression and symptoms which overlap those of other diseases, clinicians often miss this diagnosis
- Largest driver of 30-day hospital readmissions for cirrhosis patients Tapper EB et al. Clincal Gastro Hepatol 2016;14:1181-1188
- LTC providers need to be both knowledgeable and vigilant when they observe cirrhosis patients exhibiting symptoms like a change in mental status

Facilitator Notes:

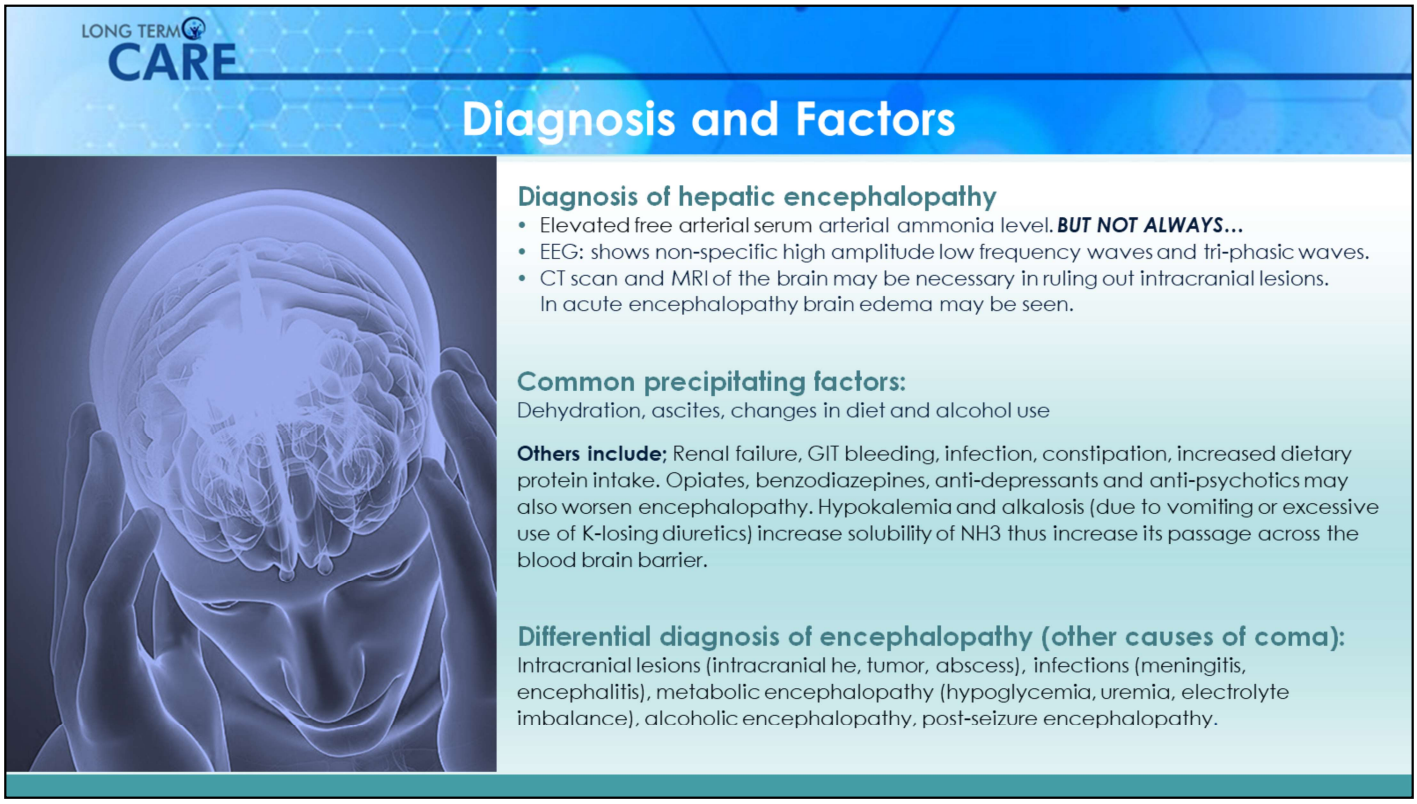
An appreciate for these details can help lead our providers to the right diagnosis and ultimately right management of HE.



Facilitator Notes:

HE is a disease of the liver which causes the accumulation of ammonia – which is the toxin responsible for the change in mental status in addition to many other problems such as brain inflammation and reduced immune function leading to infections.

Because of this pathophysiology, the major treatments target the gut and liver. Let's take just a moment to review this illustration to appreciate the roles that the liver and gut play on the neurological and immune systems.



Facilitator Notes:

So, once you suspect that a patient with cirrhosis may be suffering from HE, how does one confirm the diagnosis?

As cited on the slide and listed below here are some tests that can be utilized:

- Blood test that shows elevated ammonia levels
- EEG that shows brain wave activity
- Scan of the brain that rules out others causes and may show brain swelling

Regarding ammonia levels it is important to keep in mind that the diagnosis of HE is a clinical one, once other causes for confusion or coma have been excluded; **no test fully diagnoses or excludes it**. Serum ammonia levels are elevated in the majority of people, but not all hyperammonaemia (high ammonia levels in the blood) is associated with encephalopathy.

The American Association for the Study of Liver Diseases / European Association for the Study of the Liver (AASLD / EASL) Guideline (2014) provides guidance on testing for ammonia levels some of which are highlighted below:

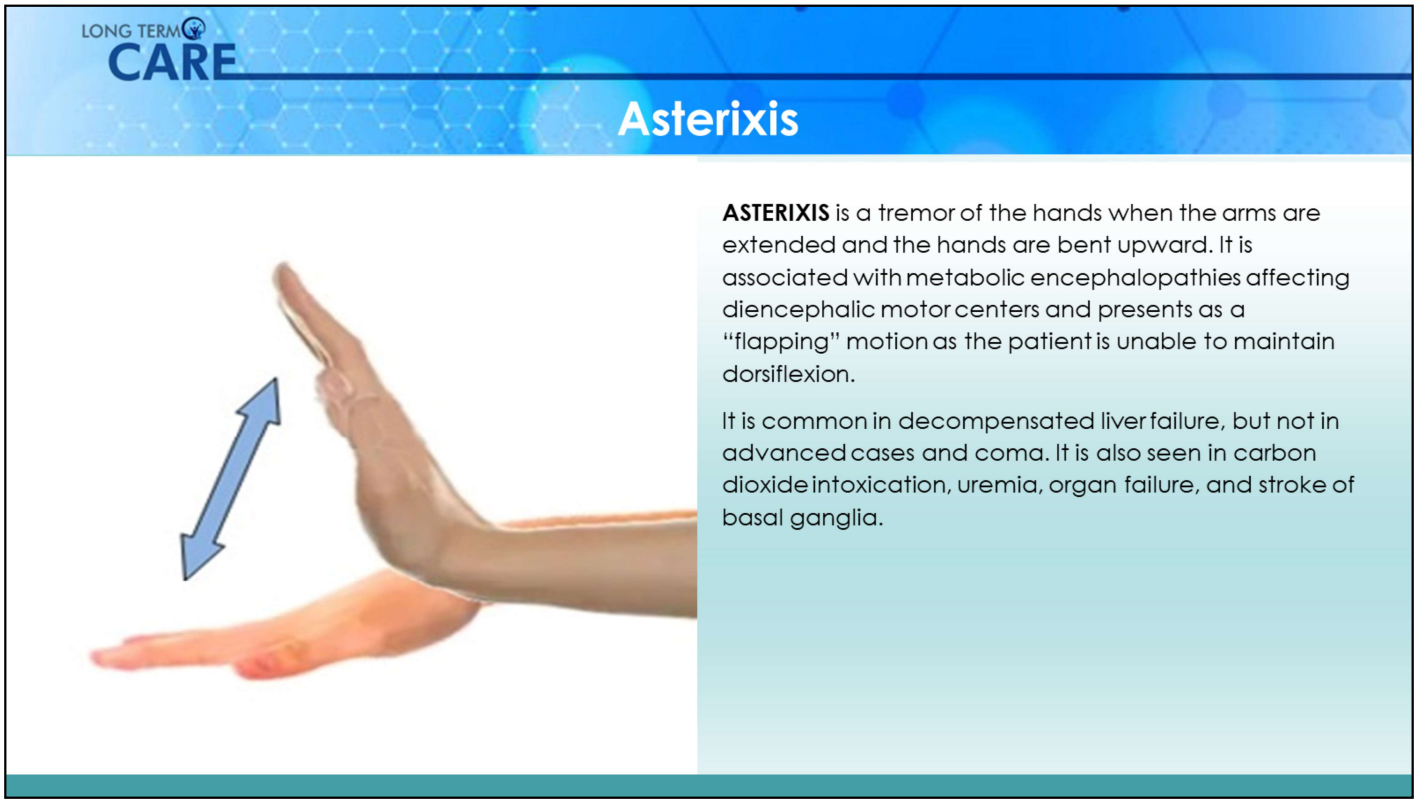
- A normal value calls for diagnostic reevaluation.
- High blood-ammonia levels alone do not add any diagnostic, staging, or prognostic value in HE patients with chronic liver disease. However, in case an ammonia level is checked in a patient with OHE and it is normal, the diagnosis of HE is in question. For ammonia-lowering drugs, repeated measurements of ammonia may be helpful to test the efficacy.
- There may be logistic challenges to accurately measure blood ammonia, which should be taken into consideration. Ammonia is reported either in venous, arterial blood, or plasma ammonia, so the relevant normal should be used.
- Multiple methods are available, but measurements should only be employed when laboratory standards allow for reliable analyses.

While diagnostic tests, of course, require a provider's order, it is beneficial for nursing staff and others to appreciate the process as a whole.

- EEG that shows brain wave activity
- Scan of the brain that rules out other causes and may show brain swelling

Common precipitating factors are dehydration, ascites, changes in diet, alcohol use, and others listed.

The AASLD/EASL Guidelines are a very credible source to build out a guide for your facility..



Facilitator Notes:

One of the key signs in HE is asterixis – which is a tremor of the hands when the arms are extended and the hands are bent upward. This is a neurological manifestation of the same systemic toxins (namely ammonia) responsible for encephalopathy and is an important early symptom nursing staff may recognize and bring to the attention of other healthcare professionals treating the patient.

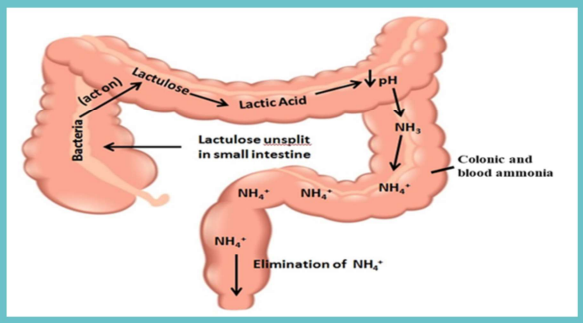
Let's spend a moment bending our own hands upward with our arms extended to see what this position looks like. Obviously, for us, we are not seeing our hands tremor, but it is important to appreciate how easy it would be to routinely utilize this test in our patients as an early indicator of HE.

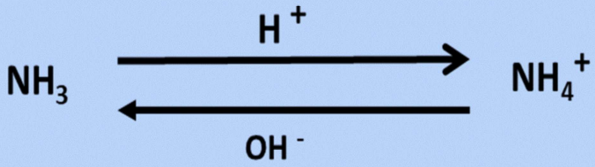
Facilitator Notes:

There are several treatment options for Hepatic Encephalopathy which can prevent mental status changes.

LONG TERM CARE

Mechanism of Action of Lactulose for OHE





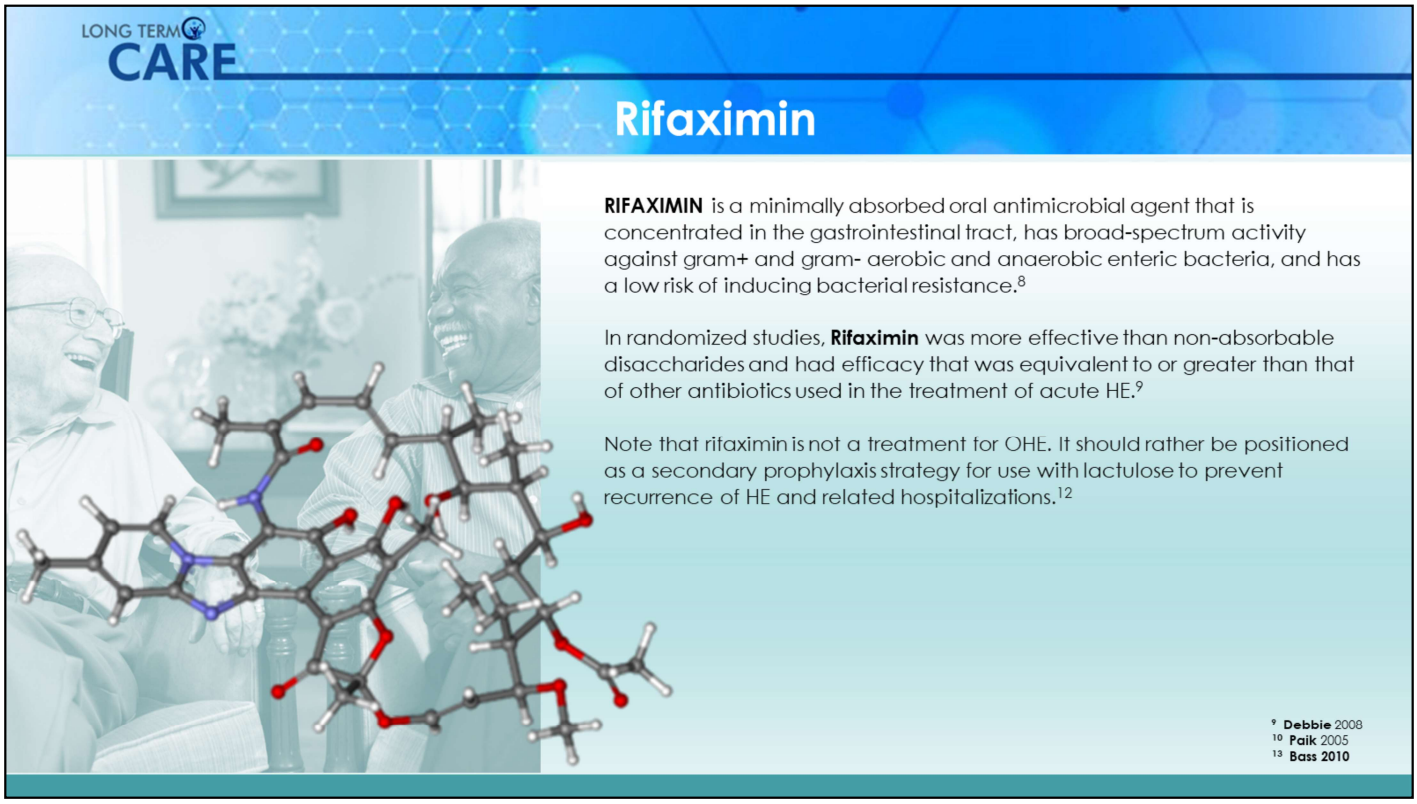
- A non-absorbable disaccharide
- It produces osmosis of water — Diarrhea [6, 7]
- It reduces pH of colonic content & thereby converts freely diffusible NH_3 into ammonium ions (NH_4^+), which cannot be absorbed and are therefore excreted.[6, 7]
- Lactulose reaches the colon unsplit. It is then converted by bacteria to organic acids and an acid stool results. This may also affect the ionization of ammonia in the colon and reduce its absorption.[6, 7]
- The current AASLD/EASL guideline (2014) recommends rifaximin as an add-on to lactulose for prevention of recurrent episodes of HE after the second episode.[8]

[6] Reena
[7] Davidson's
[8] AASLD EASL 2014

Facilitator Notes:

Since the mental status change is due to toxins – getting them out of the body is critical. In this regard, a mainstay of the treatment for acute Overt HE is lactulose, which works by getting the gut flora to acidify the colon, leading to conversion of freely diffusable ammonia (NH_3) into ammonium ions (NH_4^+) which are not absorbable by the gut and are therefore excreted. This excretion is enhanced by the laxative effect of lactulose, due to its lowering of osmotic pressure of the gut contents, thereby drawing water into it and inducing diarrhea.

To help prevent the recurrence of OHE it should be noted that the current (AASLD/EASL) guideline recommends combined lactulose plus rifaximin for prevention of HE after the second episode.[7]



Facilitator Notes:

Rifaximin works as a poorly absorbed antimicrobial agent that is thought to reduce ammonia production by eliminating ammonia-producing colonic bacteria.

Because of this mechanism of action, Rifaximin has been shown to be beneficial in combination with lactulose.

Remember rifaximin is not a treatment for acute OHE it should be positioned as a secondary prophylaxis strategy with lactulose to prevent recurrence HE and related hospitalizations[13]

LONG TERM CARE

Randomized, Double-Blind, Controlled Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 25, 2010 VOL. 362 NO. 12

Rifaximin Treatment in Hepatic Encephalopathy

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ABSTRACT

BACKGROUND

Hepatic encephalopathy is a chronically debilitating complication of hepatic cirrhosis. The efficacy of rifaximin, a minimally absorbed antibiotic, is well documented in the treatment of acute hepatic encephalopathy, but its efficacy for prevention of the disease has not been established.

METHODS

In this randomized, double-blind, placebo-controlled trial, we randomly assigned 299 patients who were in remission from recurrent hepatic encephalopathy resulting from chronic liver disease to receive either rifaximin, at a dose of 550 mg twice daily (140 patients), or placebo (159 patients) for 6 months. The primary efficacy end point was the time to the first breakthrough episode of hepatic encephalopathy. The key secondary end point was the time to the first hospitalization involving hepatic encephalopathy.

RESULTS

Rifaximin significantly reduced the risk of an episode of hepatic encephalopathy, as compared with placebo, over a 6-month period (hazard ratio with rifaximin, 0.42; 95% confidence interval [CI], 0.28 to 0.64; P<0.001). A breakthrough episode of hepatic encephalopathy occurred in 22.1% of patients in the rifaximin group, as compared with 45.9% of patients in the placebo group. A total of 13.6% of the patients in the rifaximin group had a hospitalization involving hepatic encephalopathy, as compared with 22.6% of patients in the placebo group, for a hazard ratio of 0.50 (95% CI, 0.29 to 0.87; P=0.01). More than 90% of patients received concomitant lactulose therapy. The incidence of adverse events reported during the study was similar in the two groups, as was the incidence of serious adverse events.

CONCLUSIONS

Over a 6-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than did placebo. Rifaximin treatment also significantly reduced the risk of hospitalization involving hepatic encephalopathy. (ClinicalTrials.gov number, NCT00298038.)

From the University of California, San Francisco (N.M.B.) and California Pacific Medical Center (T.F.) — both in San Francisco; Cedars-Sinai Medical Center, Los Angeles (F.P.); University of California, San Francisco, Fresno (M.Y.S.); and Scripps Clinical Research Center, La Jolla (D.H.) — all in California; Metrohealth Medical Center, Case Western Reserve University, Cleveland (K.D.M.), and University of Cincinnati Medical Center, Cincinnati (G.N.) — both in Ohio; Virginia Commonwealth University, Richmond (A.S.); University of Medicine and Dentistry of New Jersey, Newark (C.B.L.); Weill Medical College of Cornell University (S.S.) and New York University School of Medicine (L.T.) — both in New York; Asheville Gastroenterology Associates, Asheville, NC (K.B.); and Salix Pharmaceuticals, Morrisville, NC (S.H., K.M., A.S., E.B., W.P.F.). Address reprint requests to Dr. Forbes at Salix Pharmaceuticals, 1700 Perimeter Park Dr., Morrisville, NC 27560.

*Deceased.

N Engl J Med 2010;362:1071-81.

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N ENGL J MED 362;12 NEJM.ORG MARCH 25, 2010 1071

XIFAXAN reduced the risk of OHE recurrence by 58% and HE Related hospitalizations by 50% versus Placebo.

91% of patients in both arms of the trial were on lactulose which means this data reflects benefits of rifaximin over and above those which previous studies have shown are due to lactulose alone.

This is important in weighing the value of managing patients with a regimen of lactulose alone, as compared to one with a combination of lactulose and rifaximin.

[13] Bass 2010

Facilitator Notes:

The benefit of using Rifaximin with Lactulose has been demonstrated in several clinical studies. Here is a study that illustrated that benefit through a randomized double-blinded controlled trial.

In this type of trial, neither the **investigator nor the participant are aware of which drug or placebo is administered** and thus the observed drug effects are free from investigator or subject bias. Moreover, the randomization helps to ensure that findings are likewise not attributable to differences in the comparison groups prior to the study.

In this randomized, double-blind, controlled trial:

- XIFAXAN reduced the risk of OHE recurrence by 58% and HE Related hospitalizations by 50% versus Placebo.

- 91% of patients in both arms of the trial were on lactulose which means this data reflects benefits of rifaximin over and above those which previous studies have shown are due to lactulose alone

This is important in weighing the value of managing patients with a regimen of lactulose alone, as compared to one with a combination of lactulose and rifaximin.

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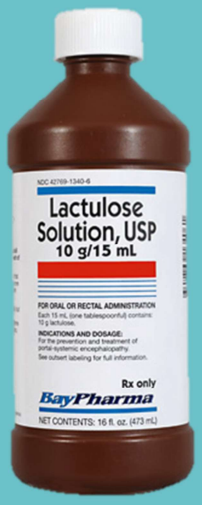
Usual Adult Dose for Hepatic Encephalopathy



Lactulose **30 mL** orally 3 times a day or **300 mL** in **700 mL** water or normal saline as an enema retained for 30-60 minutes every 4 to 6 hours.

Maintenance dose:
30-45 mL orally 3x a day.

Rifaximin 550 mg orally twice a day

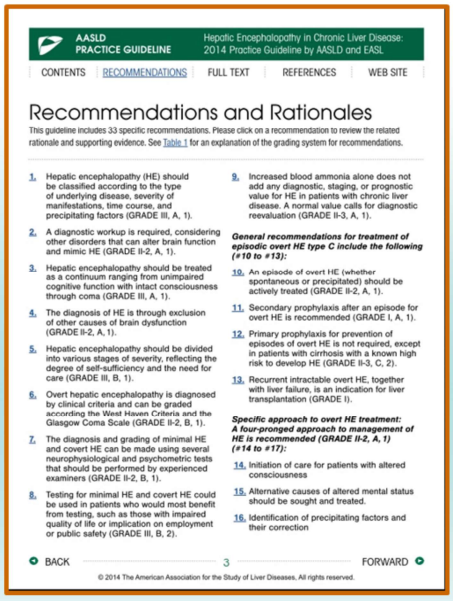
Facilitator Notes:

This illustrates a typical treatment regimen for patients with HE – one with which nurses should be familiar, both from an administration standpoint as well as from the standpoint of educating patients on the importance of these medications together.

One of the major reasons for patient non-adherence to treatments is their lack of appreciation for their benefits. This understanding can go a long way toward maintaining treatment adherence.

LONG TERM CARE

American Association of the Study of Liver Disease & European Association for the Study of the Liver (AASLD/EASL)



AASLD PRACTICE GUIDELINE — Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by AASLD and EASL

CONTENTS | RECOMMENDATIONS | FULL TEXT | REFERENCES | WEB SITE

Recommendations and Rationales

This guideline includes 33 specific recommendations. Please click on a recommendation to review the related rationale and supporting evidence. See Table 1 for an explanation of the grading system for recommendations.

1. Hepatic encephalopathy (HE) should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).
2. A diagnostic workup is required, considering other disorders that can alter brain function and mimic HE (GRADE II-2, A, 1).
3. Hepatic encephalopathy should be treated as a continuum ranging from unimpaired cognitive function with intact consciousness through coma (GRADE III, A, 1).
4. The diagnosis of HE is through exclusion of other causes of brain dysfunction (GRADE II-2, A, 1).
5. Hepatic encephalopathy should be divided into various stages of severity, reflecting the degree of self-sufficiency and the need for care (GRADE III, B, 1).
6. Overt hepatic encephalopathy is diagnosed by clinical criteria and can be graded according the West Haven Criteria and the Glasgow Coma Scale (GRADE II-2, B, 1).
7. The diagnosis and grading of minimal HE and covert HE can be made using several neurophysiological and psychometric tests that should be performed by experienced examiners (GRADE II-2, B, 1).
8. Testing for minimal HE and covert HE could be used in patients who would most benefit from testing, such as those with impaired quality of life or implication on employment or public safety (GRADE III, B, 2).
9. Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with chronic liver disease. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1).

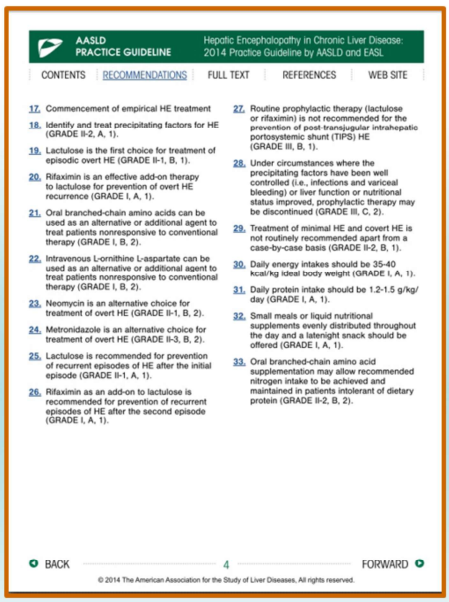
General recommendations for treatment of episodic overt HE type C include the following (#10 to #13):

10. An episode of overt HE (whether spontaneous or precipitated) should be actively treated (GRADE II-2, A, 1).
11. Secondary prophylaxis after an episode for overt HE is recommended (GRADE I, A, 1).
12. Primary prophylaxis for prevention of episodes of overt HE is not required, except in patients with cirrhosis with a known high risk to develop HE (GRADE II-3, C, 2).
13. Recurrent intractable overt HE, together with liver failure, is an indication for liver transplantation (GRADE I).

Specific approach to overt HE treatment: A four-pronged approach to management of HE is recommended (GRADE II-2, A, 1) (#14 to #17):

14. Initiation of care for patients with altered consciousness
15. Alternative causes of altered mental status should be sought and treated.
16. Identification of precipitating factors and their correction

BACK 3 FORWARD



AASLD PRACTICE GUIDELINE — Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by AASLD and EASL

CONTENTS | RECOMMENDATIONS | FULL TEXT | REFERENCES | WEB SITE

17. Commencement of empirical HE treatment
18. Identify and treat precipitating factors for HE (GRADE II-2, A, 1).
19. Lactulose is the first choice for treatment of episodic overt HE (GRADE II-1, B, 1).
20. Rifaximin is an effective add-on therapy to lactulose for prevention of overt HE recurrence (GRADE I, A, 1).
21. Oral branched-chain amino acids can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy (GRADE I, B, 2).
22. Intravenous L-ornithine L-aspartate can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy (GRADE I, B, 2).
23. Neomycin is an alternative choice for treatment of overt HE (GRADE II-1, B, 2).
24. Metronidazole is an alternative choice for treatment of overt HE (GRADE II-3, B, 2).
25. Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1).
26. Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1).
27. Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-transjugular intrahepatic portosystemic shunt (TIPS) HE (GRADE III, B, 1).
28. Under circumstances where the precipitating factors have been well controlled (i.e., infections and variceal bleeding) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2).
29. Treatment of minimal HE and covert HE is not routinely recommended apart from a case-by-case basis (GRADE II-2, B, 1).
30. Daily energy intakes should be 35-40 kcal/kg ideal body weight (GRADE I, A, 1).
31. Daily protein intake should be 1.2-1.5 g/kg/day (GRADE I, A, 1).
32. Small meals or liquid nutritional supplements evenly distributed throughout the day and a latenight snack should be offered (GRADE I, A, 1).
33. Oral branched-chain amino acid supplementation may allow recommended nitrogen intake to be achieved and maintained in patients intolerant of dietary protein (GRADE II-2, B, 2).

BACK 4 FORWARD

AASLD/EASL guidelines recommend combined lactulose plus rifaximin for prevention of HE after the second episode.[8]

Rifaximin has excellent characteristics, including a slow rate of systemic absorption, a broad spectrum of antibiotic activity, and a low frequency of side effects.[12]

This particular guideline on combination therapy is given the highest recommendation (Grade 1, A, 1) based on scientific merit and cost-effectiveness.[8,13]

[8] AASD-EASL 2014
[12] Zeneroli 2005
[13] Bass 2010

Facilitator Notes:

As we have discussed you can see in the AASLD/EASL guidelines #19 and #20 that Lactulose and Rifaximin are part of the standardized treatment of HE.

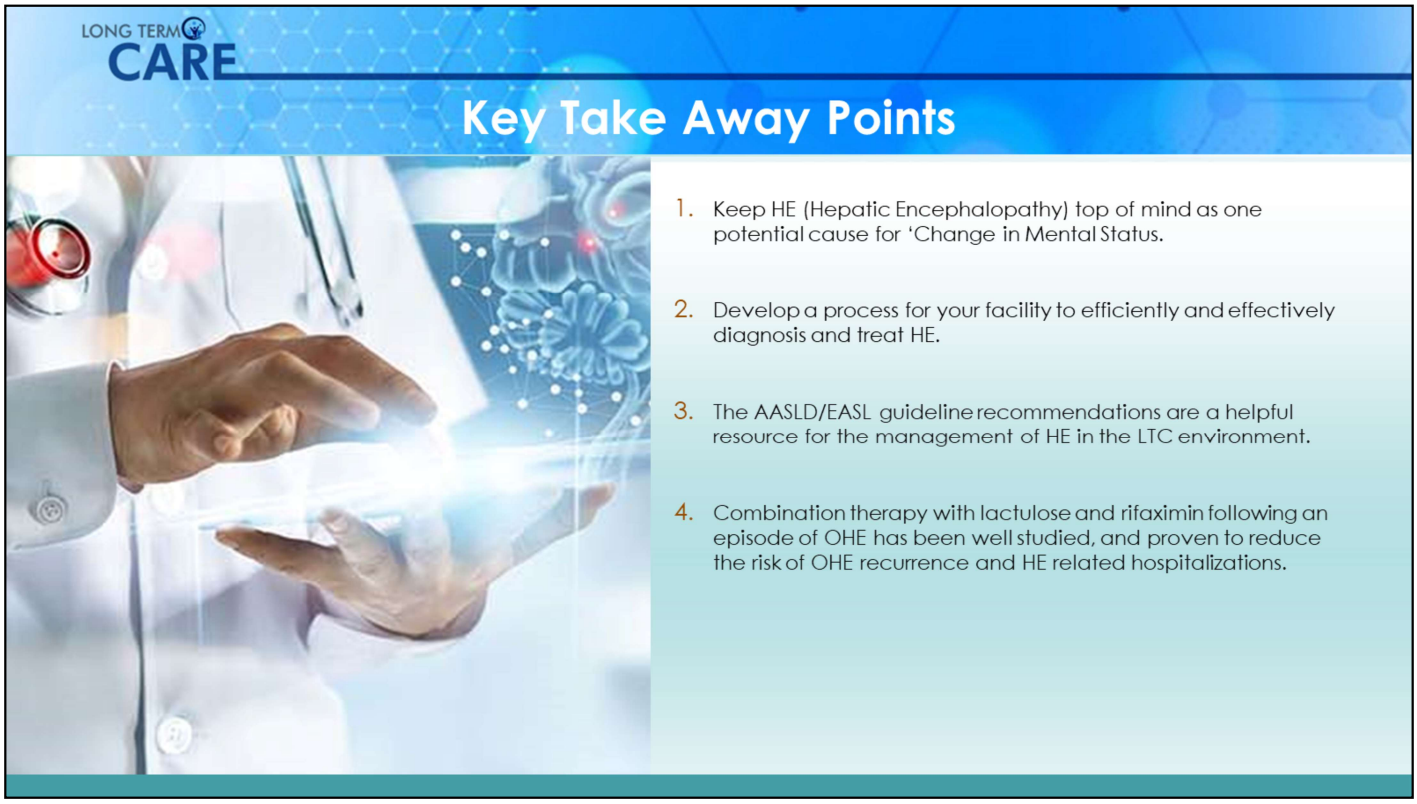
Specifically, the current AASLD/EASL guidelines recommend combined lactulose plus rifaximin for prevention of HE after the second episode.[8]

Rifaximin has excellent characteristics, including a slow rate of systemic absorption, a broad spectrum of antibiotic activity, and a low frequency of side effects.[12]

This particular guideline on combination therapy is given the highest recommendation (Grade 1, A, 1) based on scientific merit and cost-effectiveness.[13]

Facilitator Notes:

Now lets take a moment to review our key takeaway points that we can put into action to improve the care of our patients.



Facilitator Notes:

Four key points to take away include the following:

1. Keep HE (Hepatic Encephalopathy) top of mind as one potential cause for 'Change in Mental Status'.
    - It's often said that we don't know what we don't know, so if we didn't know about HE before this discussion we would never consider it as a possible reason for a change in mental status – Now that we know, it is up to us to keep it top of mind as to one of the possibilities

2. Develop a process for your facility to efficiently and effectively diagnosis and treat HE.
    - Knowing is one thing but for things to happen consistently they require a process, so let's not have it end here. Rather, work as a team to develop a process for the appropriate management of our patients with mental status changes that includes the consideration of HE.

3. The AASLD guideline recommendations are a helpful resource for the management of HE in the LTC environment.

4. Lactulose and rifaximin post an episode of OHE is a well studied combination and proven to reduce the risk of OHE recurrence and HE related hospitalizations.

Facilitator Notes:

Now let's take a few moments to address any questions or thoughts on the process we should implement to best management our patients with HE.

LONG TERM CARE

References:

1. **Kim W**, Brown R, Terrault N, et al. Burden of liver disease in the United States: summary of a workshop. *Hepatology*. 2002;36:227-242.
2. **Scaglione S**, Kliethermes S, Cao G, et al. The Epidemiology of Cirrhosis in the United States: A Population-based Study. *J Clin Gastroenterol*. 2015 Sep;49(8):690-6.
3. **Elwir S** and Rahimi R. Hepatic Encephalopathy: An Update on the Pathophysiology and Therapeutic Options. *J Clin Transl Hepatol*. 2017;5:142-151.
4. **Tapper EB et al.** Clincal Gastro Hepatol 2016;14:1181-1188
5. **Jalan**. Rifaximin in hepatic encephalopathy: more than just a non-absorbable antibiotic? *J Hepatol*. 2010 Sep;53(3):580-2.
6. **Reena**. Hepatic Encephalopathy. https://slideshare.net/RINA7373/hepatic-encephalopathy-35951607.
7. **Davidson**'s Principles & Practice of Medicine. 21st edition, Harrison's Principles of Internal Medicine -10th and 17th edition. *Current Medical Diagnosis and Treatment* – 2014 edition.
8. **AASLD-EASL.** American Association for the Study of Liver Diseases; European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol*. 2014;61(3):642-59.
9. **Debbie EA**, Maioli E. Roveta S. Marchese A. Effects of Rifaximin on bacterial virulence mechanisms at supra- and sup- inhibitory concentrations. *J Chemother* 2008:20:186-194
10. **Paik YH**, Lee KS, Han KH, et al. Comparison of Rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. *Yonsei Med J* 2005:46:399-407.
11. **Sharma B**, Sharma P, Lunia M, et al. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol*. 2013;108:1458-1463.
12. **Zeneroli M.** Avallone R, Corsi L. Management of hepatic encephalopathy: role of rifaximin. *Chemotherapy*. 2005;51 Suppl 1:90-5.
13. **Bass** N, Mullen K, Sanyal A. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362(12):1071-81.