LONG TERM CARE

PART 1

Change in Mental Status
Hepatic Encephalopathy (HE)

Management Overview

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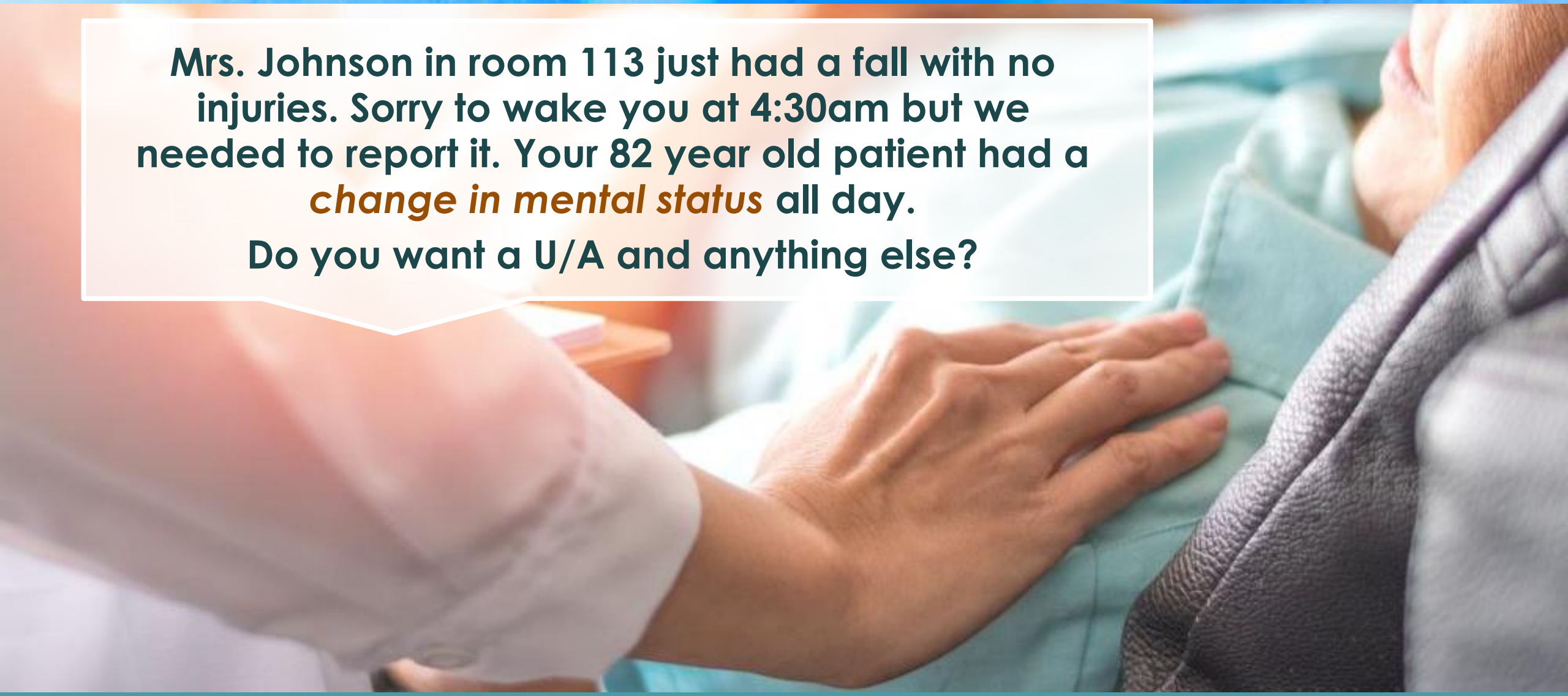
Mrs. Johnson in room 113 just had a fall with no injuries. Sorry to wake you at 4:30am but we needed to report it. Your 82 year old patient had a *change in mental status* all day.

Do you want a U/A and anything else?



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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

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Behavior / Personality Changes

- Increased fidgeting
- Change in cooperation
- Difficulty in attention
- Change in task segmentation ability
- Focus fluctuation
- Orientation fluctuation
- Liver Flap
- Delirium symptoms
- Sleep cycle alteration-night-day confusion
- Calling out, making sounds, moaning
- Less interest in surroundings
- Change in verbalization
- Change in socialization
- Withdrawal from activities or meals
- Altered ability to dress, eat or participate in activities of daily living
- May seem intentionally obstinate
- Unusual agitation
- Combativeness

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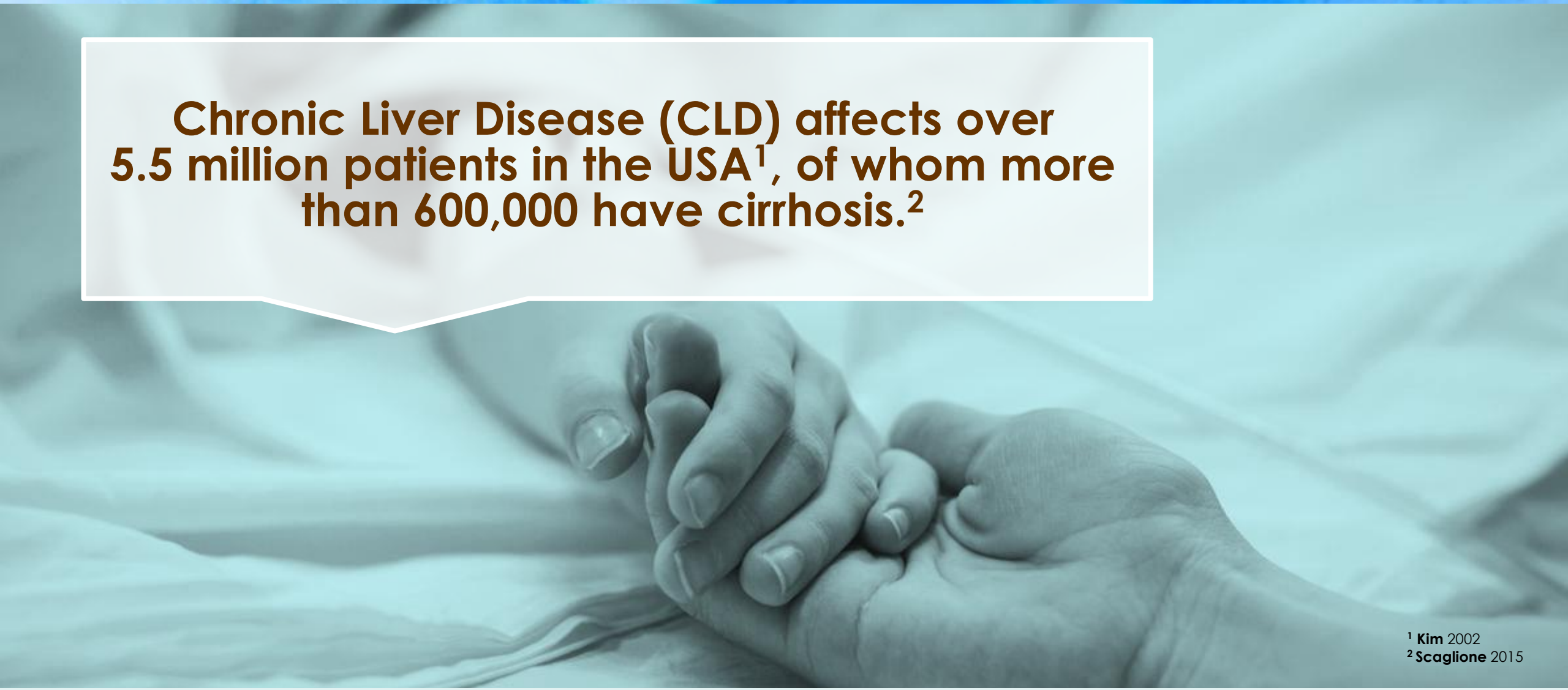
Level of Consciousness and Awareness

- Bizarre behaviors, extremely different actions for this resident
- Alteration in consciousness
- Glascow coma definitions
- Westhaven Criteria
- Significant cognitive changes
- Withdrawal and inactivity and minimal engagement
- Coma
- Shifting attention
- Combativeness


Prevalence



Chronic Liver Disease (CLD) affects over 5.5 million patients in the USA[1], of whom more than 600,000 have cirrhosis.[2]

[1] **Kim** 2002
[2] **Scaglione** 2015

Hepatic Encephalopathy (HE)

HE is most commonly a syndrome observed in patients with **cirrhosis**.

Subtle signs of it are observed in nearly 70% of these patients. Given its extremely high prevalence, HE should be a condition that LTC providers are readily able to diagnosis and treat.[3]

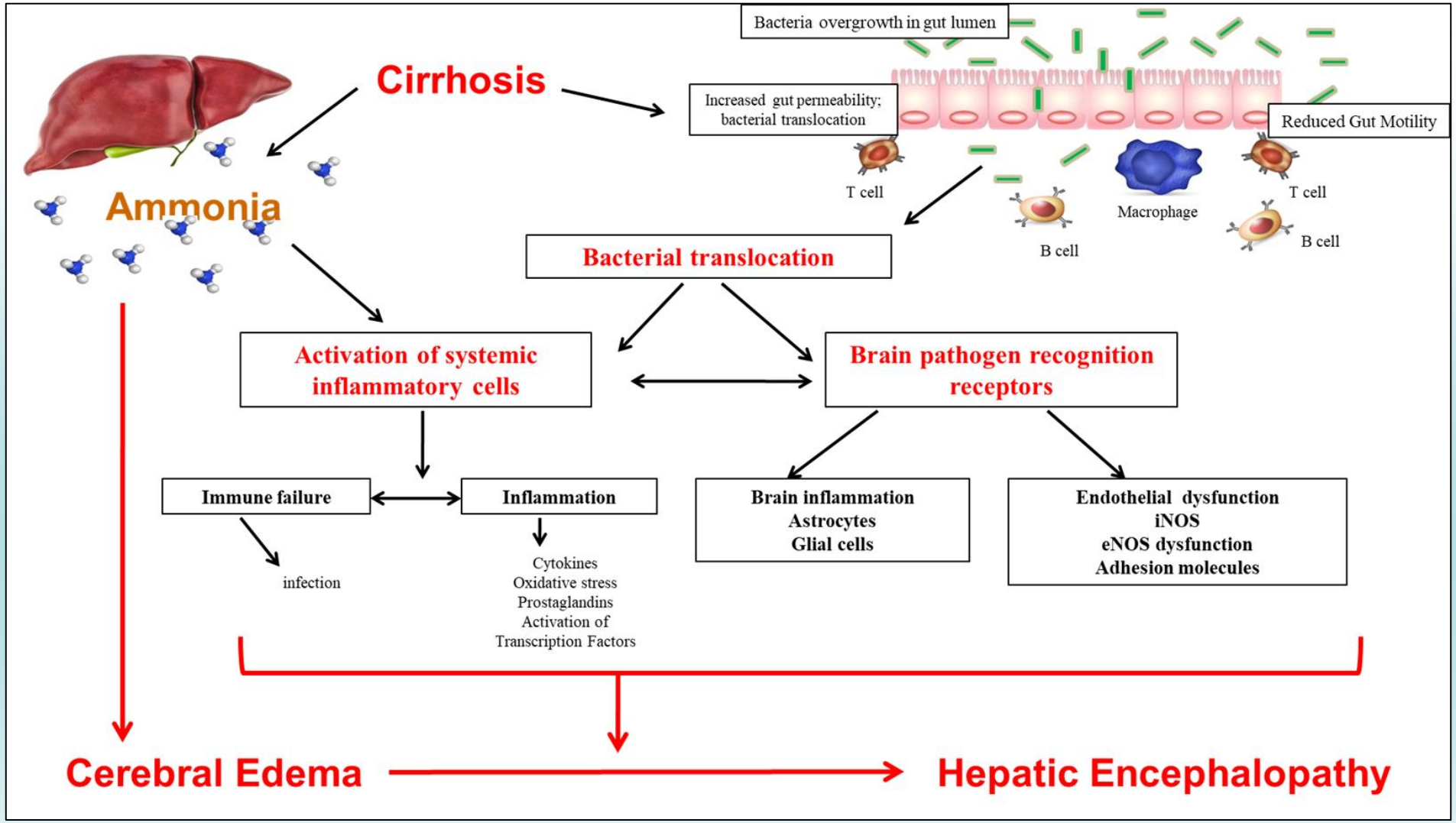
However, due to its episodic nature, slow progression and symptoms which overlap those of other diseases, clinicians often miss this diagnosis.

Top cause of 30-day hospital readmissions[4]

LTC providers need to be both knowledgeable and vigilant regarding its prevalence, pathophysiology, diagnosis and treatment.

3. Elwir 2017
4. Tapper et al 2016

Diagnosis


Bacteria overgrowth in gut lumen
Cirrhosis
Increased gut permeability; bacterial translocation
Reduced Gut Motility
T cell
B cell
Macrophage
T cell
B cell
Ammonia
Bacterial translocation
Activation of systemic inflammatory cells
Brain pathogen recognition receptors
Immune failure
Inflammation
Brain inflammation
Astrocytes
Glial cells
Endothelial dysfunction
iNOS
eNOS dysfunction
Adhesion molecules
infection
Cytokines
Oxidative stress
Prostaglandins
Activation of
Transcription Factors
Cerebral Edema
Hepatic Encephalopathy

[5] **Jalan** 2010.

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Diagnosis and Factors

Diagnosis of hepatic encephalopathy

- Elevated free arterial serum arterial ammonia level. ***BUT NOT ALWAYS…***
- EEG: shows non-specific high amplitude low frequency waves and tri-phasic waves.
- CT scan and MRI of the brain may be necessary in ruling out intracranial lesions. In acute encephalopathy brain edema may be seen.

Common precipitating factors:

Dehydration, ascites, changes in diet and alcohol use

Others include; Renal failure, GIT bleeding, infection, constipation, increased dietary protein intake. Opiates, benzodiazepines, anti-depressants and anti-psychotics may also worsen encephalopathy. Hypokalemia and alkalosis (due to vomiting or excessive use of K-losing diuretics) increase solubility of NH3 thus increase its passage across the blood brain barrier.

Differential diagnosis of encephalopathy (other causes of coma):

Intracranial lesions (intracranial he, tumor, abscess), infections (meningitis, encephalitis), metabolic encephalopathy (hypoglycemia, uremia, electrolyte imbalance), alcoholic encephalopathy, post-seizure encephalopathy.

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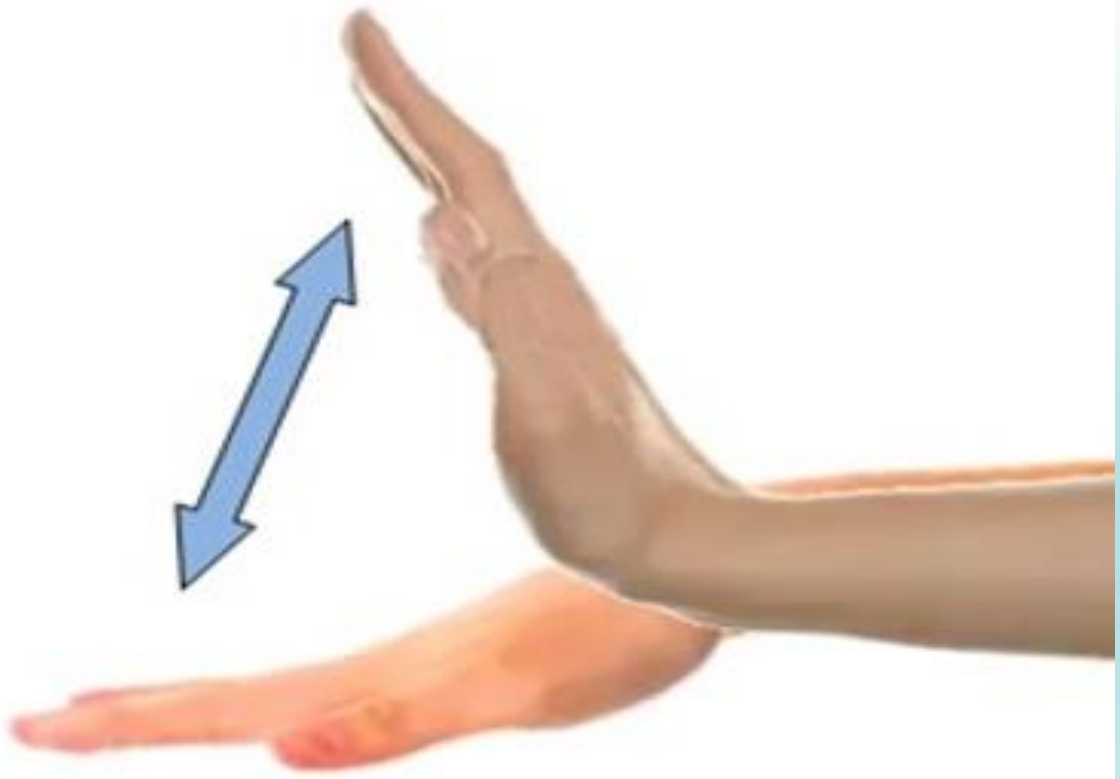
Asterixis



ASTERIXIS is a tremor of the hands when the arms are extended and the hands are bent upward. It is associated with metabolic encephalopathies affecting diencephalic motor centers and presents as a "flapping" motion as the patient is unable to maintain dorsiflexion.

It is common in decompensated liver failure, but not in advanced cases and coma. It is also seen in carbon dioxide intoxication, uremia, organ failure, and stroke of basal ganglia.

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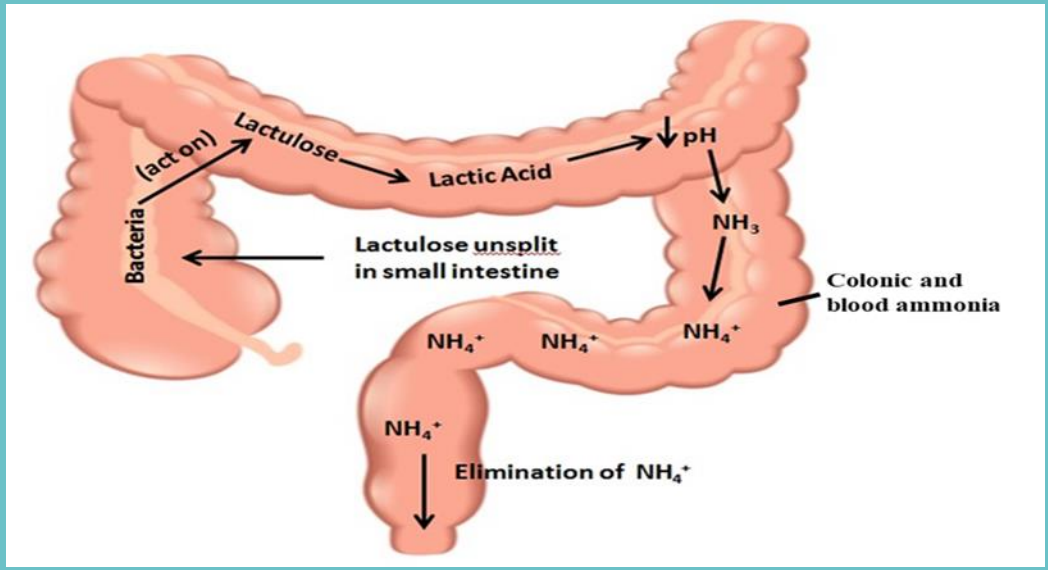
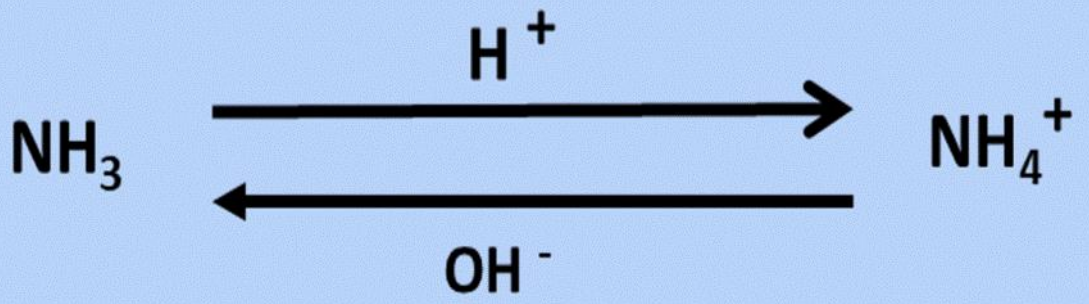
Mechanism of Action of Lactulose for OHE





- 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

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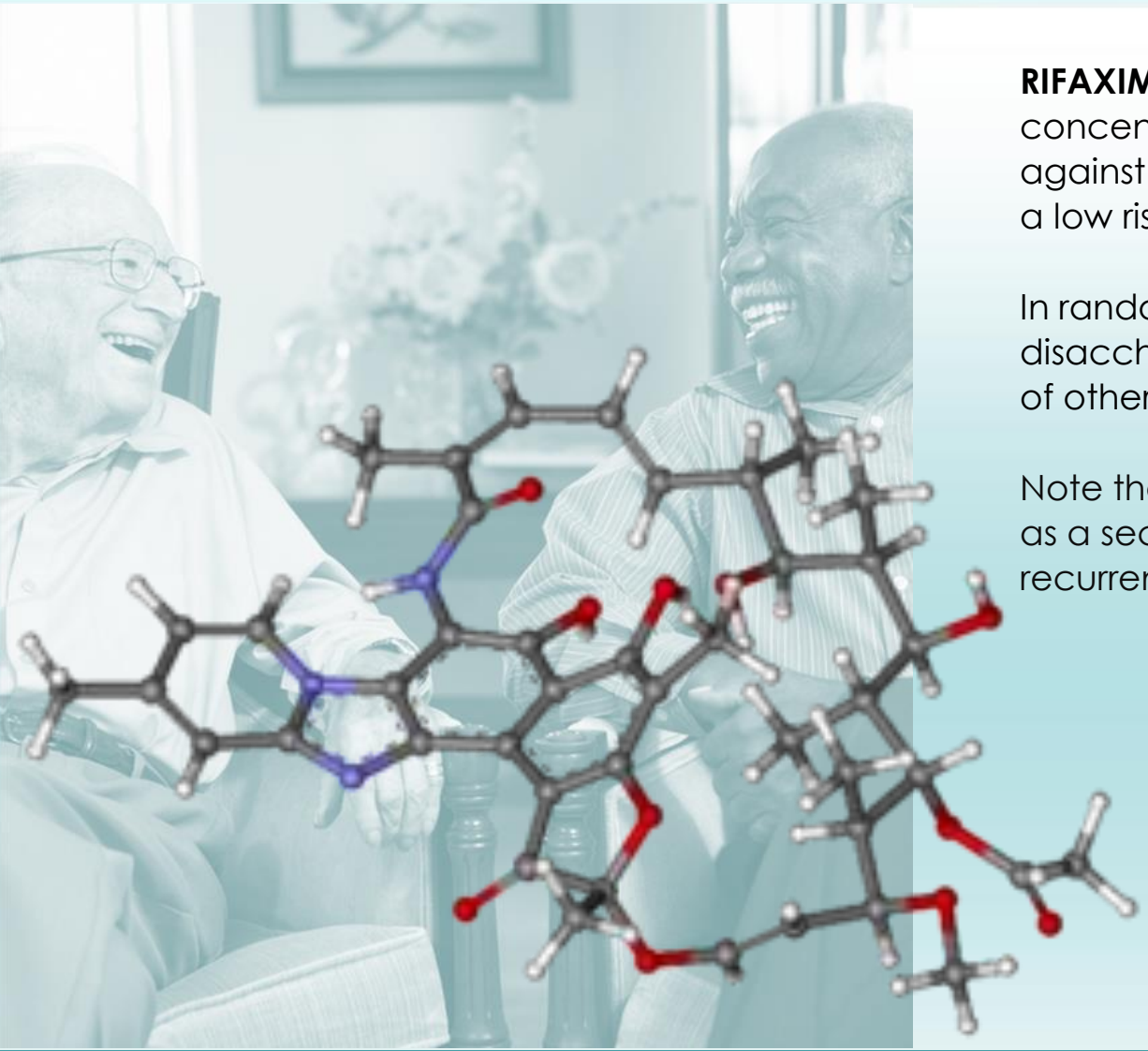
Rifaximin



RIFAXIMIN is a minimally absorbed oral antimicrobial agent that is concentrated in the gastrointestinal tract, has broad-spectrum activity against gram+ and gram- aerobic and anaerobic enteric bacteria, and has a low risk of inducing bacterial resistance.[8]

In randomized studies, **Rifaximin** was more effective than non-absorbable disaccharides and had efficacy that was equivalent to or greater than that of other antibiotics used in the treatment of acute HE.[9]

Note that rifaximin is not a treatment for OHE. It should rather be positioned as a secondary prophylaxis strategy for use with lactulose to prevent recurrence of HE and related hospitalizations.[12]

[9] **Debbie** 2008
[10] **Paik** 2005
[13] **Bass 2010**

Randomized, Double-Blind, Controlled Trial

The NEW ENGLAND JOURNAL of MEDICINE

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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.

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

LONG TERM CARE

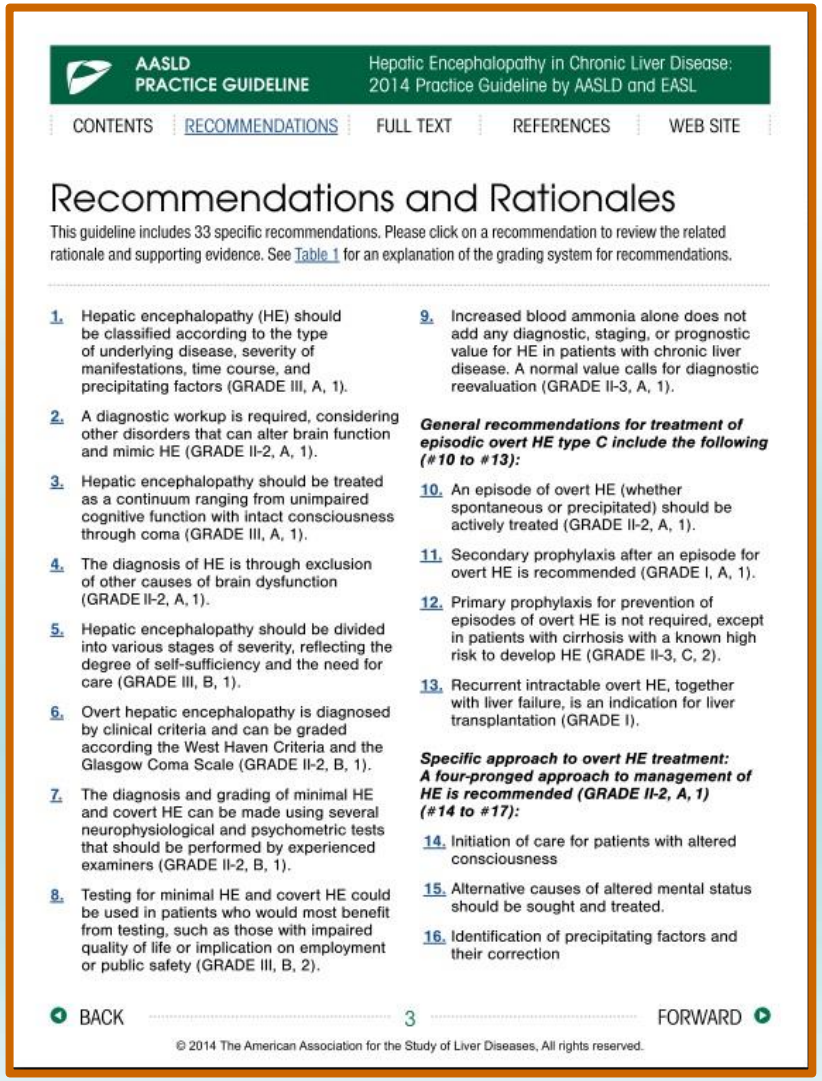
Usual Adult Dose for Hepatic Encephalopathy

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

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).

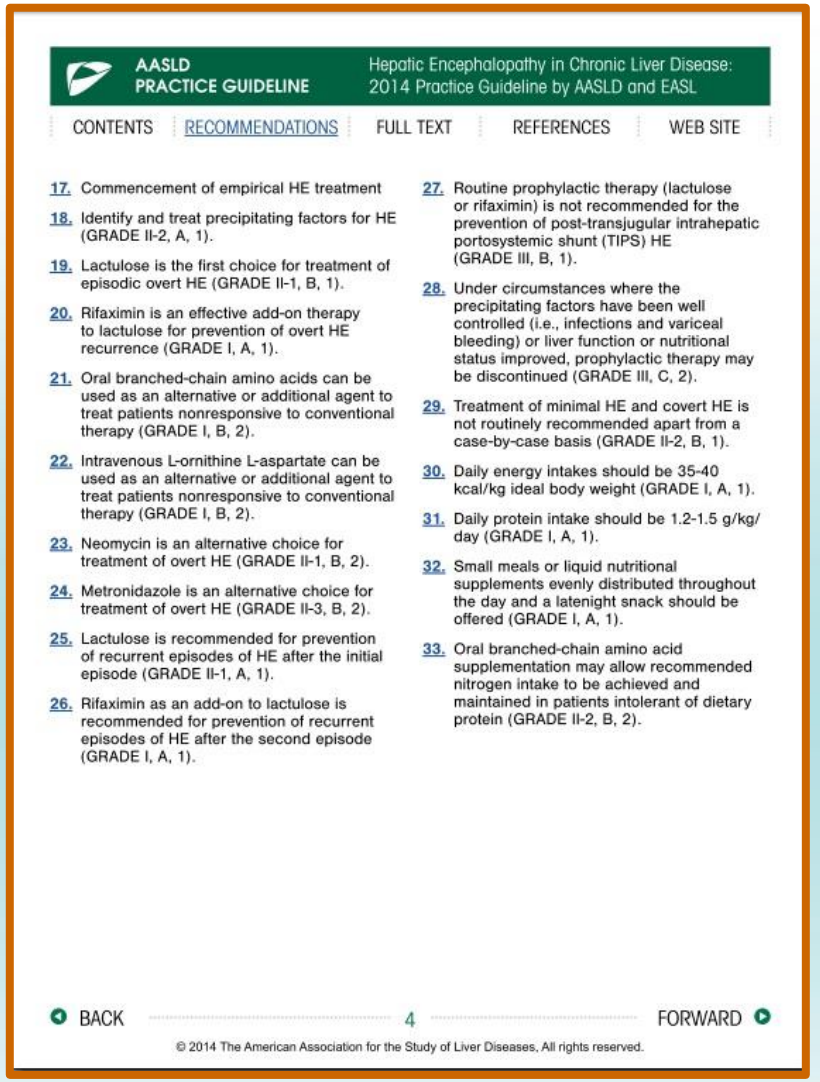
General recommendations for treatment of episodic overt HE type C include the following (#10 to #13):

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



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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**

LONG TERM CARE

KTAP

Key Take Away Points

LONG TERM CARE

Key Take Away Points

1. Keep HE (Hepatic Encephalopathy) top of mind as one potential cause for ‘Change in Mental Status.

2. Develop a process for your facility to efficiently and effectively diagnosis and treat HE.

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

4. Combination therapy with lactulose and rifaximin following an episode of OHE has been well studied, and proven to reduce the risk of OHE recurrence and HE related hospitalizations.

Q&A

Questions & Answers

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