



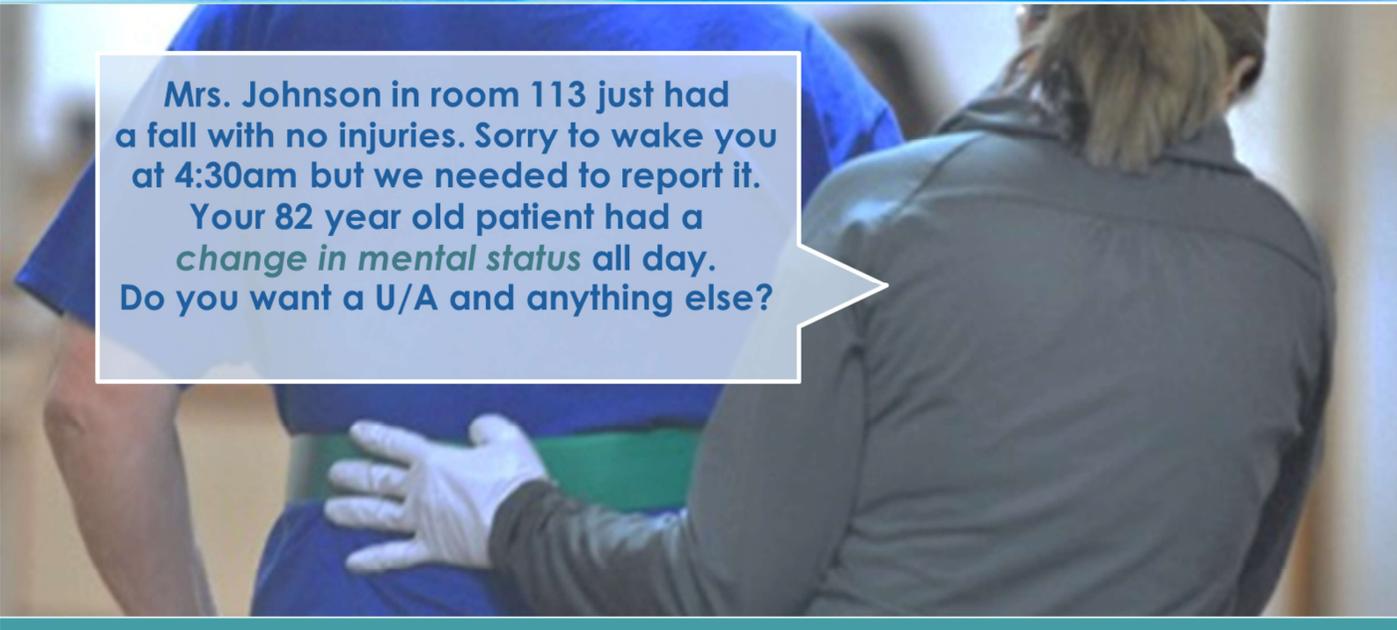
Change in Mental Status **Hepatic Encephalopathy (HE)**

Treatment & IDT Process

Facilitator Notes:

This is Part 2 of our 2 part series on Changes in Mental Status – Hepatic Encephalopathy.

This part covers in detail the treatments for HE as well as the roles and responsibilities for each member of the Interdisciplinary Team. This Part also quickly reviews the problem and diagnosis before diving into the details of treatment and IDT roles. As such this will aid your SNF, especially leaders, to best manage this critical problem.



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?

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.

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 these is the buildup of toxic levels of serum ammonia in patients with chronic liver failure, which underlies hepatic encephalopathy (HE).

Chronic Liver Disease (CLD) affects over 5.5 million patients in the USA¹, of who more than 600,000 have cirrhosis.²

¹ Kim 2002
² Scaglione 2015

Facilitator Notes:

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

This results 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.



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 readmissions⁴

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

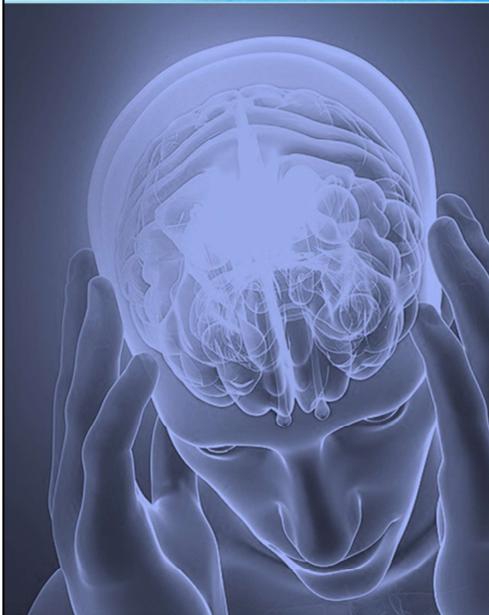
3. Elwir 2017
4. Tapper et al 2016

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
- LTC providers need to be both knowledgeable and vigilant when they observe cirrhosis patients exhibiting symptoms like a change in mental status

Diagnosis and Factors



Diagnosis of hepatic encephalopathy

- Elevated free arterial serum 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.

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 others causes and may show brain swelling

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

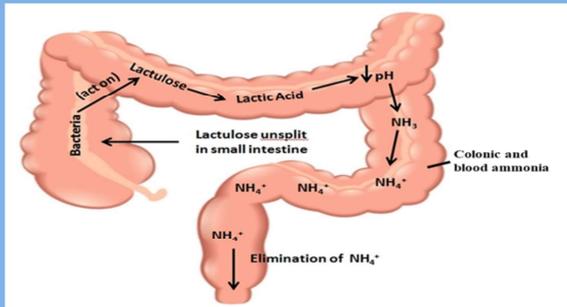
The AASLD/EASL Guidelines are a very credible source to build out a guide for your facility..



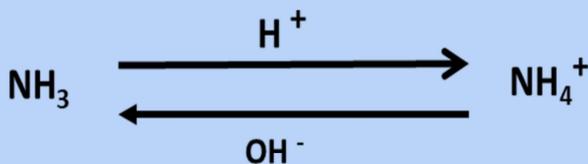
Facilitator Notes:

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

Mechanism of Action of Lactulose for OHE



- A non-absorbable disaccharide
- It produces osmosis of water — Diarrhea^{5,6}
- It reduces pH of colonic content & thereby converts freely diffusible NH₃ into ammonium ions (NH₄⁺), which cannot be absorbed and are therefore excreted^{5,6}
- 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.^{5,6}
- 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.⁷



⁵ Reena.
⁶ Davidson's
⁷ 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 (NH₃) into ammonium ions (NH₄⁺) 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

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.¹⁰

⁸ Debbie 2008
⁹ Paik 2005
¹⁰ Bass 2010

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 hospitalizations⁹

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.

Probiotics, Nutrition and Exercise

Probiotics have been found to be effective for HE compared to placebo but not more so than lactulose.¹¹

Nutrition: Cirrhotic patients commonly have malnutrition, muscle wasting (sarcopenia) and reduced survival as a consequence. Research dating back decades has debunked ideas of reducing protein intake as a means of lowering nitrogen load and ammonia burden (see reference below). Indeed, the recommendations now encourage small frequent protein meals throughout the day with a night-time snack of complex carbohydrates. This is often optimized in conjunction with a nutritional support team.

Consensus recommendations of the International Society for Hepatic Encephalopathy and Nitrogen Metabolism include optimal daily caloric intake of 35-40 kcal/kg and protein intake of 1.2-1.5 g/kg ideal body weight and provision of night time supplementation.¹² Zinc is occasionally helpful where there is deficiency or confirmed losses.

Exercise: As with normal patients, exercise in patients with liver disease can improve functional capacity, lean body mass and risk of falls.^{13,14} Exercise has the potential as an adjunct to improve nutrition, to reduce the frailty of patients that predisposes them to higher ammonia levels and greater risk of falls. However, more studies are needed to clearly identify the parameters for which it can be safe and effective. One can generally expect long-term care residents with multiple co-morbidities to benefit from exercise, with significant improvements in depression and pain relief as a consequence of endorphin release.¹⁵

¹¹ Saab 2016
¹² Amodio 2013

¹³ El-Khoury 2013
¹⁴ Roman 2016
¹⁵ Balchin 2016

Facilitator Notes:

Probiotics, nutrition and exercise may be helpful in the management of HE but it should be noted that they are not listed as a recommended treatment in the current (AASLD/EASL) guidelines on the treatment of HE

Again with a focus on the gut – probiotics may be helpful in the management of HE, but are still not as effective as other treatments.

Perhaps the most significant role for Probiotics in LTC is their use after a course of **antibiotics** in order to restore some of the healthy bacteria in the intestines that may have been killed. As such, probiotics are often ordered with antibiotics and continued for some time after the antibiotics are completed.

Nutrition is a key component to assure against malnutrition and limit the production of ammonium through a diet with the right balance of calories and protein.

As is true for most conditions, **exercise** improves the health of patients with HE, so keeping our older adults with HE active has major benefits, including reducing ammonia levels, frailty, risk of falls and mood.

Branched Chain Amino Acids (BCAA) & L-Ornithine-L-Aspartate (LOLA)

(BCAA)

- A preparation of amino acids (valine, leucine, and isoleucine) normally given orally or by nasogastric tube, has been postulated to alter the balance of amino acids in the brain as well as to provide energy supplementation. A recent Cochrane review of 16 randomized clinical trials found high quality evidence of clinical benefit but no effect on mortality, quality of life, or nutrition parameters.¹⁶ Thus, for some patients who are intolerant to the recommended protein intake, BCAA supplements may be considered as a means of meeting this nutritional need without risking detrimental effects on the mental state.¹⁷

(LOLA)

- A combination containing the amino acids ornithine and aspartic acid given by intravenous infusion. A meta-analysis of 20 randomized controlled trials showed LOLA to be as effective as non-absorbable disaccharides, with a trend towards superiority, with few adverse effects.¹⁸

¹⁶ Gluud 2017
¹⁷ Marchesini 2000
¹⁸ Zhu 2015

Facilitator Notes:

If adequate amounts of proteins can not be obtained through a diet they can be supplemented through the use of branched chain amino acids. The **branched-chain amino acids** (BCAAs) are a group of three essential **amino acids**: leucine, isoleucine and valine.

They are essential, meaning they can't be produced by your body and must be obtained from food. BCAA supplements have been shown to build muscle, decrease muscle fatigue, alleviate muscle soreness as well as assist in management of HE.

We started with the oral route by mouth with diet, then moved to NG tube options with branched chain amino acids – now we move to intravenous solutions with L-Ornithine-L-aspartate. L-ornithine L-aspartate can lower blood ammonia levels and so may have beneficial effects in people with hepatic encephalopathy or help stop them developing it.

Liver Transplantation and Embolization of Portosystemic Shunts



Patients resistant to rifaximin and lactulose may be considered for embolization of portosystemic shunts.

Evidence from retrospective studies suggests that the procedure decreases hospital admissions and improves but adverse effects include gastro-esophageal varices, worsening ascites, and renal dysfunction due to contrast-induced nephropathy.¹⁹

Liver Transplantation: Overt HE improves significantly and reverses after liver transplantation, although for some of these patients signs of cognitive impairment persist.^{20,21} Moreover, the prospect of patients with HE receiving a liver transplant in a timely manner may be hindered by the MELD score (Model for End-Stage Liver Disease), which does not correlate well with this disease entity.²²

¹⁹ Laleman 2013
²⁰ Campagna 2014
²¹ Garcia-Martinez 2011
²² Yoo 2003

Facilitator Notes:

For patients unable to be treated with medications – there are surgical options such as blocking the portosystemic shunts

When all else fails, so to speak, patients may have the opportunity for liver transplant. While liver transplant can reverse many of the issues of HE, for many patients the cognitive impairment may persist. As such, liver transplant is typically reserved for patients who do not have significant or long standing cognitive deficits.

Ongoing Care for HE Patients

Symptom / need	Assessment	Intervention
Systolic hypertension	Blood pressure, signs of headaches	Monitor vital signs QD for patients with liver failure, potential for HE
Increased muscle tonicity (partial or generalized)	Assess increased muscle tone	Monitor for changes in muscle tonicity, difficulty in moving, turning or repositioning.
Myoclonus (decerebrate posturing)	Assess muscle tightness, extremity positioning changes; fall risk; balance scores	Physical Therapy Restorative nursing plan
Dysconjugate eye movements	Monitor eye movements tonicity	Eye tracking charting: convergence, divergence
Fluid and electrolyte imbalance; clotting disorder	Changes in symptoms	Laboratory draws for electrolytes, bilirubin, prothrombin and pre-albumin; family and patient education; dietary consultation; maintain schedule
Mental status changes	Track behaviors, consciousness, aggression, uncooperative behavior, ability to attend to directions and details, and West Haven Criteria	Plan interventions which reduce distress and allow person-centered EBP care; utilize facility behavior tracking sheets; plan activity interventions; incorporate family into 1:1 intervention as needed.
Mood changes	Mood scores, Depression evaluation, BIMS, Anxiety score, MMSE, Delirium	Person-centered daily care which accommodates needs of patients and family visits; testing and interventions supportive of EBP; meds per physician / NP orders
ADL changes	Monitor ADL scores; task segmentation; SOB during care; mobility deficits	Care needs to be individualized
Eating assistance with caloric management	Weights; Assistance with eating	Small, frequent protein meals; monitor changes in food and fluid intake, as needed; labs as above; weights
Family-patient updates by IDC team	Monitor for education deficits; Care questions	Team meetings; Rounds with SBAR or IPASS; Regular charting of involvement and updates during condition changes

Facilitator Notes:

There are specific symptoms that are common in HE patients – these require specific assessments and interventions. Many of these symptoms exist with other diseases and their assessment and interventions are no different with team approach such as therapy and 1:1 when needed.

Palliative Care



The very effectiveness of treatments for HE and other aspects of chronic liver disease has enabled elderly patients to survive longer with increasingly intensive care, often with substantial discomfort and suffering of the patients and considerable burden on families, caregivers and the healthcare system.²³ Despite this, data from the UK reports that referral to palliative care is low and over 2/3 of patients with liver disease die in the hospital after multiple inpatient hospital stays. The benefits of palliative care are numerous including improved quality of life and prolonged survival.^{24,25}

²³ The Lancet 2018
²⁴ Terrei 2010
²⁵ Bakitas 2009

Facilitator Notes:

Like many other conditions affecting older adults – HE is chronic and progressive. As such, there may be a time for palliative care. However, as with hospice and other end-of-life programs, palliative care tends to be used far too late in the course of diseases. Better recognition and earlier use of this care option can certainly improve quality of life and even improve survival.



Facilitator Notes:

From recognition, to diagnosis, through to treatment, we have seen example after example for different members of the Interdisciplinary Team. – Now, let's spend our last few minutes highlighting members' roles and responsibilities.

Director of Nursing / Nursing Staff



Dx

- Monitor signs and symptoms of cognitive changes, liver flap, HE, MDS assessment for changes, interim assessment, clinically complex resident with exacerbation of symptoms care planning
- Monitor disease trajectory

Tx

- Medication administration with comfort and polypharmacy
- Compliance of medication consumption
- Community health transitions of care support and follow-up
- Patient and Family Education on medications and compliance
- Provide palliative, progressive disease care and education, and end-of-life (EOL) Hospice Care

Facilitator Notes:

Let's start with our nursing staff. As those who stand on the frontlines in most condition management, their critical role in care of patients with HE is no exception.

Here it starts with recognition of the signs and symptoms to make the attending and others aware of these issues. Of course this is not a one and done but requires ongoing monitoring and updating on changes as HE will progress and fluctuate over time.

Nursing also plays a key role in treatment – both in following orders, as well as in assisting in patient and family education regarding transitions. These included transitioning home from our subacute units or transitioning to palliative care programs within our facility.

Attending Physician / APN / PA



Dx

- Clinical History and physical
- Order psychometric tests (PHES: "gold standard")

Tx

- Prescribe Lactulose and Rifaximin
- Coordinate with other specialists on diagnostics and treatment

Facilitator Notes:

Of course, the orders for treatment must come from the attending, but again this is often based on information provided by nursing staff. For example, communicating through SBAR the critical information to attending can go a long way toward ensuring proper management. Collectively, the attending physician, APN and PA have the following roles and responsibilities:

- Describing the Situation with regard signs and symptoms of HE in detail
- Obtaining patient background with regard such factors as cirrhosis or end stage liver disease
- Assessment regarding the current situation in terms of vitals and other physician and cognitive issues
- Conducting continuous quality improvement (CQI) staff training to include the learnings from this program in addition to the scenario we started with regarding the confused patients where we requested a UA which could lead to an inappropriate use of antibiotics and missed opportunity to appropriately treat HE.

Consultant Pharmacist



Dx

- Polypharmacy monitoring
- Drug-drug interactions
- Evidence-based pharmaceutical guides
- Disease-specific evaluation
- Therapeutic response

Tx

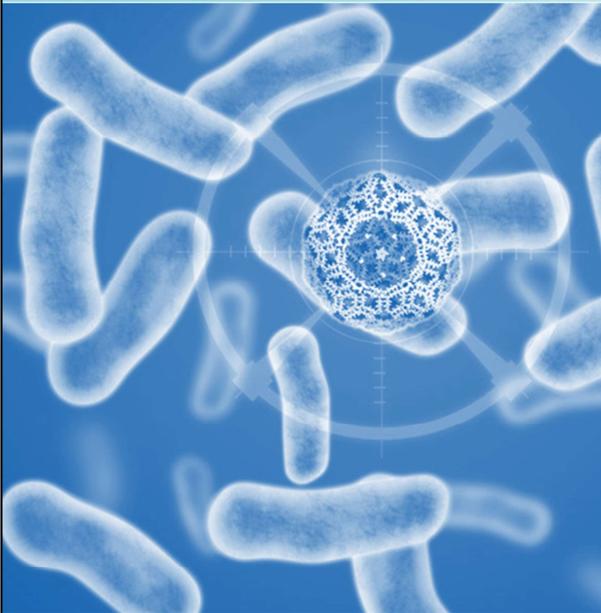
- Prescribe Lactulose and Rifaximin
- Coordinate with other specialists on diagnostics and treatment

Facilitator Notes:

Also as part of our team is our Consultant Pharmacist who, through their monthly Drug Regimen Review can make recommendations on appropriate treatment options such as adding rifaximin to Lactulose for treating HE.

Here, too, nursing can provide to the Consultant Pharmacist the SBAR for these HE patients to assure appropriate care.

Specialist



Dx

- Rule out or treat advanced renal disease and uremia or other conditions

Tx

- Treat renal disease
- Advise multidisciplinary team of implications for clearance of ammonia and other toxic substances

Facilitator Notes:

While it may be difficult to get a gastroenterologist, nephrologist, neurologist or liver specialist in to see a nursing home resident, we are seeing an increase in the use of telemedicine specialty services to improve access.

These are coming in the form of video conferences and other provider-to-provider links which can increase the specialty care options for these patients within the SNF, rather than forcing them out into the community for care.

Diagnostic & Therapeutic Roles

LTC INTERDISCIPLINARY TEAM (IDT)

Discipline	Diagnostic	Therapeutic
Nursing Team	Monitor physical and cognitive signs and symptoms of HE, and food acceptance	Patient and family education on medications and compliance, disease trajectory; administer medications, provide behavioral, palliative care.
Pharmacist	Evaluate and monitor polypharmacy, drug-drug interactions, pharmaceutical guides and evidence based pharmaceutical guides.	Coordinate with other specialists on diagnostics and treatment Recommend lactulose and rifaximin (AASLD 1-A-1 Guideline)
Primary Care Provider	Obtain clinical history, conduct physical exam, and order psychometric tests (PHES: "gold standard")	Prescribe lactulose and rifaximin; coordinate with other specialists on diagnostics and treatment.
Neurologist	Evaluate electroencephalogram (spectral, versus visual EEG)	Treat and manage neurologic disease; manage patient's pain
Psychologist	Conduct Stroop test, smartphone application	Provide patient counseling.
Psychiatrist	Assess psychiatric symptoms, alcoholic liver disease, and withdrawal	Provide patient counseling, and management of anxiety, depression and pain.
Infectious Disease	Rule out, or treat infectious disease having symptoms similar to HE, or which might precipitate or exacerbate HE	Prescribe appropriate antibiotics
Endocrinologist	Identify severe hyperglycemia and poorly-controlled diabetes	Ensure that patient's glycemic levels are well-controlled.
Nephrologist	Rule out or treat advanced renal disease and uremia	Treat renal disease; advise interdisciplinary team of implications for clearance of ammonia and other toxic substances
Social Worker	Get feedback from patient and family on adherence to therapy; Provide support and person-centered counseling; monitor for cognitive changes	Coordinate with family and other caregivers to help ensure adherence to therapy; provide support system, and adequate housing.
Occupational Therapist	Evaluate safety of home and work environments, skill evaluations, driving, and other life skills and activities affected by HE	Advise patient, caregivers and interdisciplinary team of these risks and interventions to minimize them.
Dietitian	Evaluate adequacy of total caloric and protein intake	Adjust diet to mitigate frailty and sarcopenia

Facilitator Notes:

In summary, the selection of treatment agents is only a part of the management of HE. As in most conditions, in LTC a team is needed for successful management, and this starts with nursing.

Please utilize this table, which provides guidance for the extended LTC treatment team, as a reference within your facilities.



Facilitator Notes:

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

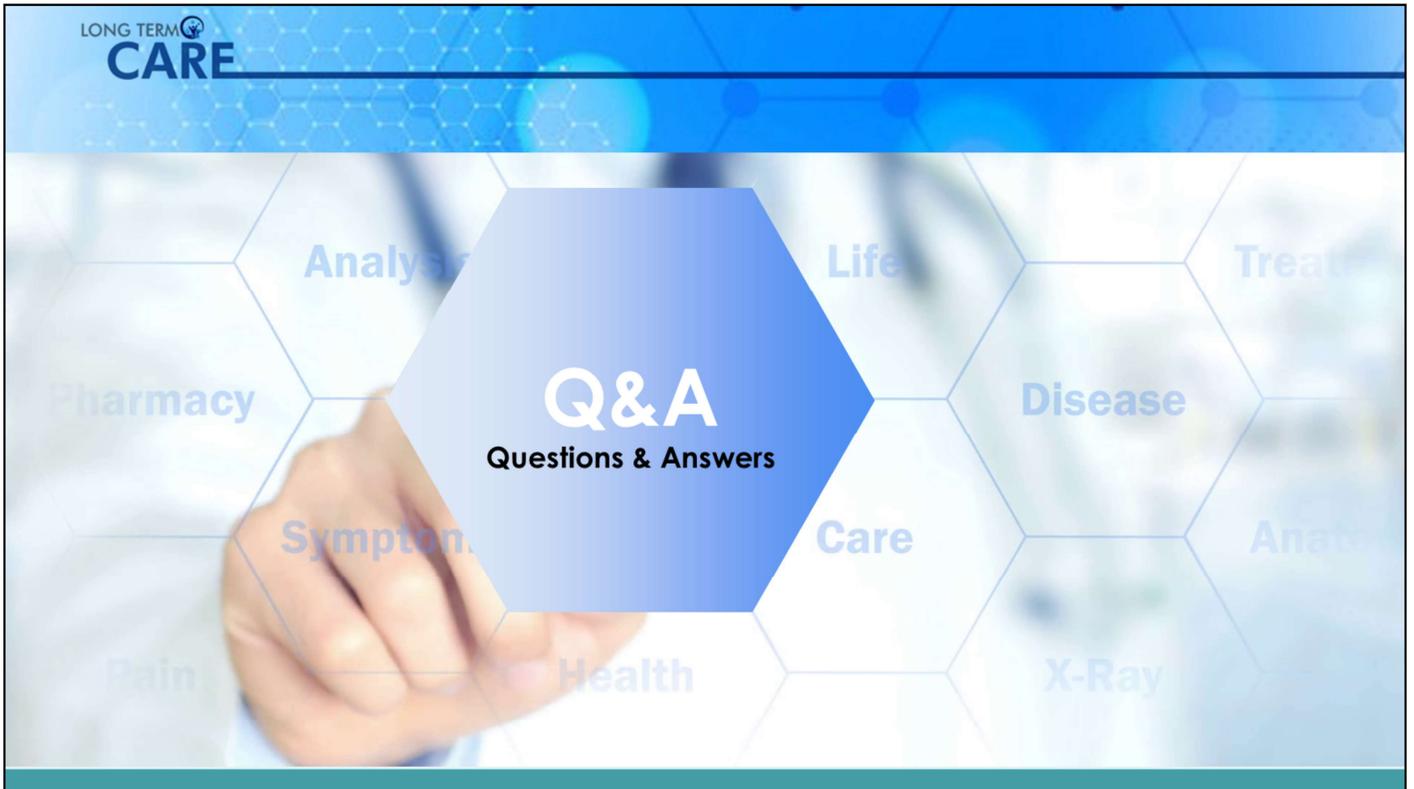
Key Take Away Points



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. 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
5. Include all members of the IDT in this process with a continuous quality improvement (CQI) process to assure that appropriate outcomes are being met.

Three 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's up to us to keep it top of mind as 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, a process needs to be instituted. So, let's not have it end here, but rather work as a team to develop a process for the appropriate management of our patients with mental status changes that includes consideration of HE.
3. The AASLD/EASL 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
5. Include all members of the IDT in this process with a CQI process to assure that appropriate outcomes are being met – This process that we develop requires all members of the IDT as well as continuous quality improvement, as it is never a one-and-done, but requires us working together each and every day to improve the care of our patients -especially those experiencing mental status changes from HE.



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

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**. *Clinical Gastro Hepatol* 2016;**14**:1181-1188
5. **Reena**. Hepatic Encephalopathy. <https://www.slideshare.net/RINA7373/hepatic-encephalopathy-35951607>
6. **Davidson's Principles & Practice of Medicine** – 21st edition, Harrison's Principles of Internal Medicine – 10th & 17th edition. Current Medical Diagnosis & Treatment – 2014 edition.
7. **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.
8. **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
9. **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.
10. **Bass N**, Mullen K, Sanyal A. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362(12):1071-81.
11. **Saab S**, Suraweera D, Au Jet al. Probiotics are helpful in hepatic encephalopathy: a meta-analysis of randomized trials. *Liver Int*. 2016;36:986-993
12. **Amodio P**, Bemeur C, Butterworth R, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. *Hepatology*. 2013 Jul;58(1):325-36.
13. **El-Khoury F**, Cassou B, Charles MA et al. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials. *BMJ*.2013;347:f6234.
14. **Roman E**, Garcia-Galceran C, Torrades T et al. Effects of an exercise programme on functional capacity, body composition and risk of falls in patients with cirrhosis: a randomized clinical trial. *PloS One*. 2016;11:e0151652.
15. **Balchin R**, Linde J, Blackhurst D, et al. Sweating away depression? The impact of intensive exercise on depression. *J Affect Disord*.2016;200:218-21.

References: (continued)

16. **Gludd L**, Dam G, Les I, et al. Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database Syst Rev*. 2017;5:CD001939.
17. **Marchesini G**, Bianchi G, Rossi B, et al. Nutritional treatment with branched-chain amino acids in advanced liver cirrhosis. *J Gastroenterol*. 2000;35 Suppl 12:7-12.
18. **Zhu G**, Shi K, Huang S, et al. Systematic review with network meta-analysis: the comparative effectiveness and safety of interventions in patients with overt hepatic encephalopathy. *Aliment Pharmacol Ther*. 2015 Apr;41(7):624-35.
19. **Laleman W**, Simon-Talero M, Maleux G, et al. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: a multicenter survey on safety and efficacy. *Hepatology*. 2013 Jun;57(6):2448-57.
20. **Campagna F**, Montagnese S, Schiff S, et al. Cognitive impairment and electroencephalographic alterations before and after liver transplantation: what is reversible? *Liver Transpl*. 2014;20:977-986.
21. **Garcia-Martinez R**, Rovira A, Alonso J, et al. Hepatic encephalopathy is associated with posttransplant cognitive function and brain volume. *Liver Transpl*. 2011;17:38-46.
22. **Yoo H**, Edwin D, Thuluvath P. Relationship of the model for end-stage liver disease (MELD) scale to hepatic encephalopathy, as defined by electroencephalography and neuropsychometric testing, and ascites. *Am J Gastroenterol*. 2003 Jun;98(6):1395-9.
23. **The Lancet**. Palliative care in liver disease: a matter of life and death. *Lancet Gastroenterol Hepatol*. 2018 Feb;3(2):73.
24. **Temel J**, Greer J, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010; 363:733-742.
25. **Bakitas M**, Lyons KD, Hegel MT, Balan S, et al. Effects of palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *J Am Med Assoc*. 2009; 302:741-749