INTERACTIVE GUIDE:

Clinical Considerations in HE

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GastroHub for Advanced Practice Providers

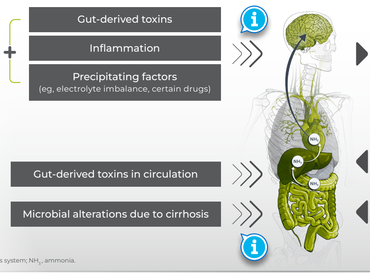
Hepatic Encephalopathy: A major neuropsychiatric complication of cirrhosis[1]

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting[2]

HE can present as a wide spectrum of symptoms, ranging from covert to overt neuropsychiatric abnormalities[2]

The pathophysiology of HE is complex and involves multiple organ systems[1,3-5]

Brain dysfunction in HE is thought to result from[1-5]:



CNS, central nervous system; NH_3, ammonia.

HE is a primary complication of cirrhosis[8]

UP TO 80% of patients with cirrhosis will develop some form of HE[2]

UP TO 40% of patients with cirrhosis will develop overt HE (OHE)[2]

ALL AT-RISK PATIENTS SHOULD BE TESTED TO HELP INFORM PROPER DISEASE MANAGEMENT[2]

Screening for early signs of OHE is important and can be used to counsel patients and caregivers about the disease, including what to look for in its progression[2]

West Haven Criteria can be used to classify HE into stages or grades based on clinical manifestations[2]

Early/covert HE signs and symptoms

Symptoms can be subtle—mild mood changes or other deficits only detectable by psychometric or neurophysiological testing[2]

Early signs of HE may include[1,2,10,11]:

- Difficulty with simple math
- Loss of small hand movements
- Euphoria or anxiety
- Shortened attention span
- Trivial lack of awareness
- Altered sleep rhythm

OHE signs and symptoms

OHE is associated with more prominent symptoms, worsening cognitive function, poorer prognosis, and increased risk of hospitalization[2,12,13]

- Cognitive symptoms can present anywhere on a continuum, spanning from confusion and lethargy to complete disorientation, semi-stupor, and even progression to coma[2]
- Patients can exhibit asterixis, a "hand-flapping" tremor[2]
- Noncomatose patients with OHE can show **motor system abnormalities and extrapyramidal dysfunction**[2]

OHE is often associated with one or more precipitating factors, which can cause hospitalization[14]

Common precipitating factors to screen for and correct include[2]:

- Infection
- Gastrointestinal bleeding
- Electrolyte disorder
- Constipation
- Diuretic overdose

GUIDELINES FROM THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES/EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (AASLD/EASL) RECOMMEND PROMPT TREATMENT OF PRECIPITATING FACTORS[2]

Once OHE occurs, patients have an increased risk of recurrence[2]

40% cumulative risk of OHE recurrence within 1 year after an initial episode[2]

OHE is a leading cause of hospital readmissions in patients with cirrhosis[15-18]

IN AN ANALYSIS OF THE NATIONWIDE READMISSION DATABASE

32% of patients hospitalized with HE were readmitted within 30 days[18]

Study utilized the 2013 Nationwide Readmission Database (NRD; represented about 49% of the US population and all hospitalizations) and focused particularly on hospitalized patients with HE (n=24,473) to assess independent predictors of 30-day readmission and develop a readmission risk model in patients with HE. The impact of 30-day readmission in patients with HE on calendar-year mortality was also assessed.[18]

Align with the guidelines by using the only FDA-approved medication indicated for the reduction in risk of OHE recurrence in adults[2,19]

AASLD GUIDELINES GRADE 1,A,1 STRONGLY POSITIVE RECOMMENDATION

XIFAXAN® (rifaximin) earned the highest possible recommendation (GRADE 1,A,1) from AASLD/EASL as an add-on therapy to lactulose to reduce the risk of OHE recurrence after a patient has a recurrence while on lactulose alone[2]

Per the GRADE System for Evidence: Grade 1=randomized; A=evidence is "high quality," and further research is very unlikely to change our confidence in the estimated effect; and 1=recommendation is "strong," with factors influencing strength of recommendation including the quality of evidence, presumed patient-important outcomes, and costs.[2]

XIFAXAN significantly cut the risk of OHE recurrence and HE-related hospitalization during 6 months of treatment[19,20]

Phase 3 clinical trial[19,20]

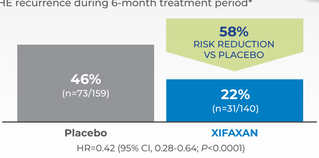
Study design: In a randomized, placebo-controlled, double-blind, multicenter, multinational, 6-month study, the efficacy of XIFAXAN 550 mg (taken orally twice a day) was evaluated in 299 adult patients

Key inclusion criteria: Age ≥18 years old, MELD score ≤25, in remission (Conn score, 0 or 1) from HE at enrollment, and ≥2 episodes of OHE (Conn score, ≥2) associated with cirrhosis during the previous 6 months

91% of patients in the placebo and XIFAXAN groups were on concomitant lactulose

Primary endpoint[19,20]

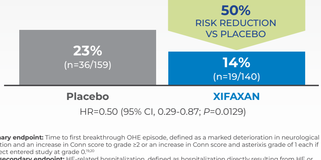
OHE recurrence during 6-month treatment period*



HR=0.42 (95% CI, 0.28-0.64; *P*<0.0001)

Key secondary endpoint[19,20]

HE-related hospitalization during 6-month treatment period†



HR=0.50 (95% CI, 0.29-0.87; *P*=0.0129)

*__Primary endpoint:__ Time to first breakthrough OHE episode, defined as a marked deterioration in neurological function and an increase in Conn score to grade ≥2 or an increase in Conn score and asterixis grade of 1 each if subject entered study at grade 0.[19]

†__Key secondary endpoint:__ HE-related hospitalization, defined as hospitalization directly resulting from HE or hospitalization complicated by HE.[19,20]

CI, confidence interval; HR, hazard ratio; MELD, Model for End-Stage Liver Disease.

INDICATION

XIFAXAN® (rifaximin) 550 mg tablets are indicated for the reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults.

IMPORTANT SAFETY INFORMATION

- XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.
- There is an increased systemic exposure in patients with severe (Child-Pugh Class C) hepatic impairment. Caution should be exercised when administering XIFAXAN to these patients.
- Caution should be exercised when concomitant use of XIFAXAN and P-glycoprotein (P-gp) and/or OATPs inhibitors is needed. Concomitant administration of cyclosporine, an inhibitor of P-gp and OATPs, significantly increased the systemic exposure of rifaximin. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-gp inhibitors may further increase the systemic exposure to rifaximin.
- In clinical studies, the most common adverse reactions for XIFAXAN (alone or in combination with lactulose) were:
  - HE (≥10%): Peripheral edema (17%), constipation (16%), nausea (15%), fatigue (14%), insomnia (14%), ascites (13%), dizziness (13%), urinary tract infection (12%), anemia (10%), and pruritus (10%)
- INR changes have been reported in patients receiving rifaximin and warfarin concomitantly. Monitor INR and prothrombin time. Dose adjustment of warfarin may be required.
- XIFAXAN may cause fetal harm. Advise pregnant women of the potential risk to a fetus.

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please click here for full Prescribing Information.

Click here to learn more about XIFAXAN

Prompt recognition and guideline-based management of OHE are important throughout the patient journey[2,21]

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