Management of hepatic encephalopathy in primary care

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This management algorithm was commissioned and funded by Norgine Pharmaceuticals Limited and was developed by a multidisciplinary group: Clayton et al. See page 6 for full disclaimer. Prescribing and adverse event reporting information can be found on page 7.

Guidelines

Hepatic encephalopathy (HE)

- HE is a frequent complication of liver disease and one of its most debilitating manifestations[1]
  - it is a reversible condition caused by accumulation of toxins normally removed by the liver, such as ammonia[2]
  - it has a wide spectrum of neurological and psychiatric manifestations, ranging from subclinical alterations to coma (Table 1)[1]
- HE is an uncommon but important condition
  - HE severely affects the lives of patients and their carers[1]
  - HE increases demand on the healthcare system[1]
  - **early identification of HE in primary care can make a difference to patient outcomes**
- Clinicians should have a high index of suspicion for HE in patients with known cirrhosis or risk factors for development of liver disease (Box 1) and who present with the symptoms in Table 1.

Box 1: Common risk factors for chronic liver disease

- Obesity, type 2 diabetes, and metabolic risk factors for NAFLD
- Alcohol misuse
- Viral—hepatitis B or C

NAFLD: non-alcoholic fatty liver disease.

Identification and management of HE in primary care

- Figure 1 summarises the expert group's recommendations for identification and management of HE in primary care.

Table 1: Possible symptoms of HE[1]

Symptom grade		Symptom description
Covert	Minimal	■ Alterations in cognitive function only detectable on psychometric or neuropsychological tests (e.g. animal naming test, see Box 2)
	Grade 1	■ Low-level lack of awareness ■ Euphoria or anxiety ■ Shortened attention span ■ Impairment of addition and subtraction (e.g. serial 7s: 100 –7 –7 –7…) ■ Altered sleep rhythm (disturbed sleep–wake cycle)
Overt	Grade 2	■ Lethargy or apathy ■ Disorientation ■ Obvious personality change ■ Inappropriate behaviour ■ Dyspraxia ■ Asterixis
	Grade 3	■ Somnolence to semi-stupor ■ Impaired responsiveness to stimuli ■ Confusion ■ Gross disorientation ■ Bizarre behaviour
	Grade 4	■ Coma

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Figure 1: Algorithm for identification and management of HE in primary care

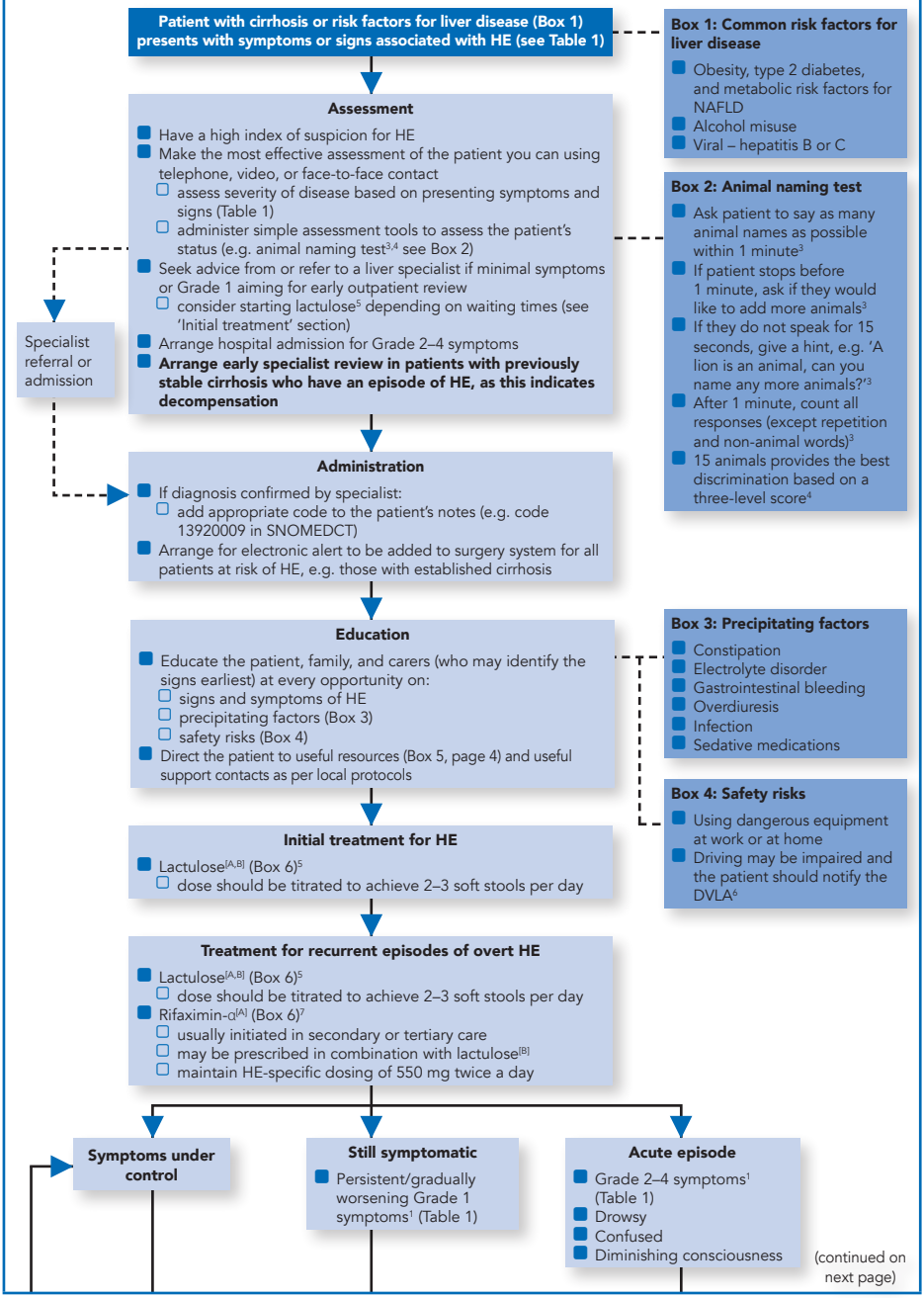
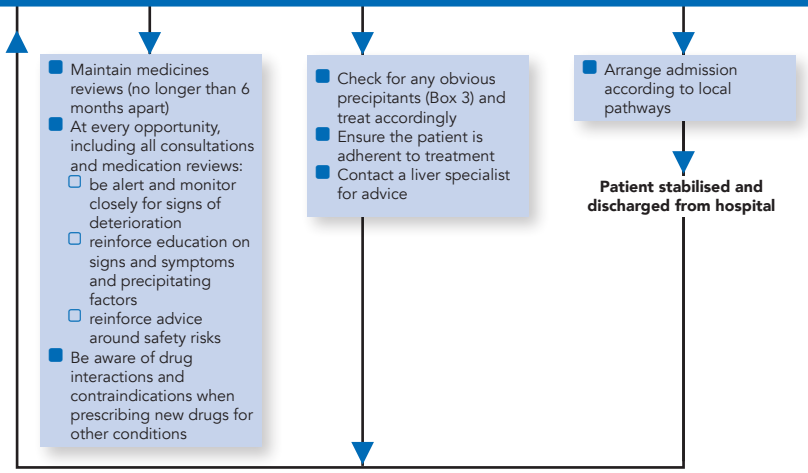


Figure 1: Algorithm for identification and management of HE in primary care (continued)



DVLA: Driver and Vehicle Licensing Authority; HE: hepatic encephalopathy; NAFLD: non-alcoholic fatty liver disease

[A] Check summary of product characteristics[5,7] or BNF[8] before prescribing to rule out contraindications, be aware of cautions, consider potential drug interactions, and for further information

[B] Lactulose changes the pH of stools to reduce growth of bacteria that produce toxins such as ammonia; do not substitute with other laxatives, as it is not the laxative effect that is useful in the treatment of HE

Assessment

- Have a high index of suspicion for HE in a patient with cirrhosis or risk factors for liver disease (Box 1) who presents with symptoms or signs associated with HE (Table 1)
- Make the most effective assessment of the patient you can using telephone, video, or face-to-face contact
  - assess severity of disease based on presenting symptoms and signs (Table 1)
  - administer simple assessment tools to assess the patient's status (e.g. animal naming test[3,4] see Box 2)
- Seek advice from or refer to a liver specialist for early outpatient review if minimal or Grade 1 symptoms
  - consider starting lactulose[5] depending on waiting times (see 'Initial treatment')
- Arrange hospital admission for Grade 2–4 symptoms
- Arrange early specialist review in patients with previously stable cirrhosis who have an episode of HE, as this indicates decompensation.

Box 2: Animal naming test

- Ask patient to say as many animal names as possible within 1 minute[3]
- If patient stops before 1 minute, ask if they would like to add more animals[3]
- If they do not speak for 15 seconds, give a hint, e.g. 'A lion is an animal, can you name any more animals?'[3]
- After 1 minute, count all responses (except repetition and non-animal words)[3]
- 15 animals provides the best discrimination based on a three-level simplified animal-naming test (s-ANT$_1$) score:[4]
  - 0 for s-ANT$_1$ ≥15
  - 1 for 10 ≤ s-ANT$_1$ <15
  - 2 for s-ANT$_1$ <10

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Administration

- If diagnosis confirmed by specialist, add appropriate code to the patient's notes (e.g. code 13920009 in SNOMEDCT)
- Arrange for electronic alert to be added to surgery system for all patients at risk of HE, e.g. those with established cirrhosis.

Education

- Educate the patient, family, and carers (who may identify the signs earliest) at every opportunity:
  - signs and symptoms of HE (Table 1)
  - precipitating factors (Box 3)
  - safety risks (Box 4)

Box 3: Precipitating factors

- Constipation
- Electrolyte disorder
- Gastrointestinal bleeding
- Overdiuresis
- Infection
- Sedative medications

Box 4: Safety risks

- Using dangerous equipment at work or at home
- Driving may be impaired and the patient should notify the DVLA (see Box 5)[6]

- Direct the patient to useful resources (Box 5) and useful support contacts as per local protocols.

Box 5: Useful resources

- British Liver Trust website: https://britishlivertrust.org.uk/
- DVLA: www.gov.uk/browse/driving/disability-health-condition

Pharmacological management

- Once any precipitating factors have been addressed (Box 3), treatment aims to minimise the production and absorption of toxins (such as ammonia) in order to reduce symptoms[5,7]
- Sedating drugs, including opioid analgesics, should be prescribed with caution in patients with HE
- Box 6 summarises treatments for HE.

Box 6: Treatments for HE

Lactulose*

- Non-absorbable polysaccharide that changes the pH of stools to reduce growth of bacteria that produce toxins such as ammonia[5]

Rifaximin-α*

- Non-absorbable antibiotic that minimises the bacterial load in the gut, which reduces the production of ammonia and other compounds implicated in the pathogenesis of HE[7]
- Licensed for the reduction in recurrence of episodes of overt HE in patients aged ≥18 years[7]
- May be prescribed in combination with lactulose or as monotherapy if intolerant to lactulose

*Check summary of product characteristics[5,7] or BNF[8] before prescribing to rule out contraindications, be aware of cautions, consider potential drug interactions, and for further information

HE: hepatic encephalopathy.

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Initial treatment of HE

- Lactulose[5]
  - primary care clinicians may consider starting lactulose while the patient waits for specialist assessment, depending on waiting time
    - starting dose of 30–45 ml (6–9 x 5 ml spoonfuls) or 2–3 sachets 3–4 times daily
    - patients may adjust their maintenance dose to 15–30 ml (corresponding to 1–2 sachets) to achieve 2–3 soft stools each day[5]
  - if lactulose does not result in 2–3 soft stools per day:
    - do not substitute with other laxatives, as it is not the laxative effect that is useful in the treatment of HE
    - contact a specialist for guidance on management, such as using rifaximin-α, which is an amber drug usually initiated in secondary or tertiary care (see 'Treatment for recurrent episodes of overt HE' and Box 6)
  - common adverse reactions of lactulose include flatulence, abdominal pain, nausea, and vomiting. If the dose is too high, diarrhoea may occur[5]
    - for full details of possible adverse reactions please refer to summary of product characteristics for lactulose at www.medicines.org.uk/emc or *British National Formulary* (BNF).[5,8]

Treatment for recurrent episodes of overt HE

- Continue lactulose[5]

- Rifaximin-α[7]
  - typically initiated in secondary or tertiary care
    - primary care may need to prescribe taking local arrangements into consideration
  - recommended dose for HE is 550 mg twice a day[7]
  - common adverse reactions are dizziness, headache, depression, dyspnoea, upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritis, muscle spasms, arthralgia, and peripheral oedema[7]
    - for full details of possible adverse reactions please refer to summary of product characteristics for rifaximin-α at www.medicines.org.uk/emc or *British National Formulary* (BNF).[7,8]

Monitoring

- Monitor patients in line with local arrangements with specialist care

- Urea and electrolytes should be monitored closely, especially in patients taking diuretics:
  - diuretics can cause hyponatraemia, hypokalaemia, or renal dysfunction, which are all triggers for HE

Practice points

- Box 7 provides some practice points of which to be aware.

Box 7: Practice points

- Avoid sedation and use opioids with caution
- Continue medicines prescribed in secondary care in line with local protocols
- Nutritional status—advise the patient to avoid prolonged fasting, and to eat frequent small meals, and carbohydrate-based late evening snack[9]
- Use animal naming test to assess cognition[3,4] (see Box 2)
- Look for marker signs, such as asterixis and disorientation[1]
- Monitor urea and electrolytes closely, especially in patients taking diuretics
- HE in patients with established cirrhosis may indicate decompensation and is a major event in the disease course

HE: hepatic encephalopathy.

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References

1. Vilstrup H, Amodio P, Bajaj J et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014; **60**: 715–735.

2. Guest J, Nanuwa K, Barden R. Utility values for specific hepatic encephalopathy health states elicited from the general public in the United Kingdom. *Health Qual Life Outcomes* 2014; **12**: 89–97.

3. Agarwal A, Taneja S, Chopra M, et al. Animal naming test—a simple and accurate test for diagnosis of minimal hepatic encephalopathy and prediction of overt hepatic encephalopathy. *Clin Exp Hepatol* 2020; **6**: 116–224.

4. Campagna F, Montagnese S, Ridola L et al. The animal naming test: An easy tool for the assessment of hepatic encephalopathy. *Hepatology* 2017; **66**: 198–208.

5. Mylan Products Ltd. *Duphalac (lactulose) 3.335 g/5 ml oral solution—summary of product characteristics.* Available at www.medicines.org.uk/emc/

6. DVLA. *Drug or alcohol misuse or dependence: assessing fitness to drive.* DVLA, 2021. Available at www.gov.uk/guidance/drug-or-alcohol-misuse-or-dependence-assessing-fitness-to-drive

7. Norgine Limited. *TARGAXAN® (rifaximin-α)—summary of product characteristics.* Available at www.medicines.org.uk/emc/

8. NICE. *British National Formulary.* Available at: https://bnf.nice.org.uk (accessed 2 July 2021).

9. Yeoman A, Aspinall R, Clayton M, Johnson J. *Consensus statement: identification and management of hepatic encephalopathy. Guidelines in Practice*, 2021. Available at www.guidelinesinpractice.co.uk/455680.article

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UK Prescribing Information: Targaxan 550mg (rifaximin-α)

REFER TO FULL SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) BEFORE PRESCRIBING

Presentation:
Film-coated tablet containing rifaximin 550 mg.

Uses:
Targaxan is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.

Dosage and administration:
Recommended dose: 550mg twice daily as long term treatment for the reduction in recurrence of overt episodes of overt hepatic encephalopathy.

In the pivotal study, 91% of patients were using concomitant lactulose.

TARGAXAN can be administered with a glass of water, with or without food.

No dosage changes are necessary in the elderly or those with hepatic insufficiency. Use with caution in patients with renal impairment.

The safety and efficacy in paediatric patients (aged less than 18 years) have not been established.

Contraindications:
Contraindicated in hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients and in cases of intestinal obstruction.

Warnings and precautions for use:
The potential association of rifaximin treatment with *Clostridium difficile* associated diarrhoea and pseudomembranous colitis cannot be ruled out.

The administration of rifaximin with other rifamycins is not recommended.

Rifaximin may cause a reddish discolouration of the urine.

Use with caution in patients with severe (Child-Pugh C) hepatic impairment and in patients with MELD (Model for End-Stage Liver Disease) score > 25.

In hepatic impaired patients, rifaximin may decrease the exposure of concomitantly administered CYP3A4 substrates (e.g. warfarin, antiepileptics, antiarrhythmics, oral contraceptives).

Both decreases and increases in international normalized ratio (in some cases with bleeding events) have been reported in patients maintained on warfarin and prescribed rifaximin. If co-administration is necessary, the international normalized ratio should be carefully monitored with the addition or withdrawal of treatment with rifaximin. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Ciclosporin may increase the rifaximin C_{max}.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Pregnancy and lactation:
Rifaximin is not recommended during pregnancy.

The benefits of rifaximin treatment should be assessed against the need to continue breastfeeding.

Side effects:
Common effects reported in clinical trials are dizziness, headache, depression, dyspnoea, upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia and peripheral oedema.

Other effects that have been reported include:
Clostridial infections, urinary tract infections, candidiasis, pneumonia cellulitis, upper respiratory tract infection and rhinitis. Blood disorders (e.g. anaemia, thrombocytopenia). Anaphylactic reactions, angioedemas, hypersensitivity. Anorexia, hyperkalaemia and dehydration. Confusion, sleep disorders, balance disorders, convulsions, hypoesthesia, memory impairment and attention disorders. Hypotension, hypertension and fainting. Hot flushes. Breathing difficulty, pleural effusion, COPD. Gastrointestinal disorders and skin reactions. Liver function test abnormalities. Dysuria, pollakiuria and proteinuria. Oedema. Pyrexia. INR abnormalities.

Prescribers should consult the SmPC in relation to all adverse reactions.

UNITED KINGDOM
Legal category: POM
Cost: Basic NHS price £259.23 for 56 tablets
Marketing Authorisation holder: Norgine Pharmaceuticals Limited, Norgine House, Widewater Place, Moorhall Road, Harefield, Uxbridge, UB9 6NS, UK
Marketing Authorisation number: PL 20011/0020

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Medical Information at Norgine Pharmaceuticals Ltd on:
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