Consensus statement: identification and management of hepatic encephalopathy

Consensus group: Dr Andrew Yeoman, Dr Richard Aspinall, Michelle Clayton, and Jill Johnson
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Background
Hepatic encephalopathy (HE) represents a major neuropsychiatric complication of chronic liver disease.\(^1,2\) HE can occur in any underlying liver disease and at any age. Around half of patients with cirrhosis will develop clinically apparent HE at some point during their disease course.\(^2\) The risk of experiencing the first bout of overt HE within 5 years of diagnosis is 5–25%.\(^1,2\) Minimal HE is also estimated to occur in between 20% and 80% of patients with cirrhosis.\(^1\)

HE is a debilitating complication that severely affects the lives of both patients and their caregivers.\(^1\) Hospital admissions are common and inpatient stays often prolonged. HE is also associated with a greater mortality risk than any other hepatic decompensation event.\(^1\) Survival after the first episode of HE is 42% at 1 year, dropping to 23% at 3 years.\(^2\) As a result, HE imposes a significant cost and resource burden on the healthcare system, which is only expected to increase in coming years as the overall incidence of chronic liver disease and cirrhosis continues to accelerate.\(^1,4,5\)

HE is a reversible condition caused by the accumulation of toxins (principally ammonia) that are normally removed by the liver.\(^6\) It produces a wide spectrum of neurological and psychiatric manifestations ranging from subclinical changes to coma. Current treatment for HE is centred mainly on reducing the production and absorption of gut-derived neurotoxins, particularly ammonia. Non-absorbable disaccharides, such as lactulose\(^*,\) and the non-absorbable antibiotic rifaximin\(^*\) are the current mainstays of pharmacological management.\(^1\)

Rationale for this consensus guidance
Although HE represents a serious complication of cirrhosis, it is a reversible and potentially treatable condition.\(^1\) Early identification and intervention are key to improving patient outcomes and reducing hospital admissions. To facilitate better identification and management of HE, two key groups of patients must be targeted: those patients with known cirrhosis, and the much bigger population of undiagnosed patients with occult liver disease. This second group of patients may remain ‘hidden’ in primary care or be moving through different departments in secondary care without a formal diagnosis. As a result, primary care physicians, practice nurses, generalists in the district general hospital setting, and clinical nurse specialists all have an important role to play in recognising and responding to potential HE in their patients.

HE can affect individuals across a wide spectrum of liver disease—not just alcohol-induced cirrhosis—and of particular relevance is the increased role of obesity in driving liver disease. Being aware of major at-risk patient groups and maintaining a high index of clinical suspicion for key signs and symptoms is, therefore, vital.

Current guidance relating to HE includes joint practice guidelines from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD)—however these recommendations have not been updated since 2014.\(^1\) At a national level, there is guidance from NICE on the assessment and management of cirrhosis in over 16s (NG50) from July 2016 which also covers HE.\(^2\)

There remains a lack of guidance on certain critical aspects of HE recognition and management and a broader need for improved care pathways. In particular, there is a need for improved communication and better conduits linking primary and secondary care to stop patients becoming trapped in a revolving door of repeated hospital readmissions. Clear consensus advice incorporating practice-based recommendations can help physicians of all types better manage the complex problem of HE. This consensus guidance seeks to promote best practice in the identification and management of HE and bring the key recommendations together in a single document.

The following statements represent the consensus opinion of a group of UK experts and pertain to any patient with chronic liver disease, irrespective of their specific underlying liver condition or its cause.

*Summary of product characteristics can be found at www.medicines.org.uk/emc
**Identification of HE**

Cirrhosis is a well-recognised risk factor for HE but patients with undiagnosed chronic liver disease (CLD) represent an additional and important at-risk cohort. Clinicians should therefore be alert to new neuropsychiatric symptoms in patients with established cirrhosis and those with signs/symptoms suggestive of potential CLD, such as malnourishment and sarcopenia, which occur almost ubiquitously in liver failure. In some cases, neuropsychiatric symptoms may even be the first manifestation of previously occult CLD. The Nottingham Scarred Liver Project provides useful clinical criteria for the identification of potential liver disease that can be easily applied in the primary care setting. Risk factor analysis can also be undertaken using established guidance provided by the British Society of Gastroenterology and as laid out in the Royal College of General Practitioners Liver Disease Toolkit. Increased clinical vigilance to detect this population of patients with undiagnosed CLD is an important step towards early and accurate identification of those at risk of HE.

**Consensus statements—defining the target population:**
- Identification of potential HE should focus not only on patients with diagnosed cirrhosis but also those with undiscovered occult liver disease.
- Key indicators that raise the index of clinical suspicion for chronic liver disease in patients over 18 years include: new-onset cognitive impairment/behavioural changes, malnutrition, sarcopenia and loss of mobility/stamina.
- Existing tools can be utilised to assess the risk of potential liver disease in an individual patient.

Within the cohort of patients with diagnosed cirrhosis, those with additional features of liver failure such as ascites, peripheral oedema, variceal bleeding and jaundice are at high risk of HE. While many of these risk markers are easily identifiable, recognition of sarcopenia can be difficult as weight and body mass index (BMI) alone are unreliable indicators—patients may be both obese and sarcopenic. Although any clinical assessment should include a visual survey of the patient’s upper body, BMI, and document any unintentional weight loss, clinicians should also be alert to changes in a patient’s physical functioning. Decreased stamina, increased fatigue and falls are all indicative of potential sarcopenia and should prompt functional assessments to fully evaluate skeletal muscle mass and strength.

A number of precipitating factors, including drug-related risk factors, have been associated with acute episodes of HE (Box 1). A clearly defined precipitating factor can be identified in approximately 50% of patients admitted with episodic HE. It is therefore important to maintain an awareness of these key precipitants that may aid in the recognition of at-risk patients in the clinical practice setting. Determining a patient’s risk of overt HE can enable closer monitoring and implementation of interventions to limit the risk of progression.

**Box 1: Precipitants of acute episodes of HE**
- Constipation
- Infection
- Abnormal urea and electrolytes blood test result (U&Es)
- Dehydration
- Drug-related risk factors:
  - concomitant opioids
  - proton pump inhibitors (PPIs)
  - benzodiazepines
  - sedatives
  - diuretics.

**Consensus statements—identifying those at greatest risk:**
- Patients with features of chronic liver failure are at high risk of HE, notably: ascites, peripheral oedema, previous variceal bleeding, and jaundice.
- Sarcopenia is an important feature of CLD and heightened HE risk. It is recommended that functional assessments be performed to assess skeletal muscle loss as BMI alone is an unreliable marker.
- Clinicians should be alert to key precipitating factors for acute episodes of HE which may help pinpoint at-risk patients.

The diagnosis of HE can prove challenging and clinical features are not always obvious. The EASL/AASLD guidelines describe the ‘elusive character’ of HE and note that there is a lack of generally accepted and utilised terms for both the description and characterisation of this condition. HE may present with a myriad of potential signs/symptoms that often overlap with more commonly-encountered conditions (Box 2), creating diagnostic confusion and uncertainty. As acknowledged in the EASL/AASLD guidelines, part of the diagnosis of HE therefore relies on exclusion of other causes of brain dysfunction.

**Box 2: HE mimics and potential misdiagnoses**
- Stroke
- Parkinson’s disease
- Dementia
- Sleep apnoea
- Delirium
- Korsakoff’s syndrome
- Wernicke’s encephalopathy
- Intoxication (alcohol or substance-induced).

In the general practice setting, vigilance for subtle features of HE is recommended, focusing on signs of impaired motor function, memory loss and poor concentration, sleep/wake reversal, impaired cognitive function and personality/behavioural changes. Specific clues, such as slowing of speech, dyspraxia, clumsiness, trips and falls, and vehicular accidents or ‘near misses’ when driving, can all suggest potential deterioration in a patient’s cognitive and motor functioning attributable to HE.
In contrast, features of advanced HE such as liver flap (asterixis) and somnolence are more overt and readily recognisable but can also be observed in other diseases (for example, uremia). The grading of the severity of HE is outlined in Table 1.

<table>
<thead>
<tr>
<th>SYMPTOM GRADE</th>
<th>SYMPTOM DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>Psychometric or neuropsychological alterations of tests without clinical evidence of mental change</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Trivial lack of awareness</td>
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<tr>
<td></td>
<td>Euphoria or anxiety</td>
</tr>
<tr>
<td></td>
<td>Shortened attention span</td>
</tr>
<tr>
<td></td>
<td>Impairment of addition and subtraction</td>
</tr>
<tr>
<td></td>
<td>Altered sleep rhythm</td>
</tr>
<tr>
<td>Grade 2: low</td>
<td>Lethargy or apathy</td>
</tr>
<tr>
<td></td>
<td>Dyspraxia</td>
</tr>
<tr>
<td></td>
<td>Asterixis</td>
</tr>
<tr>
<td>Grade 2: high</td>
<td>Disorientation</td>
</tr>
<tr>
<td></td>
<td>Obvious personality change</td>
</tr>
<tr>
<td></td>
<td>Inappropriate behaviour</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Somnolence to semi-stupor</td>
</tr>
<tr>
<td></td>
<td>Impaired responsiveness to stimuli</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>Gross disorientation</td>
</tr>
<tr>
<td></td>
<td>Bizarre behaviour</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Coma</td>
</tr>
</tbody>
</table>

**Consensus statements—presentation of HE:**
- The signs and symptoms of HE can be subtle. Particular vigilance should be paid to covert clinical clues in at-risk patients, such as:
  - impaired motor function
  - memory loss and poor concentration
  - sleep/wake reversal
  - diminished cognitive function
  - personality/behavioural changes.
- Features of more advanced HE include:
  - liver flap (asterixis)
  - confusion/disorientation
  - somnolence, potentially leading to coma
  - disinhibition/agitation.

**Diagnosis of HE**

No single diagnostic test exists for HE; diagnosis is predominantly a clinical one and can be supported by certain confirmatory assessments. Although the EASL/AASLD practice guidelines outline recommended diagnostic tests for HE to be performed by experienced examiners, these are unlikely to be applicable in a primary care setting. Instead, diagnosis is reliant on careful questioning and maintenance of a high index of clinical suspicion for HE—particularly in patients who present with risk features and/or precipitants. It is also vital to obtain a corroborative history from the patient’s family members and/or caregivers to help support the diagnosis of HE.

**CASE STUDY A**

Case Study A describes a (fictional) patient presenting in the primary care setting with more subtle features of HE and highlights the importance of early identification, intervention and ongoing education as a key step towards admission avoidance.

**PATIENT PROFILE/PRESENTATION**
- 42-year old female
- Diagnosed with primary biliary cirrhosis (PBC; 8 years)
- Subsequent progression to cirrhosis (3 years) but remains well
- GP consultation at request of family, accompanied by daughter
- Presents with:
  - lethargy
  - intermittent forgetfulness
  - disorientation

**CLINICAL ASSESSMENT**
- GP notes patient ‘drifting off’ during consultation
- Daughter reports reduced oral intake of food
- Bowel last opened 3 days previously
- No signs or symptoms of infection
- Painful hip—intermittent codeine for pain

**DIAGNOSIS**
- HE with drug toxicity as precipitating factor
- Diagnosis rationale: patient presents with known CLD, constipation, and features compatible with HE
- Alternative diagnoses considered and discarded:
  - infection
  - cognitive impairment

**TREATMENT**
- Prescribed lactulose* (at doses described on page S)
- Increased fluid intake
- Change of analgesia:
  - NSAIDs* contraindicated due to risk of renal dysfunction
  - paracetamol* remains analgesic of choice in CLD

**ONGOING MANAGEMENT**
- Patient and caregiver education:
  - explain rationale for lactulose
  - outline key goal of treatment (2–3 soft stools/day)
  - counsel on future opioid avoidance
- Safety netting:
  - refer to hepatology
  - provide information on signs/symptoms indicating deterioration and required actions.

*Summary of product characteristics can be found at www.medicines.org.uk/emc
**Consensus statements—diagnosis:**

- HE is a clinical diagnosis. No single, definitive diagnostic test exists.
- Diagnosis relies on a high index of clinical suspicion and recognition of key risk features and precipitating factors.
- It is important to always seek a corroborative history from family members/caregivers to support an HE diagnosis.

**Clinical management of HE**

Patients with minimal, Grade 1, or low Grade 2 HE can typically be initially managed in primary care with ‘safe step’ interventions centred on the prescription of lactulose*, referral to hepatology, and appropriate patient/caregiver education. In line with the summary of product characteristics, lactulose* (side-effects*—very common ≥1/10: diarrhoea; common ≥1/100 to <1/10: flatulence, abdominal pain, nausea, vomiting) should be prescribed at a starting dose of 30–50 ml daily (administered in 2–3 divided doses) and titrated to achieve 2–3 soft stools per day. Despite a relatively limited evidence base, this drug remains an accepted part of routine HE management based on decades of clinical experience. It is important not to substitute lactulose* with other laxatives as it is not the laxative effect which is useful in the treatment of HE. Rather, lactulose* is a non-absorbable disaccharide that acts to alter the pH of stools in order to inhibit the accumulation of bacteria-produced toxins, such as ammonia. The presence of any precipitating factors for HE should be assessed and addressed (Box 1). It is also important to review the patient’s nutritional requirements (Box 3) and refer to a specialist dietitian if appropriate. This is critical as the vast majority of people diagnosed with HE will be suffering from concomitant protein-energy malnutrition (Box 4) which is associated with worsening severity of HE. The key focus of treatment should therefore be on increasing protein intake and avoiding periods of fasting.

**Box 3: The importance of nutrition**

Muscle mass is used as an energy source in the absence of glycogen. This is not repleted in patients with liver cirrhosis, resulting in increased fatigue, and reduced activity, strength, and general motivation. Muscle loss will drive hepatic encephalopathy as well as other symptoms of liver disease. This consensus group’s first-line advice to patients with HE would be to:

- have something to eat every 2–3 hours
- have a starchy supper, such as cereal or toast, to preserve muscle overnight and reduce the output of toxins
- increase the frequency of protein-rich foods (e.g. meat, poultry, fish, eggs, pulses, cheese, tofu, high-protein yoghurts) to 3–4 times a day
- if appetite is poor, consider high-protein supplements.

Refer to a specialist dietitian when the patient has decompensated cirrhosis and where muscle loss is evident even as a standalone symptom.

**Box 4: What is protein-energy malnutrition (PEM)?**

Protein-energy malnutrition (PEM) describes a state of decreased body reserves of protein, with or without fat depletion, and a state of diminished functional capacity impacting physical and mental reserve. This is caused, at least in part, by reduced nutrient intake relative to demand but driven by altered energy metabolism, resulting in the use of muscle for glucose energy in short-term fasting of 2–3 hours only. PEM is one of the most common complications in CLD, occurring in at least 50% and up to 90% of patients, and is associated with increased morbidity and mortality. Most notably, PEM is linked to sarcopenia, which is characterised by the depletion of skeletal muscle mass and a negatively impact on survival and quality of life in patients with CLD. Although the pathogenesis of PEM is multifactorial, alterations in protein metabolism resulting directly from liver dysfunction play an important role. The two key tenets of clinical management are increased protein intake and minimisation of fasting periods by proactive nutritional management.

Effective education for both patients and family members/caregivers is a cornerstone of best practice HE management but an area where current guidance is patchy and non-directive. Several studies have highlighted significant gaps in patient and family members’ understanding of their diagnosis and its treatment. A 2012 study by Montagnese revealed poor HE awareness in both patients and caregivers attributable to insufficient/inadequate provision of information. Strikingly, only 6% of patients/caregivers in this study were aware of the prescribed treatment or understood its treatment effects.

It is therefore vital that clinicians provide comprehensive information on HE—including its fluctuating symptomatology and markers of escalation which require further assessment and intervention. Patients and caregivers also need to understand what drugs have been prescribed and why. The British Liver Trust leaflet on HE (available from britishlivertrust.org.uk/information-and-support/publications) is a useful resource that can be provided to patients.

All patients diagnosed with, or suspected to have, HE should be referred to their local hepatology/gastroenterology department for further review and follow-up. The majority of patients with Grade 2 or above HE will require immediate hospital admission which should be arranged via an acute medical unit (AMU). The exception is Grade 2 patients with a known diagnosis and predictable disease course who remain functional and have reliable family support. This consensus advice mirrors that in the EASL/AASLD guidelines, which recommend arbitrarily subdividing the continuum of HE into a grading scheme according to the severity of the manifestations.

*Summary of product characteristics can be found at www.medicines.org.uk/emc
From a secondary care perspective, best practice management of patients with HE should follow the BSG/BASL Decompensated Cirrhosis Care Bundle – First 24 Hours. This is a checklist that should be completed for all patients admitted with decompensated cirrhosis (a medical emergency with high mortality) within the first 6 hours of admission.

Sections of the care bundle with particular relevance to HE include appropriate investigations and assessment/management of encephalopathy (Figure 1).77 Best practice dictates that patients with complications of liver disease should ideally be managed by a hepatologist or gastroenterologist with a special interest in hepatology. However, it is recognised that such highly specialist care is not always available and many patients will be treated by generalists in district general hospital settings.

In all cases, it is important to alert the relevant hepatology/gastroenterology team. The BSG/BASL care bundle advises that gastroenterology/liver review should be carried out at the earliest opportunity – ideally within the first 24 hours.77 This recommendation is echoed in quality standards from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report ‘Alcohol-related liver disease: Measuring the Units’, which states that: ‘All patients admitted with decompensated alcohol-related liver disease should be seen by a specialist gastroenterologist/hepatologist at the earliest opportunity after admission. This should be within 24 hours and no longer than 72 hours after admission to hospital.’18

Data indicate that currently around 1 in 4 admitted patients are never seen by a gastroenterologist or hepatologist.18 The majority also fail to receive a nutritional assessment.

Other safe steps recommended for generalists managing patients with HE in the secondary care setting include liaising with critical care colleagues in cases where there are airway protection issues and escalating to enteral feeding (with referral to a specialist dietitian) if patients are unable to maintain their oral intake.

### Figure 1: Adapted from the BASL/BSG Decompensated Cirrhosis Care Bundle – First 24 Hours. Refer to the full document for the sections coloured grey.77

<table>
<thead>
<tr>
<th>1. Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) NEWS ☐ FBC ☐ U/E ☐ LFT ☐ Coag ☐ Gluc ☐ Ca/PO4/Mg ☐</td>
</tr>
<tr>
<td>b) Blood cultures ☐ Urine Dip/MSU ☐ CXR ☐ Request USS abdo ☐ CRP ☐</td>
</tr>
<tr>
<td>c) Perform ascitic tap in <strong>all patients with ascites</strong> using green needle irrespective of clotting parameters and send for ascitic PMN/WCC, culture and fluid albumin</td>
</tr>
<tr>
<td>d) Record recent daily alcohol intake</td>
</tr>
</tbody>
</table>

| 2. Alcohol | if the patient has a history of current excess alcohol consumption (>8 units/day Males or >6 units/day Females) |
| 3. Infections | if sepsis or infection is suspected |
| 4. Acute kidney injury and/or hyponatraemia (Na <125 mmol/L) |
| 5. GI bleeding | if the patient has evidence of GI bleeding and varices are suspected |
| 6. Encephalopathy | N/A ☐ |
| a) Look for precipitant (GI bleed, constipation, dehydration, sepsis etc.) | Y N |
| b) Encephalopathy – lactulose* 20–30ml QDS or phosphate enema* (aiming for 2 soft stools/day) | Y N |
| c) If clinical doubt in a confused patient request CT head to exclude subdural haematoma | Y N N/A |

| 7. Other |

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*Summary of product characteristics can be found at www.medicines.org.uk/emc
Discharge and ongoing management

Effective discharge care planning and effective strategies for the ongoing management of HE are essential steps to help avoid patients becoming trapped in a revolving door of readmissions. Optimisation of patients’ medication should be carried out prior to discharge with titration of lactulose* dose and consideration of rifaximin* where appropriate. Rifaximin-a* (side-effects*—common ≥1/100 to <1/10: dizziness, headache, depression, dyspnoea, upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia, peripheral oedema) is an important treatment modality for relapse prevention and, in line with existing guidelines (Box 5), can be recommended to reduce the risk of recurrent episodes of overt HE in patients aged over 18 years who have already experienced at least one prior episode.1,19

Box 5: Guidelines recommendations on rifaximin

› EASL/AASLD: Rifaximin* as add-on to lactulose* is recommended for prevention of recurrent episodes of HE after the second episode (Grade 1, A, 1)1
› NICE: Rifaximin* is recommended, within its marketing authorisation, as an option for reducing the recurrence of episodes of overt hepatic encephalopathy in people aged 18 years or older.20

Nutrition is vitally important to the ongoing management of HE and should be considered a key element in treatment. Nutritional information provided to patients/caregivers at discharge should be specifically tailored towards maintaining functional status and preventing readmissions.

As at other stages in the HE care pathway, information and education for patients and caregivers is essential at discharge. This should include:
› rationale for prescribed medications and advice on ongoing compliance/adherence
› strategies for keeping well
› abstinence
› avoidance of precipitating factors

CASE STUDY B

Case Study B is a real-world example from the specialist clinic setting which highlights HE as a treatable and reversible condition and also demonstrates the powerful role of nutrition in improving patients’ functional outcomes and quality of life. In this case, the patient’s existing medication regimen of lactulose* and rifaximin* was continued unchanged as an important element of ongoing management alongside nutritional intervention.

<table>
<thead>
<tr>
<th>PATIENT PROFILE/ PRESENTATION</th>
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</thead>
<tbody>
<tr>
<td>64-year old male</td>
</tr>
<tr>
<td>Undergoing assessment for</td>
</tr>
<tr>
<td>transplant due to recurrent,</td>
</tr>
<tr>
<td>refractory HE</td>
</tr>
<tr>
<td>2–6 weekly admissions</td>
</tr>
<tr>
<td>Lives with elderly mother</td>
</tr>
<tr>
<td>On maximal lactulose* and rifaximin*</td>
</tr>
<tr>
<td>Presents in specialist clinic with:</td>
</tr>
<tr>
<td>well-controlled type 2 diabetes</td>
</tr>
<tr>
<td>non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>BMI 38</td>
</tr>
<tr>
<td>no oedema or ascites</td>
</tr>
<tr>
<td>severely limited mobility</td>
</tr>
<tr>
<td>(wheelchair-bound)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited speech capacity; patient unable to provide verbal details</td>
</tr>
<tr>
<td>patient’s mother contacted to provide corroborative history</td>
</tr>
<tr>
<td>No other CLD features</td>
</tr>
<tr>
<td>Poor grip strength</td>
</tr>
<tr>
<td>Overall impression of sarcopenic obesity with proximal muscle wasting driving HE in the context of poor physical function/ deconditioning (a vicious cycle)</td>
</tr>
<tr>
<td>Dietary history:</td>
</tr>
<tr>
<td>decreased protein intake</td>
</tr>
<tr>
<td>long periods of fasting</td>
</tr>
<tr>
<td>dysgeusia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current lactulose* and rifaximin* therapy continued unchanged</td>
</tr>
<tr>
<td>Protein 100 g/day (administered 5 times daily) in form of low calorie/ low volume protein shot</td>
</tr>
<tr>
<td>Additional 40–50 g/day from food to reach overall daily protein target</td>
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<table>
<thead>
<tr>
<th>ONGOING MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuation of protein regimen in primary care setting to maintain treatment benefits</td>
</tr>
<tr>
<td>patient physical function outcomes dramatically improved</td>
</tr>
<tr>
<td>increase in quality of life</td>
</tr>
<tr>
<td>independently mobile and able to live independently</td>
</tr>
<tr>
<td>Education of patient and family to support compliance and avoid admission recurrence.</td>
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</tbody>
</table>

*Summary of product characteristics can be found at www.medicines.org.uk/emc
safety risks (Box 6)
an introduction to transplant and palliative care options
signposting to support groups at a local and national level.

Box 6: Safety risks

- Consider occupational hazards
- Patients with intermittent/recurring or persistent HE should notify the DVLA about any episodes\textsuperscript{1,21}
- Use of dangerous equipment should be avoided.

As HE represents a severe manifestation of cirrhosis, consideration should also be given to whether a particular patient is a candidate to be referred for transplant assessment. Where appropriate, anticipatory end-of-life care planning may also need to be considered.

Patients and caregivers require information on how to access specialist services after discharge. Ideally, this should take the form of a single point of contact or care such as a direct line to a specialist nurse or a day case unit. Although it is recognised that such services are not widely available, there is existing evidence from within cirrhosis management to support the positive impact of assertive follow-up services with a set point of contact. For example, an Italian study of 100 cirrhotic patients found that a new model of specialised caregiving significantly improved 12-month mortality in patients with cirrhosis and ascites, as well as reducing the rate of readmissions and the global healthcare management costs. This new model was based on a series of diagnostic facilities performed in real time and on the integrated activity of consultant hepatologists at the hospital unit for outpatients, dedicated nurses, physicians in training, and primary physicians.\textsuperscript{22}

Reconfiguring existing services and introducing new models of care for HE provides the scope to substantially improve patient outcomes while simultaneously reducing the cost burden on the healthcare system by reducing readmissions. Such an approach also aligns well with chronic care disease models and the empowerment of patients to self-manage more effectively through increased understanding of their condition and its treatment.

Moving forward, it is also important to expend concerted efforts gathering real-time data to better understand the patient/caregiver experience and improve care standards in HE. This should include routine collection of patient-reported outcome measures (PROMS) and patient-reported experience measures (PREMS). Such an approach feeds into the existing patient charter and provides the opportunity to set new standards in managing the complications of cirrhosis via improved metrics. Collection of data on patient-reported outcomes also affords a useful means of monitoring compliance and observing disease behaviour in the real-world.

Consensus statements—stabilisation, discharge, and ongoing management:

- Patients’ medication should be optimised prior to discharge:
  - lactulose* should be titrated to achieve 2–3 soft stools per day
  - rifaximin* (550 mg twice daily) is recommended for the prevention of recurrent episodes of overt HE in patients aged over 18 years with ≥1 prior episode.
- Maintenance of medications in the primary care setting is vital and should not be discontinued without specialist consultation. Treatment should be reinitiated if stopped and patients referred to hepatology for early specialist review.
- Nutritional recommendations should be reinforced as a key element of treatment.
- Comprehensive advice and education for patients and caregivers on ongoing HE management is essential.
- Consideration should be given to referral for transplant assessment. Where appropriate, anticipatory end-of-life care planning may also need to be considered.
- Information on how to access specialist services after discharge should be provided—ideally in the form of a single point of specialist contact.
- It is important to gather real-time data to better understand the patient/caregiver experience and improve care standards in HE. This should include routine collection of PROMS and PREMS.

Plugging gaps in existing HE guidance

In developing these consensus statements, the expert panel identified important gaps in the current clinical care of HE and attempted to address them. These key areas of current unmet need lie predominantly within:

- **Discharge care planning and optimised ongoing management to prevent readmissions**
  The establishment of effective discharge pathways is an important priority as readmission for HE is common. In particular, stabilisation of patients and implementation of relapse prevention measures are vital to avoid the current ‘revolving door’ phenomenon in patient care.

- **The important and central role of nutrition in HE management**
  Nutrition is frequently overlooked in HE and existing EASL/AASLD guidelines fail to provide robust guidance on nutritional interventions. On the contrary, we believe that nutrition is a cornerstone of care and should be viewed as a treatment modality in HE. Moving forward, clinicians in both primary and secondary care should place increasing focus on implementing evidence-based nutritional recommendations for patients with HE as central part of overall disease management.

\textsuperscript{*}Summary of product characteristics can be found at www.medicines.org.uk/emc
Capturing and understanding the patient perspective (PROMs and PREMs)

It is important to accrue real-time data on the patient and caregiver experience in HE by collecting routine information using tools such as patient diaries and passports. As a panel, we believe that increased focus on PROMs and PREMs as key metrics in the routine clinical management of HE has the potential to set new standards in cirrhosis care.

Lack of guidance on how to effectively educate and inform patients with HE and their caregivers

Despite a lack of clear guidance on the subject from the leading liver societies and national bodies in the UK, it is clear that patient education is an essential part of HE management and constitutes clinical best practice in the field. As a panel, it is our opinion that improved patient and family education—following the recommendations laid out in this consensus statement has the scope to significantly improve outcomes for patients with HE.

Conclusion

HE represents the most severe complication of cirrhosis and can be the hardest to reliably diagnose. As such, it carries a high morbidity in terms of impact on quality of life, hospital admissions, as well as mortality. As reflected in these consensus guidelines, clinicians should be alert for potential signs of HE in any patient (aged 18 years or over) with chronic liver disease, irrespective of their underlying condition.

It is also important to consider the possibility of unrecognised liver disease in any patient with risk features or precipitants. Misdiagnosis of HE can exacerbated by the variable mode of presentation and symptoms which mimic other common conditions like stroke and dementia. Maintaining a high index of clinical suspicion is therefore vital in order to quickly diagnose patients and start them on the appropriate treatment and referral pathways.

Effective discharge care planning and optimised strategies for the ongoing management of HE are essential steps to help avoid patients becoming trapped in a revolving door of readmissions. This requires improved communication between primary and secondary care to establish clear pathways for patients. It is particularly important to ensure that prescribed medications such as lactulose* and rifaximin* are maintained in the primary care setting and not discontinued without specialist advice.

Case Study C

Case Study C is a real-world example of a patient attending routine follow-up in the specialist clinic. It illustrates how HE can present subtly with ‘softer’ symptomatology, and also demonstrates the important role of the family in observing and reporting signs and symptoms suggestive of potential HE as patients themselves may lack insight into their own condition.

<table>
<thead>
<tr>
<th>CASE STUDY C</th>
<th>PATIENT PROFILE/ PRESENTATION</th>
<th>CLINICAL ASSESSMENT</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
<th>ONGOING MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>62-year old female</td>
<td>Patient described feeling ‘well’ and ‘unconcerned’</td>
<td>HE</td>
<td>Lactulose*</td>
<td>Education for patient and caregiver (e.g. British Liver Trust leaflet)</td>
</tr>
<tr>
<td></td>
<td>Haemochromatosis</td>
<td>Markedly slow speech</td>
<td>Diagnosis rationale: clear and florid symptomatology; no other differential diagnosis to consider</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>now on maintenance venesection</td>
<td>Mild liver flap</td>
<td></td>
<td></td>
<td>Advice on actions to take if worsening symptomatology</td>
</tr>
<tr>
<td></td>
<td>Non-alcoholic fatty liver disease</td>
<td>No jaundice or ascites</td>
<td></td>
<td></td>
<td>Plan to initiate rifaximin* if any further episodes of HE and consider transplant referral</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes</td>
<td>No history of constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Known cirrhosis—no prior complications</td>
<td>No infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Attended clinic with her husband</td>
<td>Husband confirmed patient’s forgetfulness and other ‘soft’ features suggestive of HE</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Summary of product characteristics can be found at www.medicines.org.uk/emc
Conflicts of interest

The group members received an honorarium from Norgine Pharmaceuticals Limited to develop this consensus statement.

Michelle Clayton is a member of the Norgine SLIDE committee.

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We would like to thank the British Society of Gastroenterology and Dr Stuart McPherson for permission to reproduce part of the BASL/BSG decompensated liver cirrhosis care bundle (Figure 1).

We would like to thank Helen Boreham, Medical Writer, for help with drafting this document.

References

2. NICE. Cirrhosis in over 16s: assessment and management. NICE Guideline 50. NICE, 2016. Available at: www.nice.org.uk/ng50
20. NICE. *Rifaximin for preventing episodes of overt hepatic encephalopathy*. Technology appraisal guidance 337. NICE, 2015. Available at: www.nice.org.uk/ta337
**UK&IE 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:**
Adults 18 years of age and over: 550 mg twice daily, with a glass of water, with or without food for up to 6 months.

Treatment beyond 6 months should be based on risk benefit balance including those associated with the progression of the patients hepatic dysfunction.

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

**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}.

**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:

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, UB8 6NS, UK

**Marketing Authorisation number:** PL 20011/0020

**IRELAND**

**Legal category:** Prescription only

**Cost:** €262.41 for 56 tablets

**Marketing Authorisation holder:** Norgine B.V. Antonio Vivaldstraat 150, 1083 HP, Amsterdam, Netherlands

**Marketing Authorisation number:** PA 1336/009/001

**For further information contact:**
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Norgine House
Moorhall Road
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Middlesex, UB9 6NS
Telephone: 01895 826 606
E-mail: Medinfo@norgine.com

**Ref:** UK/XIF5/0519/0509

**Date of preparation:** May 2019

**United Kingdom**

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

Adverse events should also be reported to Medical Information at Norgine Pharmaceuticals Ltd on:
Tel. +44 (0) 1895 826 606
Email Medinfo@norgine.com

**Ireland**

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); E-mail: medsafe@hpра.ie. Adverse events should also be reported to Medical Information at Norgine Pharmaceuticals Ltd on:
Tel. +44 (0) 1895 826 606
Email Medinfo@norgine.com

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