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British Society of Gastroenterology Best Practice Guidance: outpatient management of cirrhosis – part 2: decompensated cirrhosis

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ABSTRACT

There are two distinct phases in the natural history of cirrhosis: compensated disease (corresponding to Child Pugh A and early Child Pugh B disease), where the patient may be largely asymptomatic, progressing with increasing portal hypertension and liver dysfunction to decompensated disease (corresponding to Child Pugh late B-C), characterised by the development of overt clinical signs, including jaundice, hepatic encephalopathy (HE), ascites, renal dysfunction and variceal bleeding. The transition from compensated cirrhosis to decompensated cirrhosis (DC) heralds a watershed in the nature and prognosis of the disease. DC is a systemic disease, characterised by multiorgan/system dysfunction, including haemodynamic and immune dysfunction. In this second part of our three-part series on the outpatient management of cirrhosis, we address outpatient management of DC, including management of varices, ascites, HE, nutrition, liver transplantation and palliative care. We also introduce an outpatient DC care bundle. For recommendations on screening for osteoporosis, hepatocellular carcinoma surveillance and vaccination see part one of the guidance. Part 3 of the guidance focusses on special circumstances encountered in patients with cirrhosis, including surgery, pregnancy, travel, management of bleeding risk for invasive procedures and portal vein thrombosis.

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INTRODUCTION

The transition from compensated cirrhosis (CC) to decompensated cirrhosis (DC) occurs at the rate of approximately 5%–7% per year,[1] and median survival drops from over 12 years in CC to approximately 2 years in DC.[1] People with DC should be managed by a specialist with expertise in the management of patients with liver disease. While removal of aetiological factors driving liver damage is important at all stages of liver disease, the management of CC, focused on surveillance and preventing further liver damage, differs significantly from that of DC, where the focus is on managing complications, identifying suitable candidates for transplantation and ensuring good palliative care (PC). The following recommendations are accompanied by a care bundle for use in the outpatient setting (see figure 1).

Screening, surveillance and prophylaxis of variceal bleeding

All patients with DC who are not on a non-selective beta blocker (NSBB) should undergo endoscopy to screen for varices. The risk of progression to high-risk varices is higher in decompensated disease,[2] so we recommend annual surveillance in all patients not already receiving primary prophylaxis. Patients with Child-Pugh C disease and small varices should have primary prophylaxis with NSBB if tolerated. All patients with medium-to-large varices/red signs should have primary prophylaxis with NSBB or variceal band ligation (VBL) (figure 2). Patients on NSBB

for primary prevention do not require further surveillance endoscopy. Those who have VBL for primary prevention should be scoped approximately every 4 weeks until the varices are eradicated and then have ongoing surveillance annually until they recompensate and the underlying aetiological driver for their liver disease is removed (eg, abstinence from alcohol).

Secondary prevention of variceal haemorrhage is important, as the risk of rebleeding can be as high as 60% with 20% mortality for each rebleeding episode.[3] A combination of NSBB and VBL is recommended.[2 4] Transjugular intrahepatic portosystemic shunting (TIPSS) has a role in secondary prevention in high-risk cases, where patients rebleed despite NSBB and VBL, or where there are additional indications such as refractory/recurrent ascites.[5] Careful patient selection is necessary (see BSG guidelines on TIPSS in portal hypertension), including consideration of liver transplantation (LT) where appropriate.[5]

Management and assessment of chronic hepatic encephalopathy and driving

In cirrhosis, hepatic encephalopathy (HE) causes a range of neuropsychiatric disturbances from stupor and coma to subtle abnormalities in higher executive function. The annual risk of developing overt HE with cirrhosis is estimated at 20%, and 60%–80% have evidence of minimal HE on testing.[6] Overt HE is diagnosed clinically utilising the West-Haven Criteria,[7] whereas minimal HE requires specialised psychometric or neurophysiological testing.[8] Recently, to simplify diagnosis, patients with West-Haven grade 0 (minimal) and 1 HE are said to have covert HE,[9] which can be evident from a thorough history from the patient and their caregiver. Helpful clues include sleep-wake cycle reversal, short-term memory loss and loss of concentration such as they are no longer able to read the newspaper or follow their favourite TV programme. A summary of assessment and investigation in suspected HE is shown in table 1.

The animal naming test is quick and easy to do in outpatient settings. Naming 15 animals in 1 min produced the best discrimination between unimpaired and minimal HE patients.[10]

Overt HE portends a poor prognosis and the probability of transplant-free survival after developing overt HE is only 42% at 1 year and 23% at 3 years,[11] so early referral for LT should be considered.

Most HE treatments are directed towards the gut with lactulose as first line therapy.[12] A 550 mg twice-daily rifaximin is recommended second line to reduce recurrent episodes of overt HE.[13]

Weight loss and sarcopenia can worsen HE. Therefore, low-protein nutrition should be avoided, and adequate protein and energy intake should be maintained.

HE develops in 35%–50% of patients after TIPSS and is associated with increased mortality.[14] The risk of post-TIPSS HE can be reduced by using a smaller diameter (6–7 mm vs >8 mm) covered stent[15] and by prophylactic use of rifaximin started 14 days before TIPSS.[16]

Simulation studies and on-road driving tests have demonstrated impaired driving ability in patients with cirrhosis and HE.[17] Patients with cirrhosis and cognitive impairment have more traffic accidents and often overestimate their driving ability.[18 19] Treatment with rifaximin in a randomised trial improved driving simulator performance in patients with covert HE.[20] However, two studies found no increased rate of accidents in patients with cirrhosis and covert HE.[21 22]

No single psychometric test can currently reliably divide patients into safe and unsafe drivers, and there are no published guidelines on driving for patients with minimal/covert HE. Expert consensus recommends avoidance of driving within 3 months of an overt HE episode.[23] UK patients diagnosed with overt HE must inform the Driver and Vehicle Licensing Agency (DVLA) and are advised not to drive. Even in the absence of overt HE, if there are concerns of poor short-term memory, disorientation, lack of insight/judgement or impaired attention, the patient is probably not safe to drive and the DVLA should be informed.[24] If symptoms resolve (on or off treatment) and patients wish to resume driving, they should formally reapply to the DVLA—in some cases a driving assessment may be required. This includes patients with alcohol use disorder who have stopped drinking alcohol, recompensated and have had no recurrence of overt HE on or off lactulose and/or rifaximin for 12 months.

Outpatient management of ascites

The onset of ascites signifies an important stage in cirrhosis evolution: the 2-year and 5-year cumulative mortality after ascites development is 38% and 78%, respectively.[25]

Ascites is a clinical manifestation of portal hypertension related renal dysfunction, leading to sodium and water retention and impaired free water clearance. This presents progressively as ascites, refractory ascites, hyponatraemia and ultimately hepatorenal syndrome.

New-onset ascites should be evaluated to ensure it is related to portal hypertension, including calculating serum albumin gradient (SAAG) where SAAG >11 g/L is consistent with portal hypertension. In the absence of another clear cause of decompensation, CT scan of the liver to rule out hepatocellular carcinoma or portomesenteric vein thrombosis should be considered. Any significant increase in the volume of ascites, abdominal pain or fever should prompt an ascitic tap with fluid sent for white cell count to rule out spontaneous bacterial peritonitis (SBP) and ascitic fluid culture. A

Patient details

Decompensated Cirrhosis Outpatient Bundle

Varices (see over for management)		
Varices present?	**Y**	**N**
Size of varices? Small (grade 1) Medium (grade 2) Large (grade 3)		
Previous variceal bleed?	**Y**	**N**
Prophylaxis:		
Is patient on a B Blocker? (carvedilol preferred)	**Y**	**N**
If not, why not? _____		
Has dosage been optimised? (aim HR 60/min and SBP >100)	**Y**	**N**
Variceal band ligation?	**Y**	**N**
Is a repeat OGD required? If so, date booked for_____	**Y**	**N**
Hepatic encephalopathy		
Encephalopathy present:	**Y**	**N**
Lactulose	**Y**	**N**
Rifaximin	**Y**	**N**
Lactulose+/- rifaximin advised for patients with persistent or previous un-provoked HE, unless contraindicated		
Ascites		
Ascites present?	**Y**	**N**
Previous SBP?	**Y**	**N**
If yes: Date:	Organism (if known)	
Prophylactic antibiotics	**Y**	**N**
If yes: name _____		
If no: reason why_____		
Patients with ascites and an episode of SBP should be considered for antibiotics (secondary prophylaxis) as per local protocol		
Current management of ascites		
Diuretics	**Y**	**N**
Paracentesis	**Y**	**N**
Weight	_____	**Kg**
If ascites controlled consider reducing diuretics	Y	**N/A**
If requiring paracentesis:		
Predicted interval _____weeks		
Day case paracentesis booked for _____		
Or Information given to patient to contact		
Monitoring Renal function and electrolytes		
Recommended frequency of U&Es monitoring in the community:		
Nutrition		
Dietician review?	Y	N
Supplements required?	Y	N
Substance / alcohol misuse		
Alcohol misuse	**Y**	**N**
Input from alcohol care team/ Community follow up plans	**Y**	**N**
Advice on controlled reduction to abstinence	**Y**	**N**
Thiamine prescribed	**Y**	**N**

Treatment plan			
Has liver transplantation been considered?	**Y**	**N**	
Has prognosis been discussed?	**Y**	**N**	
Has information been given about complications of cirrhosis	**Y**	**N**	
Has a treatment escalation plan been documented	**Y**	**N**	
Has palliative care referral been considered	**Y**	**N**	

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Figure 1 Decompensated cirrhosis outpatient care bundle. HR, heart rate; OGD, oesophago gastroduo denoscopy; SBP, spontaneous bacterial peritonitis.

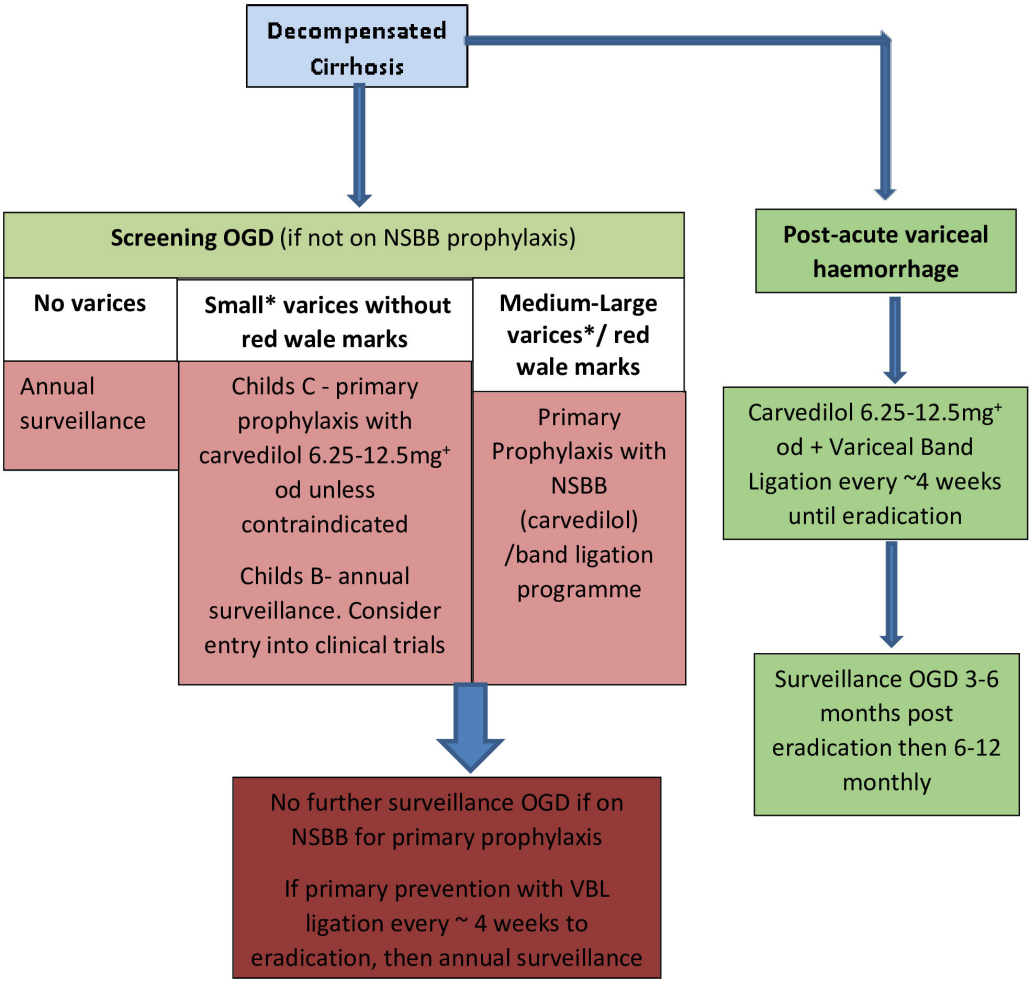

Figure 2 Surveillance and treatment of non-bleeding gastrooesophageal varices indecompensated cirrhosis. +Titrate from 6.25 mg od to target 12.5 mg od in single or divided doses if tolerated (maintain HR, 50–60, systolic blood pressure >90 mm Hg). *Small varices defined as <5 mm diameter or varices which completely disappear with moderate insufflation of the oesophagus, medium-large varices >5 mm diameter. NSSB, non-selective beta blocker; VBL, variceal band ligation.

neutrophil count of >250/mm^3 confirms SBP requiring prompt treatment with antibiotics.

The mainstay of ascites management in the outpatient setting is diuretic therapy. This involves a stepwise approach as outlined in figure 3 with the additional specific recommendations:

1. Secondary antibiotic prophylaxis should be considered in patients with a previous episode of SBP. Suitable antibiotic choices are norfloxacin 400 mg, ciprofloxacin 500 mg or co-trimoxazole 960 mg once daily.[26] The ASEPTIC trial, investigating the role of primary prophylaxis of SBP, is ongoing.[27] Some centres offer primary prophylaxis for those considered high risk of SBP (protein concentration <15 g/L)[26] but there are concerns around antibiotic resistance and this should only be considered following discussion with local microbiology teams. Rifaximin prescribed for secondary prophylaxis of HE may negate the prescription of a second oral systemic antibiotic with substantial evidence to suggest it prevents SBP.[28]
2. NSBB, when indicated, is not contraindicated in refractory ascites; although patients require close monitoring; dose reduction or discontinuation may be appropriate in those who develop hypotension or acute/progressive renal dysfunction.[26]
3. Long-term outpatient albumin administration to patients with cirrhosis and ascites is not currently recommended: despite encouraging results from the ANSWER trial, the accompanying medical supervision was a strong confounding variable[29]; further research is required to determine the efficacy, practicality, cost-effectiveness and impact on quality of life.
4. Patients with refractory ascites requiring regular large-volume paracentesis should have them performed as planned day case procedures as this reduces costs and improves patient outcomes, particularly in the last year of life.[30]
5. Indwelling abdominal drains remain experimental but can be considered in palliative patients with advanced disease as an alternative to recurrent large volume paracentesis following careful discussion involving the patient about the risk benefit ratio, and in particular the

Table 1 Summary of investigation and assessment of suspected hepatic encephalopathy

Investigation/clinical assessment		
West-Haven criteria		
Covert encephalopathy		
Grade 0 (minimal HE)	Animal naming test	Examples of psychometric/neurophysiological tests
	Critical flicker frequency	
	Stroop test	
	Psychometric Hepatic Encephalopathy Score	
	EEG	Poor sensitivity and specificity in minimal HE
Grade 1	Trivial lack of awareness, impaired attention span, altered sleep, euphoria or depression	
Overt encephalopathy		
Grade 2	Asterixis, minimal disorientation to time/place, behaviour/personality change, lethargy, ataxia/slurred speech	
Grade 3	Marked confusion/stupor, gross disorientation, somnolence but responsive to verbal stimuli	Should be used in conjunction with the Glasgow Coma Scale
Grade 4	Coma	
Exclusion of differentials (if alternative diagnosis suspected)/precipitating factors		
Brain MRI		Hippocampal atrophy suggests Alzheimer's disease. Small vessel changes suggest vascular dementia.
Ammonia		Not required routinely. A normal value brings HE diagnosis into question and other potential causes of confusion
Electrolytes		Hypokalaemia common HE precipitant—aim potassium >4
Confusion/infection screen (including CT head)		Useful in possible delirium or acute intracranial event suspected
Vascular-phase abdominal CT		Exclude large spontaneous portosystemic shunts (can be drivers of HE in otherwise well-compensated patients)

EEG, electroencephalogram; HE, hepatic encephalopathy.

potential infection risk.[26 31 32] Their use is currently being evaluated in the REDUCe2 trial.[33]

Renal impairment

Renal impairment and hyponatraemia are common complications of DC and are associated with poor outcome. Circulatory changes mean that patients with DC are more susceptible to prerenal acute kidney injury (AKI), for example due to hypovolaemia secondary to diuretics, bleeding or infection.[34] They may also suffer from renal causes of AKI (such as acute tubular necrosis) and postrenal causes, as in patients without cirrhosis. Patients with metabolic dysfunction associated steatotic liver disease (MASLD) and diabetes are more likely to have underlying chronic kidney disease.[35]

Hepatorenal syndrome refers to renal failure in patients with cirrhosis and ascites in the absence of any other identifiable cause and can develop acutely or more chronically. Management of HRS is outside the remit of this guideline. However, if patients develop renal impairment in an outpatient setting, the priority should be cessation/reduction of diuretic therapy and suspension of nephrotoxic medications. Arrangements should be made for frequent monitoring of renal function, to see whether admission for plasma expansion with fluids and/or terlipressin is required.

Special considerations for prescribing in DC

The pathophysiological changes in decompensated liver disease may significantly change the pharmacokinetic and pharmacodynamic profiles of many medicines, altering pharmacological and toxicological responses (online supplemental table 1). In addition, many medications can exacerbate fluid overload and/or HE in patients with DC. Table 2 provides a summary of prescribing adjustments to consider in some commonly used medications.[36]

Careful consideration should be given to the potential risk–benefit of treatment in each individual with advanced liver disease. Polypharmacy should be avoided, and medicines regularly reviewed to ensure all are still required. Concordance should be addressed regularly; if suboptimal, medications should be rationalised in partnership with patients to optimise concordance with the most important treatments.

Medicines should be titrated slowly, closely monitored and suspended or withdrawn if there are signs of toxicity or patient deterioration. Therapeutic drug monitoring should be employed where available.

Nutrition in DC

All patients with DC are at high risk of malnutrition and should have nutritional screening, including an assessment of dietary intake, preferably by a dietician,

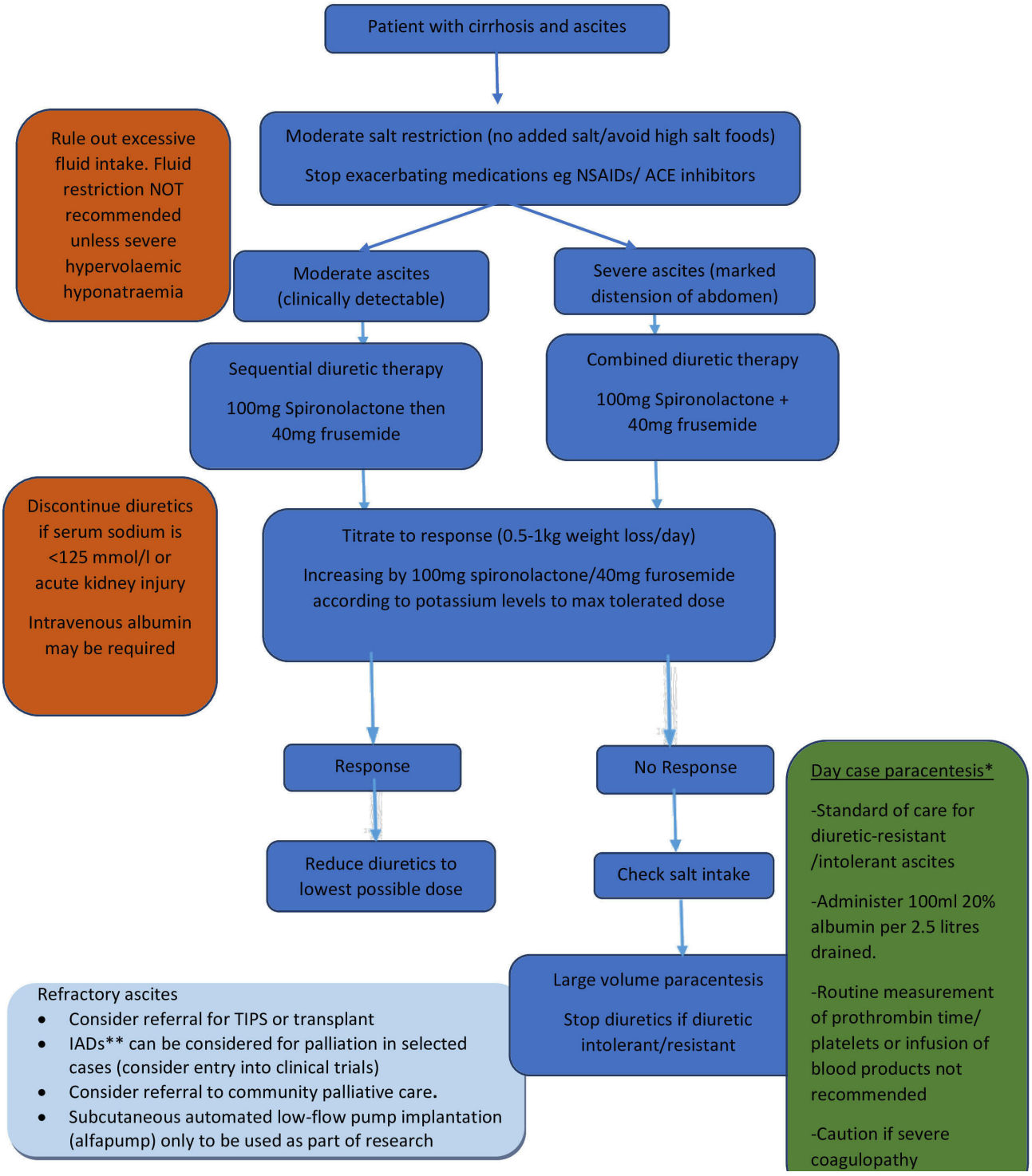

Figure 3 Management approach to the patient with cirrhosis and ascites. *A large volume paracentesis safety toolkit is available from BSG https://www.bsg.org.uk/clinical-resource/large-volume-paracentesis-in-cirrhosissafety-toolkit/. **IADs Indwelling abdominal drains. NSAID, non-steroidal anti-inflammatory drug; TIPSS, transjugular intrahepatic portosystemic shunting.

to determine the presence and severity of malnutrition and sarcopenia, both of which are independent predictors of poor outcomes in cirrhosis.[37] While outpatient dietetic services are not widespread for patients with cirrhosis, intervention to prevent/treat malnutrition is important, as its presence is associated with increased decompensation, hospitalisation and mortality.[37] Traditional nutritional screening tools such as body mass index (BMI) are unreliable in patients with ascites/oedema and dry weight should be used/estimated. Bedside tests such as grip strength, can be used to assess and monitor sarcopenia.[37]

Malnutrition is almost universal in patients with DC. Multiple factors may be involved, including

Table 2 Summary of prescribing commonly used medicines in patients with DC

Therapeutic category	Considered safe with monitoring	Avoid	Caution/modify dose	Notes
Gastric acid suppression	Simple antacids, for example, calcium carbonate		Proton pump inhibitors H2 antagonists	Altered gut microbiome may increase risk of infection and disease progression
Analgesics		NSAIDs, COX-2 inhibitors	Paracetamol Opiates	See palliative care section
Antimicrobials	Most antibiotics	Azithromycin Erythromycin Rifampicin Isoniazid	Aminoglycosides antifungals	Monitor renal and liver function
Antidiabetic drugs	Insulin GLP-1 agonists SGLT-2 inhibitors	Pioglitazone (in patients with fluid overload)	Metformin Sulphonylureas	Risk of lactic acidosis (metformin) Fluid accumulation
Drugs used in cardiovascular disease	Calcium antagonists	ACE-inhibitors ARBs Amiodarone	Beta blockers	Risk of acute kidney injury
Lipid lowering agents	Cholestyramine		Statins	Risk of accumulation/DILI
Anticonvulsants	Levetiracetam	Sodium valproate Phenobarbitone	Phenytoin Carbamazepine Lamotrigine	Risk of accumulation and increased toxicity
Antidepressants/ sedatives		Duloxetine	SSRI Venlafaxine Mirtazepine Benzodiazepines	Limited data in severe disease
DMARDs	TNF inhibitors	Methotrexate Leflunomide Budesonide	Prednisolone	Pre-screen for HBV
Drugs affecting clotting	LMWH	DOAC (Child Pugh C)	Warfarin Thrombopoietin Receptor Agonists	Lack of evidence in use of DOACs in DC

ARB, angiotensin receptor blocker; DC, decompensated cirrhosis; DILI, drug induced liver injury; DOAC, direct oral anticoagulant; HBV, hepatitis B virus; LMWH, low molecular weight heparin; NSAIDs, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitor.

reduced oral intake (due to encephalopathy, ascites or anorexia), malabsorption (due to portal enteropathy, jaundice or pancreatic insufficiency) and protein loss into ascites. Fundamental changes in energy metabolism in DC drive accelerated starvation, resulting in muscle catabolism, deconditioning and frailty. Diminished hepatic glycogen stores, due to high circulating levels of glucagon, result in gluconeogenesis as an alternative fuel and protein break down resulting in sarcopenia. Rapid transition from fed to fasting state means even short-term fasting results in muscle loss.

The priority is therefore to meet protein requirements (minimum of 1.5 g/kg dry weight) to prevent catabolism. Attenuation of muscle breakdown improves function and well-being, which in turn supports volitional oral intake. Protein intake should increase to 2 g/kg in the presence of severe sarcopenia and/or ascites. Nutritional supplements to support protein intake may be required even when overall energy intake is maintained.[38]

Nutritional supplements providing protein and energy are recommended where energy intake is low (<30–35 Kcal/kg dry weight per day).[37 38] Fasting times should be minimised to 2–3 hours, so patients should aim to have three meals and three snacks per day. Adding a carbohydrate (such as cereal/toast/milk and biscuits/cereal bar/flapjack for non-diabetic/lower BMI patients) or mixed carbohydrate/protein (such as yoghurt/cheese and crackers/peanut butter on toast for diabetic patients/those with higher BMI) bedtime snack and including carbohydrate at each meal supports fuelling and preservation of muscle protein. Where jaundice is present, a combination of lower fat diets and supplements is recommended to minimise biliary malabsorption. Patients with ascites or oedema should follow a no added salt diet, being careful to preserve protein and overall nutritional intake. Consider short-term enteral nutrition where oral nutritional support is insufficient or not consistently achieved, particularly in patients suitable for transplantation, or those with encephalopathy who are unable to eat. Nasogastric feeding is first line but nasojejunal feeding is well tolerated if nasogastric feeding is limited by early satiety.

Micronutrient deficiency is common in patients with DC. Vitamin D levels should be checked and supplemented if low in line with local protocols.[37] Specific evidence about the beneficial effect of other micronutrients and vitamin supplementation in cirrhotic

patients is not available. However, confirmed or clinically suspected deficiency should be treated[37] (including calcium, magnesium, phosphate, iron, B_{12} and folate). Oral thiamine (100 mg two times per day) should be supplemented in all patients who continue to drink alcohol. As vitamin status is not easily assessed and multivitamin supplementation is cheap and substantially side effect free, a course of oral multivitamin supplementation could be justified in decompensated patients.[37]

Physical activity can contribute to improving muscle mass and function. Nutritional stability must be achieved prior to initiating exercise. Movement can start at a low baseline with normal daily activities. Endurance exercise such as walking and cycling can support muscle functional capacity and resistance exercise can increase muscle mass. Therefore, a combination of endurance and resistance exercise is most beneficial. Simple exercises such as sit to stand can be a good first step.

When to refer for transplant

LT is the definitive treatment for selected patients with DC and should be considered when the severity of liver disease incurs a likelihood of poor survival or impaired quality of life.[39] A UK clinical guideline outlining the process of LT assessment, including who and how to refer, has recently been published.[40] To summarise, the over-riding principles of LT in the UK are that anticipated life expectancy after LT must exceed that without.[40] A UK Model for End-stage liver disease (UKELD) score of 49 is the equipoise at which the predicted 1 year mortality without LT matches that after LT and is therefore the current minimum listing threshold for elective LT in those with irreversible decompensation.[40]

In the absence of variant conditions, we recommend that referral for LT is considered when a patient with chronic liver disease develops the typical features of DC (ie, jaundice, ascites, variceal bleeding or HE) and UKELD ≥49.[40] Early referral is preferable because a patient can become too unwell for LT, if the referral is made too late. The referring clinician should consider first whether the decompensation is potentially reversible (for example with abstinence, in the case of alcohol-related liver disease (ARLD), or with antivirals in untreated chronic viral hepatitis). If not, is the patient suitable for LT? Contraindications to LT include coexisting significant extrahepatic comorbidity (with predicted mortality of >50% at 5 years), presence of extrahepatic sepsis, active malignancy and some previous extrahepatic malignancies. Some contra-indications can be temporary or relative, so if a patient is not currently suitable for LT, consider whether they may be suitable following treatment or an intervention (eg, nasogastric feeding in a patient with severe sarcopenia). If there is any doubt, advice should be sought from the LT unit.

ARLD is the leading indication for LT in the UK. Detailed recommendations for LT referral in ARLD in the UK are beyond the scope of this practice guidance. These have recently been revised.[41] To summarise, it is recommended that patients with decompensated ARLD should be referred to consider their suitability for LT if they still have evidence of decompensation after optimal management and 3 months validated abstinence from alcohol and are otherwise suitable candidates for LT,[40] in line with The National Institute for Health and Care Excellence (NICE) guidance.[42] Contraindications to LT in ARLD include active ongoing alcohol use, drinking alcohol while on the waitlist and during the period of transplant evaluation, and a history of repeated non-adherence to advice to abstain from alcohol.[41]

PC in patients with DC

DC is associated with a significant physical and psychosocial symptom burden which is most pronounced in the final year of life. Determining an accurate prognosis in patients with liver disease is challenging, due to the uncertain trajectory of the illness characterised by decompensations of disease and subsequent (partial) recovery. It is important to make patients aware of this uncertainty. It is now well recognised that there is a place for PC earlier in the patients' disease course. Parallel planning is important in the management of patients with other organ failures—'hoping for the best but planning for the worst'.[43] This is a useful phrase to use with patients when introducing the concept of PC.

Who and when to refer to PC?

Clinicians are often unsure as to when referral to PC services is appropriate. There are several tools available to identify patients with decompensated liver disease, who may benefit from referral to PC.[43] Broadly speaking, they include:

- Patients with Child Pugh C cirrhosis.
- Patients with decompensated ARLD and ongoing alcohol use.
- Patients with irreversible decompensated disease not deemed to be candidates for LT.
- Patients undergoing assessment for LT or who are on the liver transplant waiting list.
- Patients with two unplanned liver-related admissions within the past 6 months.
- Patients with hepatocellular carcinoma for best supportive care.

Symptoms and problems addressed by PC

Patients with DC often have general symptoms such as nausea, vomiting, fatigue and breathlessness frequently overlooked due to a focus on more liver specific symptoms such as itch, ascites and encephalopathy. Addressing symptoms has a clear impact on quality of life.[44] In addition, there are often broader psychosocial

Table 3 Managing symptoms in advanced liver disease

Drug	Recommended dose	Notes
Pain		
Paracetamol	2–3 g/24 hours orally (long term)	>50 kg (dry weight) 1 g four times a day orally safe for short periods (<7 days)
NSAIDs		Avoid (bleeding risk/renal toxicity)
Tramadol		Avoid (half-life>double, lowers seizure threshold)
Codeine	15–30 mg orally three times a day (short course only)	Avoid if possible—oral morphine preferable. If unable to use oral morphine monitor closely for constipation and encephalopathy
Morphine sulfate	2.5 mg 4–6 hourly as needed	first choice oral opiate if eGFR>30 Use short acting unless pain and liver function stable Titrate as required Monitor closely for constipation and encephalopathy
Hydromorphone	1.3 mg 8 hourly orally as needed (×10 as potent as oral morphine)	First choice oral opiate for eGFR<30 Increased dose interval Monitor for constipation and encephalopathy
Oxycodone	1.25 mg 6–8 hourly orally as needed (×2 as potent as oral morphine)	Ideally avoid (half-life>triples) Consider if patient not tolerating oral morphine/coexisting renal impairment (eGFR 30–60) Monitor closely for constipation and worsening encephalopathy
Buprenorphine transdermal patch	Dose according to oral opioid requirements	Can be used if pain and liver function are stable Monitor closely for constipation and worsening encephalopathy Only initiate on advice of palliative care and/or specialist pain team
Gabapentin	100 mg orally two times and titrate up as normal	Probably safe but can have sedative effect and may exacerbate HE.
Pregabalin	50 mg orally two times and titrate up as normal	Probably safe but can have sedative effect and may exacerbate HE.
Amitriptyline		Avoid
Dexamethasone	4–8 mg orally once	For patients with HCC/liver metastases and capsular pain Give gastric protection Review after 5 days
Nefopam	30–60 mg orally three times a day	An option in patients who do not tolerate other analgesia. Use with caution in decompensated disease, use lowest possible dose and monitor for side effects. Use may be limited by high cost and lack of evidence of effectiveness.
Nausea and vomiting		
Metoclopramide	5 mg orally/ intravenous/subcutaneaous three times a day Titrate to max 10 mg three times a day	First-line option if gastrointestinal (GI) cause, acts as prokinetic May increase fluid retention Consider QT interval prolongation
Domperidone	5 mg orally two times a day	Titrate to maximum 10 mg three times a day Alternative first line option, acts as prokinetic Consider QT interval prolongation
Haloperidol	0.5–1 mg orally two times aday 0.25–0.5 mg subcutaneaous three times a day	Titrate to maximum 5 mg/24 hours in divided doses First line option if opioid or centrally induced
Ondansetron	4 mg orally/intravenous two times a day Maximum dose 8 mg/24 hours	Second-line option Monitor for constipation
Levomepromazine	3 mg orally nightly Titrate to maximum 12.5 mg two times a day 2.5 mg subcutaneaous three times a day	Second-line option Causes drowsiness and can lower seizure threshold
Cyclizine	50 mg orally two times a day 25 intravenous/subcutaneaous two time a day	Third-line option Monitor closely for constipation and worsening encephalopathy

Continued

Table 3 Continued

Drug	Recommended dose	Notes
Depression		
Mirtazapine	Start at 15 mg orally every night Titrate slowly to max dose 30 mg on	Avoid in renal impairment May help stimulate appetite Can have sedating effect—15 mg on dose more sedating than 30 mg on
Citalopram	Start at 10 mg orally every morning Titrate slowly to dose 20 mg every morning	Almost double half life Can lower seizure threshold and increase risk of GI bleed.

Symptoms specific to liver disease			
Symptom	**Drug**	**Dose**	**Notes**
Hepatic encephalopathy	Lactulose	10–30 mL orally four times a day	Aim 2–3 soft stools/day
	Phosphate enema	1 enema PR once/two times	Aim 2–3 soft stools/day can be administered by district nurses regularly/PRN to prevent recurrent hospital admissions/as part of EHCP
	Rifaximin	550 mg orally two times	Second line after lactulose/enemas
Itching	Menthol 1% in aqueous cream	Apply 1–2 times daily	
	Cholestyramine	4–8 g orally once	First line for itching due to cholestasis Affects absorption of other medicines: take other meds >1 hour before or 4–6 hours after cholestyramine.
	Rifampicin, naltrexone, SSRIs (eg, sertraline)		Rifampicin can cause hepatotoxicity (see table 2) Can all be used second line but should be initiated cautiously with hepatology supervision
	Colesevelam		Off license, limited evidence of effectiveness
Ascites			See section on ascites

Adapted from British Association for the Study of the Liver clinical guideline: symptom control and end of life care in adults with advanced liver disease.[45]
eGFR, estimated glomerular filtration rate; EHCP, emergency healthcare plan; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; NSAIDs, non-steroidal anti-inflammatory drugs; PRN, as required; SSRI, selective serotonin reuptake inhibitor.

issues to address such as emotional support, dealing with carer burden and financial aspects.

There is often uncertainty about the safety of medication prescribing in patients with DC, but this should not lead to inadequate management of patients' symptoms. See table 3 for a summary of how to manage common symptoms in patients with DC.[45] The British Association for the Study of the Liver (BASL) has further guidance on anticipatory prescribing at the end of life.[45]

Patients who may be suitable for PC should be discussed in a multidisciplinary meeting with representatives from PC, hepatology/gastroenterology (including specialist nurses) and other Allied Health Practitioners (AHPs) such as dieticians and alcohol care teams. Outcomes should be clearly communicated to the community team. Patients should be given the opportunity to discuss advance care plans, emergency healthcare plans and resuscitation status, and should be added to the PC register. Consider signposting patients and families to additional practical support such as social prescribers, accessible through primary care.

Multidisciplinary care

Patients with DC have high rates of hospital admissions, long lengths of stay, high complication rates and significant healthcare costs. Liver specialist nurse led clinics can play an important role in admission avoidance and facilitating early discharge.[46] Early postdischarge clinics (within 2 weeks of patient discharge) and urgent nurse-led liver clinics can facilitate diuretic titration, early detection of HE, symptom management and offer support to patients and carers.[46] If admission is required, they can ensure early specialist input, which is crucial in improving outcomes for patients admitted with decompensation.[47]

Nurse-led day case paracentesis services significantly reduce emergency admission rates, lower costs and improve outcomes and patient experience.[30] There should be clear referral pathways in place via the gastroenterology/hepatology team to ensure patients are appropriate for the service. Patients should be given information on when and who to contact when symptoms (such as encephalopathy) deteriorate, or their ascites accumulates.

The aim should be to develop a service with an integrated MDT including dieticians, physiotherapists, pharmacists, PC nurse specialists and alcohol care teams to support a holistic approach to outpatient management of advanced liver disease.

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