Clinical Guideline

SYMPTOM CONTROL IN ADULTS WITH ADVANCED LIVER DISEASE

SETTING	Bristol Royal Infirmary
FOR STAFF	Doctors and specialist nursing staff
PATIENTS	Adult patients with Child Pugh B or C cirrhosis who are experiencing symptoms which interfere with their quality of life

GUIDANCE

Patients with advanced liver disease may experience general symptoms including pain, nausea and vomiting or symptoms related to their liver disease, such as ascites or encephalopathy, which require specific treatments. When recognised as dying these patients also experience the common symptoms we see in all patients at the end of life.

Prescribing in patients with advanced liver disease, however, can be challenging. Many drugs are metabolised or eliminated by the liver, so hepatic impairment can alter patients' response to medications. Many drugs require dose reduction; this is particularly true for patients with raised INR/prothrombin time and bilirubin or low albumin.

This guideline will cover the management of **common symptoms** in patients with advanced liver disease and offer guidance on prescribing of **anticipatory medications** at the end of life.

It should be used for all patients with **Child Pugh B or C cirrhosis**. Child Pugh Score can be calculated here: https://www.mdcalc.com/child-pugh-score-cirrhosis-mortality

Patients with advanced liver disease often have co-existing renal impairment which may require further dose alterations. See British National Formulary (https://bnf.nice.org.uk/), Renal Drug Handbook (available via Connect) or Medicines Information for further advice on dosing.

Evidence in this field is limited. Suggested doses and dosing intervals are based largely on expert opinion and may differ from standard end of life prescribing guidelines. These guidelines have been created with local agreement of hepatology, palliative care and pharmacy teams. They should not be used outside of University Hospital Bristol NHS Foundation Trust.

Medications in italics are included for general information and to prevent them being stopped inappropriately when rationalising prescribing. They should only be initiated by specialists.

PAIN

These medications can be used to manage pain in patients with Child Pugh B or C cirrhosis who are able to take medications orally and are not thought to be reaching the end of life.

Drug	Recommended Dose	Notes
Paracetamol	**2-3g / 24hrs PO** (long-term) **Maximum 3g / 24hr IV** (even short-term)	If over 50kg (dry weight), 1g QDS PO is safe for short periods If needed long-term, reduce dose Avoid IV preparation whenever possible
NSAIDs		Avoid (risk of bleeding and renal toxicity)
Tramadol		Avoid (half-life more than doubles)
Codeine	**15-30mg PO TDS** (short course only)	Avoid if possible Preferably use oral morphine If oral morphine not an option trial with caution – unpredictable effect Monitor closely for constipation and worsening encephalopathy
Oral morphine sulphate	**2.5mg 4-6hrly PO PRN**	1st choice oral preparation if eGFR ≥30 mls/min Use short-acting preparations unless pain and liver function are stable Titrate up dose as required Monitor closely for constipation and worsening encephalopathy
Hydromorphone	**1.3mg 8hrly PO PRN** (~ 10 times as potent as oral morphine)	1st choice oral opioid if eGFR <30 mls/min Note longer than usual dose interval Monitor closely for constipation and worsening encephalopathy
Oral oxycodone	**1.25mg 6-8hrly PO PRN** (Twice as potent as oral morphine)	Ideally avoid (half-life more than triples) Consider as second line strong opioid if patient cannot tolerate oral morphine, particularly if some renal impairment ie eGFR 30-60mls/min Monitor closely for constipation and worsening encephalopathy
Buprenorphine transdermal patch	Dose according to oral opioid requirements	Can use if pain and liver function are stable Monitor closely for constipation and worsening encephalopathy On advice of palliative care and/or acute pain team
Gabapentin	**100mg PO BD** and titrate up as normal	Probably safe but can have sedative effect
Pregabalin	**50mg PO BD** and titrate up as normal	Probably safe but can have sedative effect
Amitriptyline		Avoid

If patient is taking methadone consider discussion with palliative care or acute pain team for further opioid dosing advice.

Due to the structural liver changes in cirrhosis, patients do not tend to experience liver capsule pain. However, if patients with hepatocellular carcinoma or liver metastases experience this pain **Dexamethasone 4-8mg PO OD** with gastric protection can be used with review after 5 days.

NAUSEA AND VOMITING

These medications can be used to manage nausea and vomiting in patients with Child Pugh B or C cirrhosis who are able to take medications orally and are not thought to be actively dying during this admission.

Drug	Recommended Dose	Notes
Metoclopramide	**5mg PO/IV TDS**	First line option - prokinetic May increase fluid retention
Haloperidol	**0.5-1mg PO BD** Titrate to maximum 5mg / 24hrs in divided doses	First line option - opioid or centrally induced
Ondansetron	**4mg PO/IV BD** Maximum dose 8mg/24 hours	Second line option Monitor for constipation
Levomepromazine	**3mg PO NOCTE** Titrate to maximum 12.5mg BD	Third line option Causes drowsiness and can lower seizure threshold Use only if sedating effects acceptable Note: unlicensed formulation, tablets are 6mg and can be halved
Cyclizine		Avoid if possible (constipating and may exacerbate symptoms of advanced liver disease including encephalopathy)

SYMPTOMS SPECIFIC TO LIVER DISEASE

Symptoms other than pain often contribute to symptom burden in advanced liver disease. Encephalopathy is common and very distressing for both patients and their families. It is often caused by constipation, therefore educating family/carers about early signs is vital. Early recognition and treatment (often by adjusting laxatives) can prevent hospital admissions.

Symptom	Drug	Recommended Dose and Notes
Hepatic encephalopathy	Lactulose	**10-30mls PO QDS**; aim 2-3 soft stools/day
	Phosphate enema	**1 enema PR OD/BD**; aim 2-3 soft stools/day
	Rifaximin	***550mg PO BD*** *Should be initiated by a specialist*
Itching	Menthol 1% in aqueous cream	**Apply 1-2 times daily**
	Colestyramine	**4-8g PO OD** Affects absorption of other medications: take at least 1 hour before and 4-6 hours after other medications Helps if itching is due to cholestasis (build-up of bile salts)
	Rifampicin, Naltrexone, SSRIs (e.g. sertraline)	*Can all be used for itching secondary to cholestasis, but should not be initiated without hepatology guidance.*
	Antihistamines e.g. chlorphenamine	Second line - sedative effect can be helpful as patients are woken less frequently by pruritus
	Colesevelam	Off licence indication and limited evidence for effectiveness therefore not recommended
Depression	Mirtazapine	**Start at 15mg PO ON** and titrate slowly
	Citalopram	**Start at 10mg PO OD** (morning), titrate slowly maximum dose 20mg. Half-life nearly doubles. Can lower seizure threshold and increases gastrointestinal bleeding risk

Ascites

- **Diuretics** (spironolactone/furosemide/ bumetanide) – first-line in management of ascites, however patients with advanced liver disease are often resistant to diuretics or cannot tolerate them due to concomitant renal failure / electrolyte disturbances
- **Paracentesis** – outpatient ascitic drains are coordinated by Hepatology Specialist Nurses (bleep 2478) and are performed in the Ambulatory Care Unit (ACU). Avoid emergency admissions for paracentesis if possible as they are distressing for patients.
- **PleurX drains** – long term drain usually only inserted if patient too unwell to attend ACU. Insertion needs discussion with the hepatology team and should only be undertaken after patient has had opportunity for palliative care input and advance care planning discussions.
- **Alpha-pump** – subcutaneous pump inserted surgically to divert fluid from peritoneal cavity to bladder. Contact Hepatology Specialist Nurse (bleep 2478) if patient with pump in situ presents with problems with ascites or renal impairment; settings may need to be altered.

ANTICIPATORY PRESCRIBING AT THE END OF LIFE

These subcutaneous medications can be used for patients with Child Pugh B or C cirrhosis to manage commonly occurring symptoms at the end of life. These doses are a safe starting point for patients who are opioid naïve and / or not already established on medications to aid symptom control.

Symptom	Drug	PRN dose (SC)	Usual starting dose in syringe driver over 24hrs (If needed)
Pain if eGFR ≥30ml/min	Morphine sulphate	**2.5mg SC 1hrly** 1.25-2.5mg or 2.5-5mg depending on age and body habitus	Use PRN doses for 24hrs to establish opioid requirement
if eGFR <30ml/min	Fentanyl	**25-50micrograms SC 1hrly** 12.5-25mcg if elderly or multiple comorbidities	Use PRN doses for 24hrs to establish opioid requirement
	Patients at the end of life who were previously established on **methadone** may require this in a syringe driver to reduce agitation secondary to withdrawal. Liaise with supportive and palliative care team.		
Nausea *Opioid or centrally induced*	Haloperidol	**0.25-0.5mg SC TDS**	0.5-1.5mg
Prokinetic	Metoclopramide	**5mg SC TDS**	15mg. Titrate slowly.
Second line	Levomepromazine	**2.5mg SC TDS**	6.25mg
Respiratory secretions	Hyoscine butylbromide	**20mg SC 2hrly**	60mg
Agitation + *confusion*	Haloperidol	**0.25-0.5mg SC TDS**	1.0-1.5mg
+ *anxiety*	Midazolam	**1.25-2.5mg SC 1hrly** Note: Patients who are alcohol dependent may require larger doses as they can be tolerant	5-20mg
Second line	Levomepromazine	**6.25-12.5mg SC TDS**	6.25-12.5mg
Breathlessness	Morphine / fentanyl	See doses for pain	See doses for pain
+ respiratory panic (can talk/swallow)	Lorazepam	**0.5-1mg PO/SL 4-6hrly**	N/A
+ respiratory panic (NBM/can't swallow)	Midazolam	**1.25-2.5mg SC 1hrly**	5-10mg

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SAFETY

Evidence in this field is limited. Suggested doses and dosing intervals are based largely on expert opinion and may differ from standard end of life prescribing guidelines, but are felt to be a safe starting point.

QUERIES

Contact Hepatology Registrar (bleep 2330), Palliative Care Team (extension 23507 / bleep 2972) or Medicines Information (extension 23409).