Clinical Guideline

SYMPTOM CONTROL AND END OF LIFE CARE IN ADULTS WITH ADVANCED LIVER DISEASE

FOR STAFF:	Hospital doctors, GPs, specialist nursing staff and clinical pharmacists
PATIENT GROUP:	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 often have a high symptom burden, including general symptoms such as pain and nausea/vomiting, as well as symptoms related specifically to their liver disease, such as ascites or hepatic encephalopathy. When recognised as dying, they experience symptoms common to all patients at the end of life, including pain and agitation.

Prescribing in patients with advanced liver disease can be challenging. Many drugs are metabolised by the liver, therefore hepatic impairment can alter patients' response to medications. Drugs may require dose reduction or increased dosing interval; this is particularly true for patients with raised INR/prothrombin time, bilirubin and low albumin. However, it is important that uncertainty about prescribing does not lead to patients suffering unnecessarily due to inadequate symptom management.

This guideline covers the management of **common symptoms** in patients with advanced liver disease and offers guidance on prescribing of **anticipatory medications** at the end of life. It should be used for 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/), the Renal Drug Database or contact local Medicines Information Service 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 input from hepatologists, palliative medicine specialists and specialist pharmacists. **Prescribing practices vary both locally and nationally and prescribers should refer to local guidelines and use medications they are familiar with whenever possible.**

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. Suggestions for subcutaneous doses can be found on page 5.

Drug	Recommended Dose	Notes
Paracetamol	**2-3g / 24hrs PO** (long-term)	If over 50kg (dry weight), 1g QDS PO is safe for short periods (≤ 7 days) If needed regularly long-term (> 7 days), reduce dose
	Maximum 3g / 24hrs IV (even short-term)	**Avoid IV preparation whenever possible and always dose reduce when prescribing**
NSAIDs		Avoid (risk of bleeding and renal toxicity)
Tramadol		Avoid (half-life more than doubles and lowers seizure threshold)
Codeine	**15-30mg PO TDS** (short course only)	Avoid if possible – preferably use oral morphine If oral morphine not an option trial with caution as has unpredictable effect Monitor closely for constipation and worsening encephalopathy
Morphine sulphate	**2.5mg 4-6hrly PO PRN**	1st choice oral opioid for pain if eGFR ≥ 30 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 Note longer than usual dose interval Monitor closely for constipation and worsening encephalopathy
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 there is co-existing renal impairment i.e. 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	**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 acute pain team or palliative care 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 (e.g. ranitidine 150mg BD or omeprazole 10-20mg OD) 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 not thought to be actively dying.

Drug	Recommended Dose	Notes
Metoclopramide	**5mg PO/IV/SC TDS** Titrate to maximum 10mg TDS	First line option if gastrointestinal (GI) cause, acts as prokinetic May increase fluid retention Consider QT interval prolongation
Domperidone	**5mg PO BD** Titrate to maximum 10mg TDS	Alternative first line option, acts as prokinetic Consider QT interval prolongation
Haloperidol	**0.5-1mg PO BD** Titrate to maximum 5mg / 24hrs in divided doses	First line option if opioid or centrally induced
	0.25-0.5mg SC TDS	
Ondansetron	**4mg PO/IV BD** Maximum dose 8mg/24 hours	Second line option Monitor closely for constipation
Levomepromazine	**3mg PO NOCTE** Titrate to maximum 12.5mg BD	Second 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
	2.5mg SC TDS	
Cyclizine	**50mg PO BD**	Third line option Monitor closely for constipation and worsening encephalopathy
	25mg IV/SC BD	

DEPRESSION

Mirtazapine	**Start at 15mg PO ON** and titrate slowly to maximum dose 30mg ON	Avoid if patient has renal impairment May help to stimulate appetite Can have sedating effect
Citalopram	**Start at 10mg PO OD** (morning), titrate slowly to maximum dose 20mg	Half-life nearly doubles Can lower seizure threshold and increase gastrointestinal bleeding risk

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** Indicated if ≥ 2 episodes of encephalopathy Should be initiated after discussion with a specialist
Itching	Menthol 1% in aqueous cream	**Apply 1-2 times daily**
	Colestyramine	**4-8g PO OD** First line if itching is due to cholestasis (build-up of bile salts) Affects absorption of other medications: take other medications at least 1 hour before or 4-6 hours after colestyramine
	Antihistamines e.g. chlorphenamine	Second line - sedative effect can be helpful if given at night as patients are woken less frequently by pruritus Sedating effect can mask or worsen encephalopathy
	Rifampicin, Naltrexone, SSRIs (e.g. sertraline)	*Can all be used for itching secondary to cholestasis, but should not be initiated without Hepatology guidance*
	Colesevelam	*Off licence indication and limited evidence for effectiveness therefore not recommended*

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** – Emergency admissions for paracentesis should be avoided if possible as they are distressing for patients. Many hospitals provide a day case paracentesis service and patients with ascites should be provided with advice about when and who to contact to arrange this.
- **Long term drains (e.g. PleurX™ or Rocket®)** – usually only inserted if the patient is too unwell/prefers not to attend day case services. Insertion needs discussion with the hepatology team and should only be undertaken after the patient has been offered the opportunity to have advance care planning discussions +/- palliative care input.
- **Alfapump®** – limited use in specialist centres for ambulatory patients to improve quality of life. A subcutaneous pump is inserted surgically to divert fluid from peritoneal cavity to the bladder. If a patient with a pump in-situ presents with ascites or renal impairment, settings may need to be altered and the centre which inserted the pump should be contacted.

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 ≥ 30	Morphine sulphate	**2.5mg SC 1hrly** Consider prescribing 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 < 30	Fentanyl	**12.5-25micrograms SC 1hrly** Low threshold for increasing to 25-50mcg 1hrly in young and less frail patients	Use PRN doses for 24hrs to establish opioid requirement
if eGFR < 30 (2nd line)	Alfentanil	**50-100micrograms SC 1hrly**	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** Note: hyoscine hydrobromide should be avoided	60mg
	Glycopyrronium	**200micrograms SC 2hrly**	600mcg
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 – choice based on eGFR	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

REFERENCES AND RELATED DOCUMENTS	See separate document on BASL EOL SIG website
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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 the BASL secretariat on Samantha@basl.org.uk