Leeds Palliative Care Network

Liver Failure - Prescribing at the End of Life (including last days and hours of life) in the Community

(note there is a separate document for Secondary Care LTHT)

Developed by: Evidence Into Practice, a LPCN working group

Produced in partnership with;
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This document is intended to highlight special considerations when prescribing for patients with synthetic liver dysfunction e.g., liver disease associated low albumin / raised INR / low platelet count / raised bilirubin.

Prescribing guidance is presented for:

1. Palliative patients in the last weeks/months of life with liver failure.
2. Patients in the last days of life with liver failure.

Background information

- Chronic liver disease is more predictably associated with impaired metabolism of drugs than acute liver dysfunction. The greater the liver dysfunction, the greater the impairment of drug metabolism.
- Hepatic reserve is large so ability to metabolise drugs is usually preserved until there has been significant damage as indicated by synthetic dysfunction i.e., low albumin/raised INR (above 1) / low platelet count / raised bilirubin level.
- This guideline applies to patients with synthetic liver dysfunction. There is no single marker for hepatic clearance that can be used as a guide for drug dosing, but drug metabolism is likely to be impaired in those with a Child-Pugh Class of C (score of 10 points or more) or MELD score of ≥15.
- In moderate to severe liver dysfunction rates of drug metabolism can be reduced by 50% but will vary according to severity and aetiology of disease and additional co-morbidities.
- Cirrhotic patients are often very sarcopenic, and a serum creatinine within the “normal” range might therefore represent significant renal dysfunction. It is useful to check the patient’s usual baseline creatinine, and the rate of change (e.g., a doubling of creatinine in 48 hours) may be a better marker of kidney function than the absolute creatinine value.
- There is a lack of good quality data examining the pharmacological and adverse effect profile of analgesia in end stage liver disease.
- This guideline is based on the limited evidence available and on expert opinion.

General principles

- Prescribing should be individualised, balancing the risks vs. benefits and considering the patient’s goals of care.
- Optimise medicines and reduce polypharmacy as much as possible. Refer below to further guidance.
- Avoid hepatotoxic drugs
- Use low starting dose and titrate upwards slowly
- Consider reducing frequency of administration and avoid modified release preparations including patches
- Monitor for both late and delayed onset toxicity (accumulation more likely if plasma half- life is prolonged)
- Monitor for constipation to avoid precipitation of hepatic encephalopathy.
- Beware of sedation- may worsen or mask encephalopathy.
- Note, when prescribing for patients in the last days of life, the risk of encephalopathy may be outweighed by the benefit of managing other symptoms

Consider Renal Function

- eGFR reported by pathology labs can be used for most patients. However, consider calculating creatinine clearance (mL/min) using the Cockroft - Gault formula in the following circumstances:
    - At extremes of muscle mass (BMI <18 kg/m2 or > 30 kg/m2)
    - Elderly patients (aged 75 years or older)
    - Patients taking nephrotoxic drugs / drugs with narrow therapeutic index if predominantly renally excreted
    - Other comorbidities or clinical concern
- Calculate using either:

  Cockcroft-Gault formula: CrCL (mL/minute) = $\frac{n \times (140 - age) \times weight\ (kg)}{Serum\ creatinine\ (micromoles/L)}$

  where n = 1.04 (females), n= 1.23 (males)

  or online calculator at https://www.mdcalc.com/

- Consider seeking advice from a pharmacist.

1. Symptom advice in the last weeks or months of life

Pain management

- Consider reversible causes and non-pharmacological management of symptoms.
- Caution with NSAIDs; increased bleeding tendency and risk of renal function deterioration. This may be less relevant in the last days of life - please seek specialist advice.
- Paracetamol is safe to use: max dose 3g PO daily. For patients less than 50kg, IV dose is 15 mg/kg.
- If already prescribed a regular opioid seek specialist palliative care advice.
- First line opioid is:
    - **Morphine sulfate immediate release**. Start with a low dose, 1 to 2.5 mg PO **as needed**, minimum dosage interval 2 hours is preferred. A 1-hour dosing interval could be prescribed but because of risk of accumulation patients should be monitored for signs of opioid toxicity **OR**
    - **Oxycodone immediate release,** if morphine is contraindicated or GFR below 20 mL/min prescribe (i.e., below a GFR of 20 mL/min prioritizing renal dysfunction is felt to be safer). Start with a low dose, 1 to 2 mg PO **as needed**, minimum dosage interval 2 hour.
    - Generally modified release opioids should be avoided. However, if immediate-release morphine is well tolerated then modified release morphine products may be tried cautiously.
    - If unable to take oral medication, consider subcutaneous (SC) route - *refer to further guidance below for prescribing guidance in the last hours/days of life.*

Delirium

- Consider reversible causes.
- May have hepatic encephalopathy:
    - Review sedating medication which may be exacerbating this and consider other reversible causes (e.g., infection, dehydration, bleeding) as appropriate.
    - If able to take oral medication, consider **lactulose** 15-30mL three times a day aiming for bowels to open 2-3 times per day.
    - Consider daily **phosphate enemas,** if appropriate, and ongoing encephalopathy refractory to lactulose.
    - **Rifaximin** 550mg twice daily can be used if encephalopathy refractory to lactulose.

Nausea and vomiting

- Consider sedative side effects of anti-emetics.
- Avoid constipating anti-emetics such as **cyclizine** and **ondansetron**. Less constipating options:
    - **Domperidone** - at a reduced dose 5 mg PO twice daily. Maximum 10 mg three times a day. Note this can cause QT prolongation.
    - **Metoclopramide -** there is a risk of encephalopathy which needs to be considered when weighing up the benefits and burdens of treatment. It can be used at reduced dose 5 mg PO twice a day and titrated up if tolerated
    - **Haloperidol or levomepromazine** - starting with a low dose.
        - Haloperidol 500 micrograms PO daily OR
        - Levomepromazine 3 to 6.25 mg PO daily.
        - Caution as centrally acting drugs

Breathlessness

- Look for reversible causes. Note, ascites management may improve breathlessness.
- Trial non-pharmacological measures first line when possible.
- **Opioids** can be used for breathlessness. See prescribing advice under pain.

Pruritus

- Consider reversible causes, e.g., of cholestasis.
- Treat dry skin with emollients such as Diprobase® or Zeroderm®
- Bile acid sequestrants for cholestatic itch. No dose reduction required in hepatic impairment; avoid in complete biliary obstruction. Options include:
    - **Colestyramine** 4g once a day. Can increase to 8g once a day.
    - **Colesevelam** 625 mg three times a day. Can increase to total daily dose of 3.75 g, given on divided doses
- Antihistamine - e.g., **chlorphenamine**
- **Sertraline** 25 to 100 mg PO once a day
- Seek specialist advice if symptoms are persisting.

2. Symptom management for patients in the last days of life

The below guidance is for SC medication. If the patient is able to take oral medication please see above guidance *Palliative patients in the last weeks/months of life*

Pain

- Consider reversible causes and non-pharmacological management.
- **Morphine sulfate** 1 to 2.5 mg SC **as needed**, minimum dosage interval 2 hours OR
- **Oxycodone** 1 to 2 mg SC **as needed,** minimum dosage interval 2 hours.
- For both **morphine** and **oxycodone** request clinical review if TWO or more **as needed** doses have been given in the last 24 hours (continue to give up to 4 as needed doses in 24 hours until clinical review is undertaken if required)

Agitation/Delirium

- Consider reversible causes.
- Non drug management is the most important strategy
- Prescribing advice:
    - **Midazolam** (10mg/2mL) 1.25 to 5mg SC as needed (minimum dosage interval of 30 minutes) It is suggested that as needed dose range is prescribed. **OR**
    - **Haloperidol** (5mg/mL) 500 micrograms to 1mg SC needed (minimum dosage interval of 1 hour). It is suggested that as needed dose range is prescribed.
    - For both midazolam and haloperidol start at the lowest dose of the range. Request medical review if TWO as needed doses have been given in the last 24 hours.

Nausea and vomiting

- If on effective antiemetic this can be continued. If unable to take oral medication convert to SC route. The conversion from oral to SC is 1:1 for most antiemetics
- For those with new or anticipated symptoms:
    - **Haloperidol** (5mg/mL) 500 micrograms SC as needed (minimum dosage interval of 1 hour). Request a medical review of if TWO as needed doses have been given and patient remains symptomatic OR
    - **Levomepromazine** (25mg/mL) 2.5 mg SC as needed (minimum dosage interval of 1 hour). Request medical review if 6.25mg or more has been given in the last 24 hours and patient remains symptomatic.
    - For persistent symptoms both drugs have relatively long half-lives so may be given as intermittent injections (daily or twice daily) or given by continuous SC infusion.

Breathlessness

- Opioids can be used for breathlessness. See prescribing advice under pain.

Retained respiratory secretions

- Consider cause of secretions refer **to LCH Symptom Management Guidance in the Last Days of Life**
- Non-pharmacological management such as positioning is the most important component of treatment.
- Avoid hyoscine hydrobromide because of its central effects.
- **Hyoscine butylbromide** is the favoured drug treatment as it is non-sedating,
    - Hyoscine butylbromide (20mg/mL) 20mg SC as needed (minimum dosage interval of 1 hour).
    - *Note* it is short-acting therefore if effective consider a continuous subcutaneous infusion (typical starting dose 60mg SC over 24 hours).
    - Ensure good mouth care as dry mouth is a side effect.

Pruritus

- Treat dry skin with emollients such as **Diprobase®** or **Zeroderm®**
- **Midazolam** for sedation if causing distress and sedation acceptable.

Further guidance

- Yorkshire and the Humber End of Life Care Group: A Guide to Symptom Management in Palliative Care. Version 8 (2023).
- Symptom Management Guidance in the Last Days of Life Last Days of Life (leedsth.nhs.uk)
- The Leeds Opioid Conversion Guide for Adult Palliative Care Patients
- Specialist Community Palliative Care Team:
    - Wheatfields Hospice: 0113 2787249
    - St Gemma's Hospice 0113 2185500
    - **or** the palliative medicine consultant on call via switchboard OOH

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