

Review

Symptom control in advanced chronic liver disease: integrating anticipatory palliative and supportive care

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ABSTRACT

The number of patients coming to hospital with liver disease is increasing. There was a worrying trend before the pandemic, and this has intensified. Despite improvements in the management of patients with advanced cirrhosis many patients will die within 6–12 months of first presentation, and, despite this, the field of palliative and supportive care in liver disease is still in its infancy. This is a narrative review. Evidence is often thin in this field. Where it exists it is cited, but much of the commentary here is based on the authors own experience and readers are free to consider it and debate it. Most patients who die of liver disease receive palliative care very late in their illness (if at all). There are many barriers to supportive and palliative care in liver disease which are discussed. Symptom control is often poor because of these barriers. Before symptomatic control can be established, patients in need of it must to be identified and conversations had about the severity of their situation and what their wishes would be. Interest in palliative and supportive care for patients liver disease is growing as is the number of hepatologists and palliative care clinicians within the UK with an interest. It is important that this enthusiasm and interest can be rolled out and scaled up across the UK so that all patients, wherever they are, can benefit. The aims of these articles are first to highlight and bring into focus the unmet need for palliative and supportive care in liver disease and second to provide suggestions for its integration into liver services. Ask yourself the question: where would I start in my hospital to help these patients?

INTRODUCTION

The number of patients coming to hospital with liver disease is increasing. There was a worrying trend before the pandemic,¹ and this has intensified.²

Key points

- ⇒ Supportive and palliative care in advanced liver disease is a growing area.
- ⇒ Identification of those in need of it is key and best achieved through formal screening tools.
- ⇒ Delivery of care is best organised through multidisciplinary teams including hepatologists, palliative care specialists and specialist nurses.
- ⇒ Paracentesis services for ascites provide a vanguard for the introduction of palliative and supportive care in liver disease.
- ⇒ Most symptom control in liver disease is easier than it appears, where medicines are required the principle of ‘start low and go slow’ applies.
- ⇒ Having honest discussions with people and initiating advanced care planning facilitates the best outcomes for patients.

Despite great improvements in the management of patients with advanced cirrhosis and decompensation based on large randomised controlled trials with a huge body of published evidence,^{3–5} many of our liver disease patients will still die, and, within the field of palliative care there is only (currently) a weak evidence base for interventions that help. This is starting to be addressed but it is notable that the recent AASLD palliative care practice document describes itself as guidance rather than guidelines given the lack of randomised control evidence to inform them.⁶ Most patients who die of liver disease receive palliative care very late in their illness (if at all) and often only after exhaustion of curative options. Integral to palliative and supportive care is good quality symptom control throughout all stages of disease.



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However, interest in palliative and supportive care for patients liver disease is growing with increasing numbers of reviews and references in practice guidelines.^{6–9} There is a growing body of high-quality clinical studies and now a number of randomised controlled trials,^{10–13} looking at interventions designed to help those at the end stage of their liver disease. There is a growing group of hepatologists and palliative care clinicians within the UK with an interest in this area. It is important that this enthusiasm and interest can be rolled out and scaled up across the UK so that all patients, wherever they are, can benefit from the insights being gained.

BARRIERS TO GOOD PALLIATIVE AND SUPPORTIVE CARE

First, is the term itself. The perception that palliative care is mutually exclusive to disease modifying treatments, (in particular liver transplantation) has been recognised as a key barrier to its timely initiation^{14 15} Palliative care is often mistakenly thought to be synonymous with end-of-life care by healthcare workers, patients and carers. Clinicians report concerns that use of the term ‘palliative’ would cause unnecessary distress to patients and families, that it might compromise patients’ hope, or result in the idea that the clinician has ‘given up’ on them or has nothing else to offer. This can lead to a reluctance to initiate conversations about anticipatory care planning or referral to specialist palliative care until patients are clearly reaching the end of life. Palliative care is therefore often considered late, when the patient is obviously dying rather than earlier, potentially alongside active treatment, when there may be more benefit to the patient and their family. Three studies, from transplant units each retrospectively assessed the proportion of patients either delisted or assessed unsuitable for transplantation who were referred for SPC over a 12-month period. The UK study reported that 19% of patients were referred, on average 4 days before death¹⁶ with similar findings in Canada and the USA (box 1).^{17 18}

Until recently, there has been an absence of evidence in the palliative care literature specific to the liver but

there is a wealth of evidence elsewhere relating to other conditions. It is well established that provision of good-quality palliative care improves HRQoL, improves symptoms and is also better for carers. A prospective evaluation of a palliative care intervention delivered in parallel to assessment for liver transplantation demonstrated an improvement in 50% of moderate to severe symptoms among study participants after 3 months, with 43% of participants also demonstrating improvements in mood. The intervention consisted of a single consultation with a palliative care specialist focusing specifically on physical symptoms, mood, social well-being and spiritual care. Patients with a higher initial symptom burden showed the greatest improvements.¹⁹ In an outpatient and community setting, models of nurse-led supportive care have also been shown to improve quality of life, and to be acceptable to/valued by patients and carers.²⁰ For patients presenting to services at the point of critical illness, intensive care unit (ICU)-based palliative care interventions have been studied. An ICU-based intervention consisting of family support, a discussion around prognosis and patient preference, and discussion of do not attempt resuscitation orders was prospectively compared with a control group. Patients receiving the intervention had earlier documentation of resuscitation status. The time between do not attempt resuscitation decisions and death was increased, thereby potentially increasing the period where loved ones were aware of the gravity of the clinical situation, possibly allowing time to say goodbye. There was a decreased length of ICU stay, and a shorter time to withdrawal of organ support. Importantly, there was no difference in mortality between the groups.^{21 22}

Design of good-quality randomised controlled trials looking at palliative and supportive care in liver disease requires novel approaches and endpoints. Public, patient involvement (PPI) from patients and their carers is crucial to ensure that the right things are measured as conventional endpoints such as survival or hospitalisation are not the most valid.

IDENTIFICATION OF PATIENTS WHO WOULD BENEFIT FROM PALLIATIVE CARE

When we discuss patients at mortality and morbidity meetings it is usually obvious in retrospect that they were going to die. Despite this, very few of them received palliative care and often the prospect of their death was not even being raised with them (at least not until the last few days). Colleagues reading this will recognise that the patients themselves and their caregivers may have been completely unaware that death was likely, alternatively they may have been in a distressed state due to the uncertainty of their condition.

Liver disease has an unpredictable trajectory. Parallel planning allows ongoing active management while preparing for sudden deterioration, with almost all

Box 1 Barriers to palliative and supportive care in liver disease

- ⇒ Terminology.
- ⇒ Palliative versus end of life.
- ⇒ Recognition that it is needed.
- ⇒ Variable disease trajectory.
- ⇒ Transplant bias.
- ⇒ Delivery of care.
- ⇒ Medical staff-skills gaps.
- ⇒ Patients-specific challenges.
- ⇒ Hospital systems-patient safety focused.
- ⇒ Community services-gaps.

patients including those who are actively on transplant lists. Due to the way hepatology developed as a specialty in the UK, there was historically an over-emphasis on aiming for transplant as the definitive management when the majority of patients with liver disease never come to liver transplant or are ineligible from the start. Obviously anyone with decompensation should be considered, but once ruled out they are obvious candidates for palliative and supportive care.

THE ROLE OF THE ADVANCED CHRONIC LIVER DISEASE MULTIDISCIPLINARY TEAM IN GUIDING ESCALATION DECISIONS AND CEILINGS OF CARE

Over the past 5 years, various instruments have been developed with the aim of supporting liver health-care professionals to deliver high quality palliative care. Clinical scoring systems have been designed which routinely identify patients with poor prognosis,^{23 24} such that clinicians are signposted to palliative care interventions in a timely fashion—in parallel to ongoing curative/disease modifying care where appropriate. Experience tells us that simply asking your self the question; ‘would I be surprised if this patient died in the next 12 months’ is both simple and very useful. Communication aids have been developed to assist clinicians with difficult conversations with patients and carers (eg, in the delivery of news of poor or uncertain prognosis).^{23 25}

Multidisciplinary team (MDT) meetings are being increasingly used as a means to afford a wider breadth of expertise to patients with advanced liver disease, to improve co-ordination of care between the hospital and community, and to inform anticipatory care planning (including establishing reasonable ceilings of care where appropriate). Typically, MDTs include hepatologists, specialists in palliative care, community nursing, alcohol support, dietetics and physiotherapy/occupational therapy. They allow patients’ individual needs to be addressed, for example, in the use of physiotherapy for patients with frailty, expert dietetic input for patients with malnutrition, or specialist palliative care for patients requiring complex anticipatory care planning or who have physical symptoms that are difficult to control.

Various structures for MDT working have been established across the UK, and we have reviewed them and included examples of best practice in our previous work.⁷ These incorporate the key personnel as listed above and are based around the group meeting regularly and specialist clinics in settings appropriate to local services. Involvement of carers as well as the patients is encouraged and education is key to empowerment and self management.

Good conversations (box 2) take time and time is a scarce resource in modern medicine. Creating time in job plans or indeed additional posts such as specialist liver nurses is not free and is an additional barrier. However, proper organisation of care can actually

Box 2 Having an honest dialogue

- ⇒ Accept uncertainty.
- ⇒ Thinking ahead—advanced care planning.
- ⇒ Preferred place of death.
- ⇒ LPA.
- ⇒ Goals, limits.
- ⇒ Resus status, respect document.

save time, lead to reduced bed stays and less expensive investigation. This has been demonstrated in hospitals providing paracentesis units, wider proof of this is required from further studies.

OTHER BARRIERS TO GOOD CARE

The nature of our patients presents challenges. Early discussion is important because later on, encephalopathy may make discussions and proper planning difficult. Identification of surrogate decision makers and establishment of lasting powers of attorney can be very helpful later on. Liver disease is frequently associated with social isolation, economic deprivation and ongoing addiction. These factors contribute to a well-recognised stigma associated with liver disease, which can lead to self-blame and the feeling of not being ‘worthy’ of healthcare. This can accentuate the difficulties in providing care to this cohort.

Medical personnel can also be a problem. Doctors particularly, often express over optimism or at least don't like to give bad news. They feel discomfort discussing these issues. and most training has focused on longevity. In our experience, a goal of getting everybody to a transplant, means death is often seen as a failure and something to avoid discussing. Many doctors lack skills and have misconceptions about palliative care. This is amenable to education. There is a particular lack of confidence in prescribing with fear of administering adequate pain relief and medicines for anxiety. However, increasingly studies demonstrate that palliative care conveys the same benefits in liver disease.^{13 21 26 27} Readmission rates also appear to be lower.¹³

It must be appreciated that while specialist palliative and supportive care services exist and increasingly are becoming much more involved in non-cancer areas such as liver disease, all doctors need to know about and to be able to provide primary palliative care in a symptom driven way. As the patient's primary caregiver the hepatologist is the one who is best able to discuss their prognosis.

As technology becomes increasingly integral to modern medicine with care pathways and algorithms to be followed, particularly early warning systems, it is very easy for patients get assimilated into a web of safety with protocolised responses. This is often not the most appropriate route and can be dehumanising. It is important when designing palliative and supportive

care services that we create our own algorithms with human decision points (taken in conjunction with patients and their carers) so that we can reinforce appropriate care.

GENERAL PALLIATIVE CARE

Once established who needs it, a lot of palliative care can be provided by hepatologists. Most of this revolves around having honest conversations in a timely way earlier in the disease trajectory than is currently undertaken. Being mindful of the patients financial, social and psychological status is important as well as spiritual beliefs where appropriate. Using this information together with the patient to craft an anticipatory care plan can make a huge difference later on, perhaps when the patient is lost capacity, so that wishes are understood and the difficult decisions have been made already.

Increasingly for the more complex situations and cases specialist palliative care is becoming more integrated into liver medicine and this is discussed in the lecture series.

MANAGING SYMPTOMS AND BREAKING BARRIERS

Symptom control is required throughout all stages of advanced liver disease and should be differentiated from actual end-of-life care. The transition point to end-of-life care is hard to define in words but usually clinically obvious, and at that point objectives change to emphasis on for example relief of pain and distress including provision of opiates and benzodiazepines. Symptoms among people with advanced liver disease are frequent and distressing. Pain is present in a majority (30%–79%), breathlessness in 20%–88%, cramps (56%–68%), sleep disturbance (26%–77%), daytime sleepiness (30%–70%), psychological symptoms including depression and anxiety as well as sexual dysfunction.²⁸ The first step in resolving these symptoms is to ask the patient about them. Checklists/symptom directed tools exist and should be used. This may not suit all patients due to literacy problems. The use of question prompts may also be of benefit.

NON PHARMACOLOGICAL INTERVENTIONS

Draining ascites can resolve many of these symptoms at a stroke: Pain, breathlessness lack of appetite, mobility and fatigue. Proper mattresses and pressure care, physiotherapy, all play a role. Optimising the patients general state through screening for frailty^{29 30} and nutritional input can help in multiple ways, importantly in managing encephalopathy.

It will be immediately obvious that a large component of symptomatology revolves around ascites and fluid overload, and it is here perhaps unsurprisingly the most of the strides in palliative care have been made as this is a focal point for some of the sickest patients and also an ideal place to start in terms of a palliative care

service. Linkage to an advanced liver disease MDT strengthens this. Increasing provision of paracenteses units around the country have been shown to reduce inpatient days and indeed cost as well as improving patients symptoms and quality of life.³¹ Many of these units also attract the services of specialist hepatology nurses- key individuals in the long-term care of these patients and someone with whom they can discuss their symptoms issues and concerns.

Large volume paracenteses is still the mainstay for managing ascites and can be improved through the use of day case paracentesis when the problem is recurrent. Ongoing randomised controlled trials are assessing the use of long-term ascitic drains are discussed in the accompanying article and in a proportion of patients transjugular intrahepatic portosystemic shunting may be an option.

PHARMACOLOGICAL INTERVENTIONS

Many clinicians feel ill equipped to prescribe because of concerns about hepatic metabolism, the risk of provoking encephalopathy and the risk of renal failure. The general principle of starting low (dose) and going slow (less frequent administration, gentle upwards titration) stands.

Suggested medications for various symptoms have been published extensively elsewhere.^{6 32}

When it is appropriate to use them will depend largely on where the patient is on their journey towards end of life. Earlier on things like depression, sexual dysfunction, general frailty, for example, may be more relevant and need to be actively considered.

Management of pain in Liver patients is the same as that in anyone but with some nuances. A proper history, where the pain is, what might be causing it and whether it is acute or chronic is vital. Common causes of pain would be; relating to the liver itself, perhaps due to due to ascites, osteoporotic fractures, etc. Neuropathic pain is also common, particularly in those whose disease is caused by alcohol. Where possible assessing and treating reversible causes is the best approach.

When pharmacological measures are required, paracetamol as the first line drug is preferred but still barriers exist persuading non liver clinicians to prescribe it. Standard doses are safe and acceptable. There is a need to avoid NSAIDS because of the fluid retention and renal impairment they can cause but topical application of these is probably safe. When opioid's are required there is a risk/benefit balance to consider which is why important communication with the patient about their goals and objectives is required; most would probably choose to not be in pain during their last weeks then to suffer it. Measures to avoid the constipation associated with them and therefore and encephalopathy are important. Awareness of hepatic metabolism means that in general we should start with low dose morphine or fentanyl rather than other opiates. Oxycodone may be suitable for some,

especially if renal impairment, but the half life triples in advanced liver disease. Starting with spaced out lower doses and building up is the safest way to proceed.

Dyspnoea has multiple causes including ascites but also portopulmonary and hepatopulmonary syndrome's and fluid overload. Acidosis, renal failure and anxiety could also all contribute. Again there is a balance to be struck between possible side effects of treatment and patient preferences. Simple things such as fans and oxygen even when people are not hypoxic can help the symptomatic feeling of breathlessness. Towards end of life, benzodiazepines and opiates are appropriate although with the recognition then they may depress consciousness.

Encephalopathy is a big problem because it is distressing for the patient, makes it difficult for them to make decisions and hard on their caregivers. It often ends up precipitating unplanned admissions to hospital. Management is with lactulose and administration of rifaximin keeps people out of hospital.^{33 34}

In cramp, often correcting deficiencies of electrolytes can help. Vitamin E, taurine, branched chain amino acids, quinidine and baclofen have all been suggested but trials are small.^{35 36}

Insomnia leads to fatigue, depression and anxiety. Good sleep hygiene is useful. The causes of insomnia in liver disease are multifactorial including altered metabolism of melatonin and aberrant thermoregulation.³⁷ An altered sleep pattern can be a manifestation of encephalopathy which should be looked for and managed. Other non-pharmacological methods such as meditation and cognitive behavioural therapy may help. When pharmacological measures are required it is best trying to avoid benzodiazepines until the very end of life. Hydroxyzine, melatonin and zolpidem in small doses for short periods of time are acceptable.

Fatigue is difficult to treat. Assess contributing factors and to look out for things that may be reversible. Explanation that this is common can relieve symptoms of guilt from not being able to fulfil roles may help. Assessing and supporting nutrition is clearly important. The pros and cons of tube feeding need to be weighed carefully and discussed with the patient. Use the liver frailty index to identify problems early.³⁸

Pruritus, particularly in cholestasis can be very debilitating for patients. Aqueous cream with menthol followed by cholestyramine or colestipol help in some can be unpalatable. If the patient is not jaundiced then Rifampicin is the next step followed by naltrexone and then sertraline. All of these work in some people but not all.

Many patients disease complain of sexual dysfunction if asked about it but otherwise remain silent. Stopping things that might be making it worse helps. Sildenafil and its analogues is safe in the majority.

Depression and anxiety are very common and screening tools, for example, Hospital Anxiety and Depression Score exist but are seldom used. It is

important to remember to address these things as they will respond to standard treatments in a high proportion of cases. Lower starting doses are required.

There multiple causes for nausea and vomiting including ascites, medication, electrolyte imbalance, GI congestion in relation to portal hypertension and also constipation. Reflux and acid type symptoms may respond to a proton pump inhibitor. Care should be taken with metoclopramide because of extrapyramidal side effects but a 50% dose reduction seems a reasonable approach. Ondansetron may also help.

Sadly most patients still die in a healthcare facility. Some factors that make patients more likely coming to hospital are specific to liver disease, for example, variceal bleeding but this is something that can be discussed in anticipatory care planning. Again it's important this takes place early because once people have become encephalopathic it is difficult to know their wishes. Paracenteses towards the very end of life is still appropriate because of the symptom relief it brings.

Anticipatory care plans can be created and stored on hospital electronic records. Liver-specific events should be discussed and decisions made about where the patient would like to be should one occur at the end of their life. A letter detailing poor prognosis to the GP and completion of the ReSPECT form aid decision making in the community. Although in general there is a move to try to reduce the frequency of hospital as the place of death, for some liver patients this may be preferable to their home environment which often may be a hostel or even the street. For this reason it may be perfectly acceptable for the end-of-life care plan to include hospitals in place of home as long as admission does not stimulate heroic efforts by clinicians.

REASONS TO BE OPTIMISTIC

There is an increasing focus on educating trainees about palliative and supportive care which is now included in most registrar curricula at least at the basic

Box 3 How to achieve best practice through reorganisation rather than remortgaging!

The patients are already there

Good clinical care

- ⇒ Set up an ascites service.
- ⇒ Manage encephalopathy.
- ⇒ Use existing tools to spot those with poor prognosis.
- ⇒ Use existing tools to screen for symptoms.
- ⇒ Pain management.
- ⇒ Early dietetics.

Establish an advanced liver disease multidisciplinary team and invite your palliative care colleagues and social services colleagues.

- ⇒ Create a mindset of parallel planning and realistic prognosticating-honest conversations.
- ⇒ Engage in R&D.
- ⇒ Join special interest groups for ideas and peer support.

level. Online training is available for those with an interest.³⁹ It would appear self evident that conversations with patients in relation to their prognosis and their wishes take place but sadly this does not always happen given working patterns within hospitals. Further workforce training and programme development to support education is important. Formal communication between palliative care agencies and hepatology is one way of achieving this locally within the hospital. It is encouraging that in the UK IQILS now seeks to include palliative care as a quality metric. This will hopefully in time provide strategic levers for acquisition of sufficient resource to provide the care. In the meantime, establishing day case paracentesis and an advanced liver disease MDT in your hospital is the most powerful first step (box 3).

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