AASLD Practice Guidance: Palliative care and symptom-based management in decompensated cirrhosis

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INTRODUCTION

Palliative care is defined as multidisciplinary, specialized medical care that addresses the physical, spiritual, and psychosocial needs of patients with serious illness and their caregivers. [1,2] The benefits of palliative care are increasingly recognized across disease states and for patients with decompensated cirrhosis (DC). [3–5] This American Association for the Study of Liver Diseases (AASLD) guidance to providing palliative care for patients with cirrhosis was developed with the support and oversight of the AASLD Practice Guidelines Committee.

The AASLD Practice Guidelines Committee chose to commission a guidance, rather than a guideline, because of the paucity of randomized controlled trials (RCTs) on this topic. AASLD guidelines are supported by systematic reviews of the literature, formal ratings of evidence quality and strength of recommendations, and, if appropriate, meta-analysis of results using the Grading of Recommendations Assessment Development and Evaluation system. In contrast, this document was developed by consensus of an expert panel and provides guidance statements based on formal review and analysis of the literature on the topics and questions related to palliative care for patients with decompensated cirrhosis.
to the palliative care needs of patients with cirrhosis and their caregivers. Although palliative care can be considered regardless of the stage of cirrhosis, this guidance document predominantly addresses issues pertinent to adult patients with DC because this group bears considerable physical, psychosocial, and financial burden. We specifically focus on topics that are not covered in existing AASLD practice guidelines/guidance documents and thus refer the readers to the AASLD practice guidelines for specific recommendations for the diagnosis and management of ascites, hepatic encephalopathy (HE), hepatocellular carcinoma (HCC), and portal hypertension. In addition, the complex palliative care needs for patients with HCC are not specifically addressed by this guidance, but are addressed by other guidelines.

**PALLIATIVE CARE DEFINITIONS**

Palliative care can be provided at any stage of a serious illness and concurrently with disease-directed and curative treatments (including organ transplants). Over the past decade, the body of evidence supporting early palliative care has expanded to include persons with nonmalignant conditions, such as cirrhosis. Palliative care takes a comprehensive, person-centered approach to care, focusing on the aspects of care most important to patients and their families/informal caregivers. Because of this comprehensive scope, management typically relies on a team, including physicians, nurses, chaplains, social workers, and other providers.

Table 1 illustrates the conceptual distinctions between primary and specialty palliative care. Specialty palliative care refers to care delivered by specialists with advanced palliative care skills such as board-certified palliative care physicians or palliative-certified nurses, social workers, pharmacists, and chaplains. However, primary palliative care describes care aligned with the principles of palliative care (e.g., person-centered, communication-focused symptom management) that can be delivered by any medical professional. The National Consensus Project for Quality Palliative Care defined eight core domains of high-quality palliative care around which this guidance is framed (Figure 1). Although all eight domains can apply to patients with DC, their relative importance may vary across the illness trajectory.

Advance care planning (ACP) is a component of palliative care that involves the iterative and longitudinal process of medical decision making for patients and their families over the course of their illness trajectory. ACP includes identifying surrogate decision makers, illness education and prognostic disclosure, and formal documentation of goals for medical and end-of-life care (EoLC) through advance directives that center on the goals, values, and preferences of patients and their families.
Hospice is EoLC focused on allowing people in the last phases of incurable disease to live as fully and comfortably as possible.[14] Hospice is different than palliative care in that it focuses exclusively on comfort, rather than disease-directed curative treatment, and includes only persons with a life expectancy measured in months. In the USA, the hospice benefit is provided under Medicare Part A, and patients must have a defined, time-limited prognosis (certified by one or more physicians as ≤6 months).[18] DC is in many cases incurable, and life expectancy, which can be predicted with models such as the Model for End-Stage Liver Disease (MELD) and Child-Pugh-Turcotte scores, may be well below 6 months.[6,19–21] Because of the poor prognosis of DC, many patients with DC qualify for hospice benefits, which can help support patients and their caregivers.

**Guidance statements**

1. Palliative care can be provided to patients with DC at any stage of their illness.

2. Palliative care can be delivered by any member of the care team (primary palliative care) as well as teams with subspecialty training (specialty palliative care) for more-complex cases.

3. Palliative care does not preclude the delivery of disease-directed or even curative treatments.

4. Hospice is different than palliative care in that it focuses exclusively on comfort, rather than disease-directed curative treatment, and includes only persons with life expectancy measured in months.

**THE ROLE OF CAREGIVERS IN PALLIATIVE CARE**

Attention to patients’ families and support persons, herein called caregivers, is a core value and component of palliative care (Figure 1). Caregivers are discussed in The National Consensus Project under the heading of clinical implications. Throughout this document, we address the role of caregivers in each aspect of palliative care. Caregivers of patients with DC often face...
under-recognized psychological, physical, and financial burdens.[22–27] Their symptoms include stress, anxiety, depression, insomnia, decreased health-related quality of life (HRQoL), and worse physical health.[23,25–27] Psychological symptom burden among caregivers is associated with patients’ alcohol use, encephalopathy, ascites, liver disease (LD) severity, repeated hospitalizations, prognostic uncertainty, and lack of information.[25–28] Caregivers of patients with DC report feeling unprepared to provide physical care, medication management, and transportation to their loved ones and often experience significant financial burdens.[23–25,27,30–32] Importantly, the financial, social, and psychological burdens of cirrhosis experienced by caregivers can continue to impact caregivers after patients die. As such, support for caregivers of patients with cirrhosis should start early and extend through the bereavement period. This support can include inquiring about how they are doing during a medical visit, acknowledging the challenges of caregiving, and referring to services for support. Hepatology providers should assess caregivers’ goals and consider their needs. Being knowledgeable about and providing a list of ancillary services to caregivers is something that can occur in hepatology. Services of interest to caregivers may include pastoral care or spiritual support, mental health resources, bereavement support, grief counseling, caregiver support websites, and peer support groups.

Guidance statements

5. Caring for caregivers is a central component of providing palliative and hospice care.
6. Caregiver support should be provided across the trajectory of liver disease and is critically important in the context of DC, EoLC, and after the patient’s death.

PALLIATIVE CARE IN PATIENTS WITH DC: CURRENT PRACTICES AND BARRIERS

Cirrhosis is associated with poor HRQoL attributable to multiple physical, cognitive, psychological, and social stressors that are challenging to manage.[35,33,34] Although the prognosis for patients with DC is variable, with a 5-year mortality ranging from 20% to 80% across studies, the overall disease trajectory is progressive, with declining health and increasing symptom burden and frequent hospitalizations at the end of life.[19,35–37] Though liver transplantation (LT) can be curative, few patients are ever waitlisted for or receive LT.[38]

Palliative care needs of patients with cirrhosis and their caregivers are frequently underaddressed.[39] Only 11% of patients with cirrhosis receive specialty palliative care or hospice care referrals, and consultation often occurs very late in the disease course.[40–44] Consequently, patients with cirrhosis receive EoLC that is more resource intensive and invasive than that of patients with other serious, life-limiting illnesses.[27,44,45]

There are several barriers to palliative care implementation that have been identified specifically in hepatology. These barriers include a shortage of specialty palliative care providers, absence of evidence-based referral criteria, lack of role clarity between specialists, stigma that palliative care is synonymous with “giving up” on curative treatments, lack of provider training, competing demands on providers’ time, and prognostic uncertainty.[22,27,41,46–50] In addition, many of the symptoms experienced by persons with DC are highly liver specific and managed longitudinally by liver teams. This is in contrast to oncology practice models in which palliative care teams frequently have a key role managing malignant pain syndromes throughout the disease course.[51] Transplant evaluation and listing may also present a unique barrier to palliative care for patients with cirrhosis, related to the perceived incompatibility of transplantation and palliative care. One study found that patients with cirrhosis undergoing transplant evaluation received lower-quality EoLC.[52] Similarly, a qualitative study of 42 patients and 46 clinicians found that transplant teams avoided discussing nonaggressive treatment options with patients, leading caregivers to feel unprepared to support their loved ones at the end of life.[53] Finally, hepatology training does not routinely include palliative care training, and palliative care competencies for hepatologists have not been developed.

Despite these barriers, hepatology clinicians, especially those with a longitudinal relationship with patients and families, can play a key role in delivering primary palliative care to address patients’ and caregivers’ needs. Some elements of primary palliative care that could be provided as part of routine hepatology care include evaluating and managing symptoms, identifying and documenting surrogate decision makers, eliciting patient preferences about treatment and aligning care plans with these preferences, providing counseling about what to expect in the future, and referring patients for social services to increase support in the community.

Guidance statements

7. Patients with DC and their caregivers often have significant unmet, unrecognized palliative care needs that include psychological, physical, social, financial, and spiritual health burdens.
8. Evaluation for unmet palliative care needs and specialty palliative care consultation should be considered for all patients with DC and their caregivers.
9. In patients with DC, disease-directed care, such as transplantation evaluation and listing, does not
preclude palliative care delivery or specialty palliative care consultation.

10. Given shortages of specialty palliative care providers, hepatology clinicians should play a central role in offering primary palliative care services to patients with cirrhosis, including symptom assessment and management, basic ACP (e.g., identifying surrogate decision makers), counseling, and referral for additional support when feasible and necessary.

**EFFECTIVENESS OF PALLIATIVE CARE INTERVENTIONS FOR PATIENTS WITH CIRRHOSIS**

A growing body of evidence supports the integration of curative and palliative care approaches for patients with DC (Table 2). Observational studies have demonstrated reduced resource use, decreased symptoms, and improved HRQoL for patients with cirrhosis who receive palliative care services. Single-arm, single-center study found that outpatient specialty palliative care referral for all patients undergoing LT evaluation resulted in improved physical and psychological symptom scores. Likewise, an outpatient primary palliative care intervention led by hepatology nurses with palliative care and communication training was feasible and acceptable to recently discharged patients and their health care teams. The intervention was associated with improved HRQoL, care coordination, coping, and anticipatory planning.

Two studies that examined inpatient palliative care also had favorable findings. A specialty palliative care intervention in a single academic surgical intensive care was associated with earlier consensus around goals of care, reduced length of stay, and earlier provision of comfort-focused care without any change in mortality. Caregivers also reported having more time to say goodbye. This intervention included early consultation with an interdisciplinary palliative care team, who provided a comprehensive evaluation within 24 h of admission, including discussion of prognosis, caregiver support, ACP, and symptom assessment. The palliative care team then participated in daily rounds and conducted a caregiver meeting within 72 h of admission.

To the best of our knowledge, Shinall et al. conducted the only RCT of a palliative care intervention in inpatients with cirrhosis. The intervention included patients with a life expectancy <12 months and involved an inpatient specialty palliative care consultation and monthly postdischarge follow-up with the palliative care team, who reviewed medications, symptoms, and goals of care. The comparison group received usual care that included palliative care at the discretion of the hepatologist (19% received palliative care), and results were analyzed on an intention-to-treat basis. Although this trial was prematurely terminated because of low enrollment, patients in the intervention group had significantly reduced readmission rates and more days alive outside of the hospital as compared with patients in the control group. The researchers cited barriers to enrollment including patients and family feeling overwhelmed at the time of index hospitalization, concerns about whether insurance would cover palliative care, and challenges with identifying caregivers, and a narrow screen-in to enrollment window.

Few interventions have included caregivers of patients with cirrhosis. A randomized trial of a cognitive behavior-based coping intervention delivered by trained nurses or social workers by telephone (as compared with LD education as an attention control) did not significantly impact mental health or HRQoL for patients or caregivers. However, a mindfulness-based stress reduction and supportive group therapy intervention was associated with improved patient and caregiver mental health symptoms and HRQoL. More trials are needed to understand how to best help caregivers of patients with cirrhosis.

Although these early data generally support the effectiveness of palliative care interventions for patients with cirrhosis and their caregivers, larger trials are needed to further characterize the optimal timing and content of these interventions. Conducting palliative care trials in this population is especially challenging for several reasons. Such trials are resource and time intensive; the population is heterogeneous (in terms of illness severity, trajectory, and treatments) with considerable prognostic uncertainty; trials require rigorous, potentially intrusive study monitoring; and there is limited interest in the topic from commercial sources, among others. The ongoing PAL LIVER trial, funded by the Patient-Centered Outcomes Research Institute, is recruiting patients with advanced liver disease and their caregivers from 18 clinical centers in the United States, comparing the effectiveness of palliative care delivered by specialists versus trained hepatologists for improving patients’ HRQoL, symptoms, caregiver burden, and health care use. PAL LIVER and other studies are needed to establish which palliative outcomes matter most to patients and their caregivers.

**Guidance statements**

11. In patients with DC, outpatient palliative care may be associated with improved symptoms, improved care coordination, and better anticipatory planning.

12. Inpatient specialty PC consultations with postdischarge follow-up may be associated with greater consensus between patients and clinicians about the goals of care, reduced life-sustaining treatment use, earlier provision of comfort-focused care, and reduced readmission.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Setting and population</th>
<th>Intervention</th>
<th>Comparator arm (study design)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Palliative care domain addressed</th>
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</thead>
<tbody>
<tr>
<td>Baumann et al. 2015[54]</td>
<td>Outpatients being evaluated for LT</td>
<td>One-time nurse practitioner and board-certified PC physician performing comprehensive physical and psychological symptom assessment; ACP</td>
<td>None (pre-/post single-arm quality improvement study)</td>
<td>Physical and psychological symptom burden; ACP</td>
<td>Improved pruritus, fatigue, well-being, appetite; decreased depression; increased ACP</td>
<td>1, 2, 3, 8</td>
</tr>
<tr>
<td>Kimbell et al. 2018[57]</td>
<td>Outpatients with DC</td>
<td>Nurse specialists assisted in care coordination, illness education, financial and psychosocial support, and ACP and provided a summary of this discussion to the patient’s primary care physician and hepatologist</td>
<td>None (single-arm feasibility study)</td>
<td>HRQoL; perceived care coordination, coping, anticipatory planning (qualitative)</td>
<td>Improved HRQoL and secondary outcomes</td>
<td>1, 4, 8</td>
</tr>
<tr>
<td>Lamba et al. 2012[55]</td>
<td>Surgical ICU admission for patients pre-LT and post-LT</td>
<td>Two-part communication-based intervention involving palliative care team (APRN, family support counseling, chaplain): initial physical and psychological symptom assessment with ACP, followed by interdisciplinary family meeting within 72 h</td>
<td>None (prestudy/poststudy design)</td>
<td>Length of stay in ICU, mortality, goals of care consensus (qualitative)</td>
<td>Decreased ICU length of stay, better consensus in goals of care, lower receipt of life-sustaining treatment, and earlier provision of comfort-focused care; no difference in mortality</td>
<td>7, 8</td>
</tr>
<tr>
<td>Shinall et al. 2019[56]</td>
<td>Inpatients with DC</td>
<td>Board-certified PC physician, during which patients were provided with an informational packet containing education on LD and PC</td>
<td>Control group of inpatients with DC receiving usual care (RCT)</td>
<td>Time until first readmission; days alive outside the hospital, referral to hospice care, death, readmissions, patient quality of life, depression, anxiety, and quality of EoLC over 6 months</td>
<td>Increased time to readmission; no change in other outcomes; poor enrollment</td>
<td>1, 3</td>
</tr>
<tr>
<td>Bailey et al. 2017[60]</td>
<td>Outpatient dyads of patients awaiting LT and their caregivers</td>
<td>Six-week telephonic intervention of a self-management intervention (n = 56 dyads) vs. LD education (n = 59 dyads); self-management intervention included coping skills and uncertainty management strategies.</td>
<td>Attention control group of patient-caregiver dyads receiving LD education alone (RCT)</td>
<td>Illness uncertainty, uncertainty management, depression, anxiety, self-efficacy, and quality of life at 10–12 weeks postintervention</td>
<td>No significant differences between groups and in most measures pre- to post-, though there was a numerical improvement in self-efficacy in both patients and caregivers.</td>
<td>3, 4, CG</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting and population</td>
<td>Intervention</td>
<td>Comparator arm (study design)</td>
<td>Outcomes</td>
<td>Results</td>
<td>Palliative care domain addressed</td>
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<td>Bajaj et al. 2017</td>
<td>Outpatients with cirrhosis (n = 20) and depressive symptoms (Beck Depression Inventory &gt;14) and their caregivers</td>
<td>Mindfulness-based stress reduction intervention with four weekly hour-long group sessions and audio-guided home practice</td>
<td>None (pre-/post- single-arm study)</td>
<td>Depressive symptoms, sleep, anxiety, encephalopathy, HRQoL, perceived caregiver burden, and caregiver depression, sleep quality</td>
<td>Significant reduction in depressive symptoms, improvement in sleep and overall HRQoL but not in anxiety or encephalopathy rates in patients; improved caregiver burden, depression, sleep quality</td>
<td>2, 3, CG</td>
</tr>
<tr>
<td>Ufere et al. 2021</td>
<td>Transplant-ineligible inpatients and outpatients with advanced LD (n = 50)</td>
<td>Five-minute ACP video decision-support tool depicting three levels of goals of care: life-prolonging care (CPR and intubation); life-limiting care (hospitalization, no CPR/ intubation); and comfort care</td>
<td>Control group listened to verbal narrative of the three levels of goals of care (RCT).</td>
<td>Feasibility; acceptability, knowledge of EoLC options, postintervention goals of care and CPR/intubation preferences</td>
<td>High enrollment rate; video highly acceptable to patients in video arm, who had higher EoLC knowledge scores and were less likely to prefer to receive CPR</td>
<td>1, 7</td>
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Abbreviations: APRN, advanced practice registered nurse; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; PC, palliative care.
EFFECTIVENESS OF PALLIATIVE CARE INTERVENTIONS IN GENERAL POPULATIONS

As cirrhosis-specific data accumulate, trials of palliative care in other similar populations may help to inform care. Over the past decade, several landmark studies have assessed the impact of multicomponent, interdisciplinary palliative care interventions in patients with advanced heart, lung, renal, and hematological diseases across multiple domains of palliative care (Table S1).[13,14] Palliative care interventions have improved physical (e.g., fatigue, pain), psychological (e.g., depression, anxiety, and mood), social, spiritual, EoLC, ACP, caregivers’ quality of life, and cost-effectiveness of care.[63–77] However, evidence for improvement in religious, existential, and cultural aspects of care remains limited.[14] In general, interventions with a comprehensive evaluation by palliative care specialists, including nurses, social workers, or physicians, were associated with improved quality of care and symptom management.

Guidance statements

13. A wide range of studies have demonstrated the effectiveness of palliative care interventions in patients with other chronic illnesses, with benefits including reduced symptom burden, improved mental health, better quality of life, and decreased health care use.

14. Palliative care interventions can positively impact caregivers’ symptoms.

ADVANCE CARE PLANNING (ACP)

ACP is a proactive, ongoing, collaborative process of decision making about health care preferences, goals, and values in the context of a life-limiting illness.[16,17] Decisions around life-sustaining treatments, completing advance directives, and identifying surrogate decision makers are all part of ACP, which is based on continuous assessment and documentation of patients’ personal values, preferences, and caregiver input.[14,17] Written documentation (such as advance directives) can help ensure that these values and preferences are respected across clinical teams and health care settings. ACP interventions are also associated with greater concordance between patient preferences and care delivery, completion of advance directives, and improved end-of-life management.[76] Thus, facilitating ACP is an important component of caring for persons with DC.

Table 3 outlines key ACP definitions, and Figure 2 illustrates key components of ACP, including assessing patients’ capacity and willingness to engage in ACP, identifying surrogate decision makers who should be present for conversations, and eliciting and documenting preferences.[14,17,76] It is critical to document this information early in the trajectory of cirrhosis, before the onset of encephalopathy, for example. It is also notable that a person who is present at an outpatient appointment or at the hospital bedside may not be the person that local surrogacy laws identify as a default surrogate or the person that the patient wants to be making decisions on their behalf.

Ideally, clinicians with a continuity relationship with a patient and an understanding of their prognosis should regularly engage in conversations regarding prognosis and goals of care.[14] Unfortunately, these conversations often do not occur until the end of life for patients with DC.[36,43,48,53,59,80–83] Insufficient and delayed discussions likely contribute to receipt of high-intensity EoLC.[84] Conversely, early palliative care referral has been associated with higher rates of goals-of-care discussions in retrospective cohort studies.[58,59] One pilot trial found that provider education and standardized documentation were associated with a 23% increase in advance directive completion and a 51% increase in goals-of-care conversations.[85] Similarly, specialty palliative care consultation with transplant evaluation led to early identification of surrogate decision-maker and ACP documentation.[54] In a single-site pilot RCT, a 5-min ACP video decision support tool for transplant-ineligible patients with DC significantly improved their knowledge about EoLC, informed their preferences for resuscitation and intubation, and was highly acceptable to patients (Table 2).[86]

**TABLE 3** ACP definitions[14,17,74]

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Advance directive</td>
<td>Legal documents that can guide care when the patient is unable to engage in decision making</td>
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<tr>
<td>Living will</td>
<td>Advance directives that specify the types of medical care acceptable vs. unacceptable to the patient if they cannot communicate at the end of life</td>
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<tr>
<td>Health care proxy (also referred to as durable power of attorney for health care)</td>
<td>Identification and documentation of a health care agent by the patient</td>
</tr>
<tr>
<td>Physician orders for life-sustaining treatment/medical orders for life-sustaining treatment</td>
<td>Orders signed by physicians (or advance practice providers in some states) that document patient preferences around specific treatments (e.g., code status, hospitalization, artificial nutrition/hydration)</td>
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</tbody>
</table>
An expert panel, supported by modified Delphi methods, provided guidance on the timing of ACP in patients with DC.[87] They recommended that advance directives should be completed as early in the course of cirrhosis as possible and preferably before hepatic decompensation and potentially loss of decision-making capacity. Similarly, goals-of-care discussions, with or without the support of specialty palliative care services, should be prioritized when LT is being considered or if death is anticipated within 6 months.[87,88] Resources that can support hepatologists in leading ACP include patient-facing visual aids, communication training, and goals-of-care communication training workshops and webinars (Table S2).[16,89–95]

**Guidance statement**

15. ACP is an iterative process that should start with a diagnosis of cirrhosis and preferably occur before hepatic decompensation and loss of decision-making capacity.

**Structured communication frameworks to support complex conversations around prognosis and goals of care**

Communication skills are a key component of ACP and palliative care. Uncertainty of the illness trajectory in cirrhosis complicates communication about prognosis. Furthermore, care preferences can fluctuate with a patient’s changing clinical status. Clinicians may struggle to effectively communicate the complexity and uncertainty associated with the fluctuating and unpredictable clinical course—indeed, 80% of respondents in a large survey of hepatologists felt that the communication training they had received (in this study, around end-of-life communication) was inadequate.[48] Patients and families struggle to get the information they need or desire, particularly in the setting of critical illness.[84] Several published communication frameworks may be well suited to address the unpredictability associated with cirrhosis (Figure 3).[89–95] Although communication training is associated with improved person-centered outcomes, more work is needed to tailor approaches to training and communication in hepatology settings.[90] The medical team should also ensure that communication occurs in the language preferred by patients and families using a professional medical interpreter, if the preferred language is different than that of the provider.[96]

**Guidance statements**

16. Structured communication frameworks can be used to communicate uncertainty, discuss serious news, and establish a plan of care that is aligned with patient values.

17. Serious illness conversations should occur in the language preferred by the patient and their family. Medical teams should use a professional medical interpreter to facilitate these conversations.

**Psychosocial, spiritual, and cultural aspects of palliative care**

Psychosocial, spiritual, and cultural aspects of care are understudied in all patient populations, despite being important to patients.[44] In general, an interdisciplinary, person-centered approach is recommended.
when addressing these potentially sensitive topics, and it is important to be aware of the local supportive care resources through ongoing conversations with social work, pharmacy, patient navigation, chaplaincy, spiritual care, and pastoral care, where available.\textsuperscript{14} A key component of person-centered palliative care is assessing patient and caregiver psychosocial needs across social determinants of health, including financial stability, employment, food insecurity, housing, transportation, and access for necessary equipment/supplies.\textsuperscript{14} Assessing financial burden is also important for patients with DC, who often report high rates of cost-related nonadherence to medications and food insecurity.\textsuperscript{31,97,98} The question “Are you having difficulty paying for your medical care?” is an effective early screen for financial burden and engaging social work and pharmacy services to help support patients and their families in mitigating financial stress.\textsuperscript{31,97,98} Cirrhosis carries a significant financial burden for patients and families. Patients with DC require a high number of informal caregiving hours each week compared with persons with other illnesses, which can lead to difficulty maintaining employment for family caregivers.\textsuperscript{31} Patients differ in their beliefs and approaches to  

A key component of person-centered palliative care is assessing patient and caregiver psychosocial needs across social determinants of health, including financial stability, employment, food insecurity, housing, transportation, and access for necessary equipment/supplies.\textsuperscript{14} Assessing financial burden is also important for patients with DC, who often report high rates of cost-related nonadherence to medications and food insecurity.\textsuperscript{31,97,98} The question “Are you having difficulty paying for your medical care?” is an effective early screen for financial burden and engaging social work and pharmacy services to help support patients and their families in mitigating financial stress.\textsuperscript{31,97,98} Cirrhosis carries a significant financial burden for patients and families. Patients with DC require a high number of informal caregiving hours each week compared with persons with other illnesses, which can lead to difficulty maintaining employment for family caregivers.\textsuperscript{31}

Patients differ in their beliefs and approaches to palliative care, and death and dying related to their spiritual and cultural frames of reference.\textsuperscript{20} The limited relevant spirituality research in cirrhosis includes two qualitative studies that identified spirituality as a key determinant of HRQoL and perceptions of medical care.\textsuperscript{99,100} General palliative care guidelines recommend routinely evaluating the spiritual and cultural needs of patients and their families through
Symptom management is a core component of caring for patients with DC, who suffer from several, often inter-related, symptoms. Based on a recent systematic review, the most frequently reported symptoms are pain (prevalence range, 30%–79%), breathlessness (20%–88%), muscle cramps (56%–68%), sleep disturbance (insomnia, 26%–77%; daytime sleepiness, 29.5%–71.0%), psychological symptoms (depression, 4.5%–64.0%; anxiety, 14%–45%), and sexual dysfunction (53%–93%). Because often not all symptoms can be addressed in a single clinical encounter, it is important to develop an approach to track and prioritize symptoms. Although a full review of patient-reported outcomes and measurement tools is out of scope for this Guidance, the approach to addressing symptoms may include unstructured to structured questions asking about generic or disease-specific symptoms. Several such instruments have been used in palliative care, including the Functional Assessment of Chronic Illness Therapy-Palliative Care and the Edmonton Symptom Assessment scales.

Clinicians should assess symptom severity, exacerbating and relieving factors, and the functional impact of symptom(s) to the patient. Symptoms are experienced through the cognitive and emotional lens of the patient and must be evaluated in the context of the whole patient. Therefore, symptom ratings should be interpreted relative to past ratings from the same person over time. Because clinicians may be unfamiliar with the management of certain symptoms, particularly at the end of life, a team approach and early referrals to specialty palliative care, social work, and other services are important in providing comprehensive palliative care to patients and caregivers.

In the following section, we discuss the most common patient-reported symptoms and their management. Nonpharmacological approaches, such as physical therapy and cognitive behavioral therapy, should be tried when possible, given that these can address multiple symptoms with minimal risk. Pharmacotherapeutics can be challenging in patients with cirrhosis, so a conservative, “start low, go slow” approach is generally recommended. Table 4 highlights common side effects of common classes and types of medications used for palliative care of patients with cirrhosis.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Side effects, cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nociceptive pain</strong></td>
<td></td>
</tr>
<tr>
<td>acetaminophen</td>
<td>Generally safe at low dose (2 gram daily maximum), can cause hepatic failure at high dose</td>
</tr>
<tr>
<td>Topical NSAIDs</td>
<td>Not tested in patients with cirrhosis (note that systemic NSAIDs are generally avoided in patients with cirrhosis)</td>
</tr>
<tr>
<td>Lidocaine patch</td>
<td>Site reactions (erythema), petechia, edema, pruritus, nausea, vomiting</td>
</tr>
<tr>
<td>Capsaicin cream</td>
<td>Site reactions (burning, pain, erythema), limb pain, hypertension</td>
</tr>
<tr>
<td>Opioids</td>
<td>HE, habit forming, respiratory depression, constipation/obstipation, overdose; preferred are oxycodone and hydromorphone</td>
</tr>
<tr>
<td><strong>Neuropathic pain</strong></td>
<td></td>
</tr>
<tr>
<td>Gabapentinoids</td>
<td>Ataxia, sedation, myoclonus/asterix, dose adjust in renal impairment, withdrawal syndrome, possible increased viral infections</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Discontinuation syndrome, nausea, vomiting, sexual dysfunction</td>
</tr>
<tr>
<td>Tricyclic antidepressant medications</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle cramps</strong></td>
<td></td>
</tr>
<tr>
<td>Baclofen</td>
<td>HE, confusion, dizziness, sedation, nausea, vomiting, rare neurotoxicity in patients with renal failure, discontinuation syndrome</td>
</tr>
<tr>
<td>Zinc</td>
<td>Gastric irritation, rare neurological side effects</td>
</tr>
<tr>
<td>Methocarbamol</td>
<td>Hypotension, bradycardia, dyspepsia, pruritis, confusion, ataxia, HE, headache, sedation, changes in taste, seizure, vertigo, leukopenia, jaundice, changes in vision (dose reduced in cirrhosis)</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Palpitations, tachycardia, confusion, sedation, pruritis, constipation, nausea, vomiting, tremor, urinary retention, blurred vision, central nervous system depression</td>
</tr>
<tr>
<td>L-carnitine</td>
<td>Side effects common with intravenous formulation; oral formulation generally tolerated well at normal doses</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Nausea, diarrhea</td>
</tr>
<tr>
<td>Taurine</td>
<td>Nausea, dizziness, headache</td>
</tr>
<tr>
<td>BCAAs</td>
<td>Possible nausea</td>
</tr>
<tr>
<td><strong>Depression/anxiety</strong></td>
<td></td>
</tr>
<tr>
<td>SNRIs</td>
<td>Discontinuation syndrome, nausea, vomiting, sexual dysfunction, rare hepatitis</td>
</tr>
<tr>
<td>SSRIs</td>
<td>QTc prolongation and seizure risk with citalopram, sedation with mirtazapine, nausea, vomiting, weight gain, sexual dysfunction, insomnia, bleeding risk</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Physical dependence, sedation, HE, only for short-term use at the end of life in cirrhosis</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>HE, habit forming, respiratory depression, constipation/obstipation</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Physical dependence, sedation, HE, only for short-term use at the end of life in cirrhosis</td>
</tr>
<tr>
<td>HEa</td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>Gastric irritation, rare neurological side effects</td>
</tr>
<tr>
<td>L-carnitine</td>
<td>Side effects common with i.v. formulation; p.o generally tolerated well at normal doses</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>Headache, fragmented sleep, confusion</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Headache, drowsiness, dizziness, palpitations, anxiety, disorientation, hallucination, use with caution and only in low doses for short time periods in patients with cirrhosis, particularly in the presence of HE</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td></td>
</tr>
<tr>
<td>Modafinil</td>
<td>Headache, abdominal pain, decreased appetite, chest pain, tachycardia, anxiety, insomnia, confusion, diarrhea, exacerbation of psychiatric symptoms, dose reduction is generally recommended; evidence is poor</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Not studied in cirrhosis, insomnia, headache, irritability, weight loss, anorexia, xerostomia, nausea, tachycardia, hypertension, emotional lability, dizziness, depression, anxiety, nausea, vomiting, diarrhea, abdominal pain, possible increased infection risk; evidence is poor</td>
</tr>
</tbody>
</table>
The etiology of pain in persons with cirrhosis can be divided into liver-associated mechanical pain, inflammatory pain, and non-liver-associated pain. Cirrhosis can directly lead to somatic or nociceptive pain through splenomegaly, ascites, and hepatic capsular stretch or indirectly because of elevation of proinflammatory cytokines. Nonhepatic etiologies of pain can range widely, but the most common are neuropathic (e.g., diabetic neuropathy) and musculoskeletal (e.g., osteoarthritis).

Table 5 summarizes the general approach to chronic pain management for patients with cirrhosis, which can be divided into pharmacological and nonpharmacological approaches. The first step in addressing pain is to assess and treat reversible causes (e.g., tense ascites, local infection, and musculoskeletal injury). The chronicity of pain also determines the approach. For example, acute pain (≤12 weeks) is more responsive to short-term opioid therapy than chronic pain. Optimal chronic pain management often involves multimodal, nonpharmacological approaches, including behavioral management, physical therapy, and procedural approaches. As such, more-complex, chronic pain (e.g., pain refractory to conservative management, of unclear etiology, or with associated symptoms) may require consultation with palliative care specialists or experts in procedural pain management.

Behavioral approaches to pain management have not been specifically evaluated in patients with cirrhosis, but pain self-management programs, cognitive behavioral therapy, and physical and occupational therapy are safe and efficacious in other populations for the management of chronic pain. Procedural approaches have been largely untested in cirrhosis, but acupuncture is efficacious for chronic musculoskeletal pain and headache in general populations. Although there are no direct data about the safety of acupuncture in patients with cirrhosis, observational studies of drug-related thrombocytopenia indicate that acupuncture is likely safe in patients with platelets >50,000/ml, and a recent review evaluated the potential benefits of acupuncture for cirrhosis more generally. Similarly, injections can be used for limited indications, such as knee osteoarthritis, though physical therapy remains first line.

Because of impaired hepatic metabolism and the risk of precipitating encephalopathy, lower doses and less systemic therapies are generally preferred for pharmacological management of chronic pain in patients with cirrhosis. Local pharmacotherapies are generally first line for localized pain. These can include injections, as discussed previously, or topical creams or patches. Although there are no data supporting the use of topical analgesics in patients with cirrhosis, they are generally considered safe and have demonstrated efficacy in other populations. Lidocaine patches are applied directly to a site of discomfort, and topical creams for localized neuropathic (e.g., capsaicin) and musculoskeletal pain (e.g., topical nonsteroidal anti-inflammatory drugs [NSAIDs]) are effective and have limited systemic absorption, rendering them likely safe (though untested) in persons with cirrhosis.

Acetaminophen (APAP) up to 2 g daily (typically prescribed as 500 mg, every 6 hours, as needed) is
The management of pain is complex and requires treatment of other contributing symptoms (e.g., sleep disorders, depression). Multidisciplinary approaches are often beneficial.

Nonpharmacological options
- Hot/cold
- Physical therapy
- Mindfulness/meditation
- Other behavioral pain self-management strategies (e.g., cognitive behavioral therapy)
- Acupuncture (caution if platelets <50,000)
- Other complementary options based on preferences (e.g., transcutaneous nerve stimulation)

Pharmacological options
- Topical/injection treatments
  - Lidocaine patches
  - Capsaicin cream or patch
  - Topical nonsteroidal anti-inflammatory medications (e.g., diclofenac sodium 1% gel)
  - Injections by pain specialists (e.g., osteoarthritis of knee)
- Systemic therapies
  - APAP 500 mg q6h for a maximum of 2 g/d is safe in most patients with.
  - Gabapentin 300 mg daily (starting dose) or pregabalin 50 mg b.i.d. (starting dose) for neuropathic pain
  - Fentanyl patch 12-µg starting dose (typically not recommended as the initial agent; avoid in patients with sarcopenia/cachexia or fever)
  - Hydromorphone 1-mg q6h prn starting dose
  - Oxycodone 2.5-mg p.o q6-8h prn starting dose

Note: Once the goals of care are focused on comfort, opioid medications should be titrated up to meet the patient’s needs without concerns for long-term impacts.

Abbreviations: b.i.d., twice a day; d, day; h, hour; q, every; g, grams; prn, as needed.

*Renal dosing adjustments needed; cannot be stopped without tapering; can cause nausea, sedation, and ataxia.

TABLE 5 Palliative management of pain for patients with DC

<table>
<thead>
<tr>
<th>Pharmacological options</th>
<th>Nonpharmacological options</th>
</tr>
</thead>
<tbody>
<tr>
<td>APAP, which counts toward the daily limit.</td>
<td>Hot/cold</td>
</tr>
<tr>
<td>Gabapentin 300 mg daily (starting dose) or pregabalin 50 mg b.i.d. (starting dose) for neuropathic pain</td>
<td>Physical therapy</td>
</tr>
<tr>
<td>Fentanyl patch 12-µg starting dose (typically not recommended as the initial agent; avoid in patients with sarcopenia/cachexia or fever)</td>
<td>Mindfulness/meditation</td>
</tr>
<tr>
<td>Hydromorphone 1-mg q6h prn starting dose</td>
<td>Other behavioral pain self-management strategies (e.g., cognitive behavioral therapy)</td>
</tr>
<tr>
<td>Oxycodone 2.5-mg p.o q6-8h prn starting dose</td>
<td>Acupuncture (caution if platelets &lt;50,000)</td>
</tr>
</tbody>
</table>

Although much has been written regarding analgesic side effects in cirrhosis, a more nuanced approach to analgesia may be warranted, particularly when comfort is prioritized over disease-directed care. Although opioids are associated with increased pain-related disability, encephalopathy, ascites, post-transplant mortality, and readmission in patients with cirrhosis, patients at the end of life may accept these risks and prioritize short-term analgesia over cognition. That said, chronic opioid medications are not effective for the management of chronic pain, and patients with LD are among the group with the highest risk of opioid-related adverse events.

When opioids are required, there are several notable safety considerations. First, prophylactic medications should be considered proactively to prevent constipation and encephalopathy (e.g., lactulose). Opioids have unique pharmacodynamics, such that codeine, morphine, and tramadol should generally be avoided in patients with cirrhosis. Tramadol is often inappropriately selected for first-line use in patients with cirrhosis because of the perception that it is not an opioid. However, tramadol is an opioid that requires first-pass hepatic metabolism, has variable pharmacokinetics across persons with cirrhosis, is challenging to titrate, and has notably unpredictable side effects, including hypoglycemia. Although i.v. fentanyl is a preferred opioid analgesic in persons with cirrhosis because of its favorable metabolism profile, outpatient use is limited by its delivery in this population. The patch comes in set doses with the lowest outpatient dose of a 12-µg/h patch, which may be too high for patients with cirrhosis. Furthermore, cachexia is a relative contraindication to transdermal fentanyl, rendering it impractical to use in many patients with cirrhosis. Because of a long and variable half-life and multiple drug interactions, methadone should only be used in consultation with a specialist. First-line opioids for patients with cirrhosis generally include low-dose hydromorphone (e.g., 1 mg p.o or 0.4 mg i.v.) or oxycodone (e.g., 2.5 mg p.o.) with extended dosing intervals.

Prescribing clinicians should adhere to best practices for risk assessment, setting patient expectations, and monitoring when starting opioids. For example, first-line treatment should be a 7-day supply of low-dose, short-acting opioids. Patients require close follow-up, and risk factors for adverse opioid-related events should be assessed (e.g., past opioid use disorder, concurrent benzodiazepine use, or other opioid prescriptions in the prescription drug monitoring program data). Conversations with patients and caregivers should include information about risks and benefits and setting of expectations (e.g., taking medications as prescribed, proper disposal).

Other analgesics have potential benefits as low-dose adjuvants, but have notable risks in persons generally safe and should be the first-line systemic pharmacological therapy for pain in this population. However, patients should be informed that other over-the-counter and prescription formulations may include APAP, which counts toward the daily limit. NSAIDs are among the most commonly inappropriately used medications in patients with cirrhosis. Multiple studies demonstrate the deleterious impact of NSAIDs in patients with cirrhosis attributable to risk of renal injury, bleeding, and ascites. One trial of 23 patients with cirrhosis demonstrated that receiving five doses of 500 mg of naproxen (vs. placebo or celecoxib) was associated with significantly worsened renal function, suppression of furosemide responsiveness, and inhibition of platelet aggregation and thromboxane production. Thus, systemic NSAIDs should be avoided in patients with cirrhosis.
with cirrhosis. Gabapentinoids are effective in treating neuropathic pain, though they are increasingly recognized as potentially habit forming and are associated with somnolence and mental status changes. For patients with cirrhosis, very low starting doses of gabapentin (e.g., ≤300 mg/d) are recommended. Serotonin-norepinephrine reuptake inhibitors (SNRIs) can provide good adjuvant pain medication at low doses, though there is a low risk of hepatotoxicity. Although tricyclic antidepressants are often used as adjuvant analgesia, their anticholinergic effects and associated mental status impairments generally preclude their use in patients with cirrhosis.

Medical cannabinoids, which have notable central nervous system and gastrointestinal side effects, are U.S. Food and Drug Administration (FDA) approved for the treatment of nausea, vomiting, and anorexia. Cannabis (marijuana), which is often used for pain management, is not FDA approved for any indication at this time. Although early data suggest that cannabinoids may be effective as short-term adjuvant treatment for chronic neuropathic pain, there is not strong enough evidence to recommend cannabis for the treatment of chronic noncancer pain, particularly in patients with DC. Existing studies of cannabinoids for analgesia have excluded patients with comorbid illnesses (e.g., cirrhosis) or a history of substance use disorders and have not included optimal outcome measures. Thus, significantly more data are needed before recommending cannabinoid/cannabis as an analgesic for patients with DC.

Guidance statements

27. Multimodal pain management approaches are ideal and include a person-centered holistic, multidisciplinary approach, engaging a combination of expertise from across a number of specialties (e.g., palliative care, psychiatry, pain management, pharmacy, physical and occupational therapy, or social work).

28. Pain in patients with DC requires a systematic approach that starts with assessing and treating reversible causes of pain (e.g., ascites, local infection, or musculoskeletal injury).

29. Localized pain (e.g., knee osteoarthritis) should first be addressed with local, rather than systemic, therapies.

30. Acetaminophen, 500 mg every 6 h, up to a maximum dose of 2 g/d, is the preferred first-line pharmacotherapy for the management of pain in patients with cirrhosis.

31. Systemic NSAIDs should be avoided in patients with cirrhosis.

32. We recommend avoiding opioids, when possible, for chronic pain. However, when necessary, opioid use should be approached with caution and with careful discussion with patients and caregivers. Low-dose oxycodone or hydromorphone can be started in select cases on an as-needed basis and titrated to effect, often in consultation with pain management experts.

ABDOMINAL DISTENSION ATTRIBUTABLE TO REFRACTORY ASCITES

Ascites, the most common complication of cirrhosis, results from renal sodium retention, and specific recommendations in this population, including a large volume paracentesis (LVP), are covered in the relevant AASLD Practice Guidance. LVP requires multiple visits to the hospital and can be burdensome, especially toward the end of life. TIPS is an option, but many patients with refractory ascites are not candidates for the placement of TIPS because of encephalopathy, cardiac contraindications, or high MELD scores. Recent studies have evaluated the feasibility and safety of longer-term abdominal drains and automated low-flow ascites pumps in patients with refractory ascites. Indwelling peritoneal drains or catheters have been evaluated for the palliative management of refractory ascites. A recent review of 18 studies including 176 patients summarized the evidence for long-term ascites drains. Most catheters were placed for palliation in patients who were not candidates for LT. Patients’ MELD scores ranged from 10 to 22 in these studies, and most patients received prophylactic antibiotics either at the time of insertion or during follow-up. In these studies, technical success was 100% and rates of noninfectious complications were generally low (<12%). Spontaneous bacterial peritonitis (SBP) occurred in 0%–42% of patients across studies, with an overall combined rate of 17%. Most episodes of SBP were treated with antibiotics with the catheter left in situ. Other complications included cellulitis at the catheter insertion site (6%), transient hyponatremia (11%), and increased serum creatinine (8%). A 12-week, small feasibility, nonblinded RCT compared LVP to long-term abdominal drains in 36 transplant-eligible patients with refractory ascites. Outpatient drain insertion was performed using ultrasound guidance, and participants were maintained on chronic antibiotics. There were no drain-related serious adverse events or drain removals attributable to complications. Patients in the LVP group had more than double the ascites-related hospital time than the drain group. Self-limiting cellulitis/leakage occurred in 41% in the drain group versus 11% in the LVP group; peritonitis incidence was 6% versus 11%, respectively. Overall attrition was high (42%), mostly attributable to death (7 of 16 in the abdominal drain group and 5 of 18 in the LVP group). At the end of the study, all surviving drain participants elected to retain the drains
and reported benefits, including improved symptom control and increased time at home, whereas the LVP group reported frequent trips to the hospital with lengthy wait times and a complex care path. However, these differences were not borne out in quality-of-life measures in this small study. The study demonstrated feasibility, but was not powered to assess clinical or patient-reported outcomes. Thus, although drains can be considered in TIPS-ineligible patients with comfort-focused goals, more study is still required. Automated low-flow ascites pumps (alfapumps), which are not yet available in the USA or Canada, use a s.c.-implanted, battery-powered pump to divert ascites into the bladder for urinary elimination. A recent systematic review of nine studies included 206 patients treated with this device. After pump insertion, 48% of patients continued to require LVP, and adverse events occurred in >75% of patients. Acute kidney injury (AKI), urinary tract infection, and SBP occurred in 30%, 20%, and 27% of patients, respectively. An RCT comparing LVP to low-flow pumps found that abdominal symptoms and activity scores improved significantly only in the low-flow pump group. However, there were also significantly increased risks of adverse events (96.3% vs. 77.4%) and serious adverse events (85.2% vs. 45.2%) in the pump group. Another study of low-flow pumps in 30 TIPS-ineligible patients identified improvements in HRQoL and nutritional status with no AKI episodes in the first week postinsertion. However, in this study, patients were maintained on prophylactic antibiotics and had relatively preserved hepatic function (average MELD = 11). Finally, a case series of 21 patients who received low-flow pumps reported that 71% of patients had pump complications and only 3 patients (14%) remained enrolled at a median of 153 days because of attrition from death. Thus, there are insufficient data to recommend the use of low-flow ascites pumps in patients with DC at the end of life.

**Guidance statements**

33. Abdominal drains may be an alternative to serial LVP for patients with refractory ascites who are transplant and TIPS ineligible and whose goals are comfort focused. However, more comparative effectiveness research is needed before recommending this approach.

**Dyspnea**

Dyspnea, or the subjective experience of breathlessness, is experienced by 47%–88% of persons with cirrhosis and can be attributed to multiple causes, including ascites, volume overload, hepatopulmonary syndrome, portopulmonary syndrome, and infection. Patients close to the end of life may experience dyspnea associated with diuretic-refractory fluid

### TABLE 6

**Summary of therapies for palliative management of dyspnea, muscle cramps, pruritus, and nausea**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Nonpharmacotherapies</th>
<th>Pharmacotherapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyspnea</strong></td>
<td>• Manage reversible causes (e.g., volume overload, asthma, sleep apnea)</td>
<td>• Opioids can be used cautiously in select cases, typically at the end of life (example: starting dose i.v. hydromorphone 0.2 mg every 3 h as needed, titrated to symptom relief)</td>
</tr>
<tr>
<td></td>
<td>• Bedside fans</td>
<td>• Anxiolytics can be considered for dyspnea-associated anxiety (typically at the end of life when focus of care is comfort)</td>
</tr>
<tr>
<td></td>
<td>• Supplemental oxygen therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mindfulness, meditation, guided imagery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Paracentesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Thoracentesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Placement of drains (usually in the setting of hospice care)</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle cramps</strong></td>
<td>• Correct electrolytes</td>
<td>• Taurine (2–3 g daily)</td>
</tr>
<tr>
<td></td>
<td>• Moisturizing creams</td>
<td>• Vitamin E (300 mg three times a day)</td>
</tr>
<tr>
<td></td>
<td>• Avoid hot baths and harsh soaps and detergents</td>
<td>• Baclofen (5–10 mg three times a day)</td>
</tr>
<tr>
<td></td>
<td>• Use loose-fitting clothing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cool humidified air</td>
<td></td>
</tr>
<tr>
<td><strong>Pruritis</strong></td>
<td>• Correct electrolytes</td>
<td>• Cholestyramine (4 g/d, titrated to 16 g/d if needed)</td>
</tr>
<tr>
<td></td>
<td>• Evaluate and treat adrenal insufficiency</td>
<td>• Sertraline (25 mg/d, titrated to 75–100 mg if needed)</td>
</tr>
<tr>
<td></td>
<td>• Manage constipation</td>
<td>• Rif and naltrexone may improve pruritus, but their use is limited in palliative treatment of patients with DC.</td>
</tr>
<tr>
<td></td>
<td>• Review medications and eliminate potential triggers (e.g., lactulose, opioids)</td>
<td>• Antihistamines (e.g., diphenhydramine and hydroxyzine) may help with pruritis-associated sleep disturbance given their sedating properties</td>
</tr>
<tr>
<td></td>
<td>• Ginger</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mindfulness, relaxation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Acupuncture (use caution if platelets &lt;50,000)</td>
<td></td>
</tr>
<tr>
<td><strong>Nausea and vomiting</strong></td>
<td>• Correct electrolytes</td>
<td>• Antacids (if contributing reflux)</td>
</tr>
<tr>
<td></td>
<td>• Evaluate and treat adrenal insufficiency</td>
<td>• Ondansetron, up to 8 mg/d is preferred</td>
</tr>
<tr>
<td></td>
<td>• Manage constipation</td>
<td>• Metoclopramide up to 60 mg/d (very preliminary safety data; potential adverse reactions)</td>
</tr>
<tr>
<td></td>
<td>• Review medications and eliminate potential triggers (e.g., lactulose, opioids)</td>
<td>• May consider alternatives (e.g., prochlorperazine, haloperidol) depending on goals of care</td>
</tr>
<tr>
<td></td>
<td>• Ginger</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mindfulness, relaxation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Acupuncture (use caution if platelets &lt;50,000)</td>
<td></td>
</tr>
</tbody>
</table>
accumulation, worsening acidosis, progressive renal failure, and anxiety.\cite{166–169} Dyspnea can be both distressing and debilitating and thus requires a multidisciplinary management approach.\cite{170} Patients experience dyspnea as difficulty with air movement, effort, rapidity, or overall distress, but clinicians may need to use surrogate markers, such as hypoxia, tachypnea, and use of accessory respiratory muscles, in patients who are unable to report their symptoms.\cite{171}

Within palliative care literature, the focus of dyspnea management centers around pulmonary, cardiac, and malignant conditions; in contrast, there is a lack of direct evidence in patients with cirrhosis.\cite{172} General principles suggest that dyspnea should be approached by first assessing and addressing underlying causes, balanced with patient preferences about their care. For example, some patients with a shorter prognosis may nonetheless prefer more-intensive therapies whereas others may prefer to avoid hospitalizations, where possible, and focus on comfort. Disease-directed therapies may be used as appropriate, including diuretics, bronchodilators, phosphodiesterase inhibitors, and steroids.\cite{172,173} Procedural interventions may include paracentesis, thoracentesis, and TIPS.\cite{173,174} Indwelling abdominal drains may be used in some cases to address volume-related dyspnea when goals are comfort focused (see the section above, Abdominal Distension Attributable to Refractory Ascites).\cite{159,160}

Given the general principle of minimizing sedating medications in patients with cirrhosis, the approach to the palliative management of dyspnea (Table 6) begins with nonpharmacological treatments, such as supplemental oxygen (even in the absence of hypoxia) or a bedside fan.\cite{175,176} In the USA, patients must meet specific clinical criteria to have insurance coverage for home oxygen; however, those on hospice have more liberalized coverage of oxygen in the home. Self-care interventions like relaxation, meditation, and guided imagery may decrease dyspnea and result in better symptom-related quality of life.\cite{177}

The mainstays of pharmacological management of dyspnea at the end of life are low-dose opioids and benzodiazepines.\cite{178,179} Given the risk of potentiating encephalopathy, opioids or benzodiazepines should be used with caution, with careful discussion of risks and benefits.\cite{111} Because morphine, which is often used for breathlessness, is relatively contraindicated for patients with advanced cirrhosis, clinicians should first consider hydromorphone or oxycodone, as detailed in the Pain section above.\cite{120,129}

### Guidance statements

34. Patients should routinely be assessed for the presence of dyspnea. The impact of dyspnea on patient quality of life and function as well as on caregivers should be evaluated.

35. Nonpharmacological therapies should be used to manage dyspnea when possible and include the use of a fan, supplemental oxygen (even for nonhypoxic patients), and mindfulness exercises.

36. Pharmacological interventions for dyspnea may include opioids and anxiolytics, which may be used with careful consideration of risks, patient goals, and prognosis.

### HE

HE is a common symptom in patients with cirrhosis, with neuropsychiatric manifestations including disturbances in sleep, mood, wakefulness, and cognition.\cite{7} Patients with encephalopathy and their caregivers face profound psychological, physical, and financial burdens. Because the medical management of encephalopathy is covered in detail in AASLD guidelines, we limit this discussion to the unique palliative aspects of encephalopathy management.\cite{7}

Studies have found that patients with HE and their caregivers experience burdens that can be alleviated by education about medication administration, dose titration, and the waxing and waning course of encephalopathy.\cite{25,180} The development of encephalopathy may be an opportunity for hepatology clinicians to evaluate the needs of a patient/caregiver as a unit and augment supportive care services with consideration of referral to social work, additional care coordination, or home health support. The cognitive impairment associated with encephalopathy underscores the importance of ensuring that a surrogate decision maker is identified and documented before the onset of encephalopathy, as discussed under ACP.

Although rifaximin (RIF) and lactulose are standard for encephalopathy management, as persons approach the end of life, patient preferences and acceptability of treatment side effects may change. For example, lactulose is associated with bloating, abdominal pain, and diarrhea, and some patients or caregivers may prefer using polyethylene glycol to prevent constipation or discontinuing treatment to avoid incontinence at the end of life. Because RIF may not be available in some hospice settings because of its high cost and the capped payment model of hospice, off-label neomycin or metronidazole may be considered as an alternative to RIF.\cite{7} Also, zinc repletion, branched-chain amino acids (BCAAs), probiotics, and, possibly, carnitine can be offered as adjuvant therapies.\cite{7,181–183}

### Guidance statements

37. Evaluating reversible causes and addressing HE can benefit both patient and caregiver quality of life.
Muscle cramps

Muscle cramps are common in cirrhosis and negatively impact HRQoL. Although the precise etiology of muscle cramps is unclear, alterations in nerve function, energy metabolism, plasma volume, and electrolytes may contribute. Muscle cramping associated with cirrhosis is often spontaneous, intermittent, and nocturnal. In patients with new onset of persistent pain, other disorders, such as rhabdomyolysis, myositis, or kidney injury, should be considered. Although there are mixed data regarding associations between hypokalemia, hypomagnesemia, and zinc deficiency with muscle cramps, correcting such deficiencies is recommended, given the low risk of repleting electrolytes.

BCAAs (one sachet three times a day), taurine (2–3 g daily), and vitamin E (200 mg three times a day) have been evaluated in patients with cirrhosis. A multicenter RCT of daytime versus nocturnal BCAA supplementation in 37 patients with cirrhosis found that there was a significant decrease in cramping in both groups without adverse effects of treatment, though this agent is not yet widely used in practice. Several small, open-label studies have evaluated taurine as a treatment for muscle cramps in cirrhosis, with resolution of cramps in 30%–40% of patients over 4 weeks. These findings were confirmed in a small RCT, in which patients treated with 2 g of taurine daily experienced a reduction in cramp frequency, duration, and severity compared with placebo. Vitamin E has had mixed effectiveness in treating cramps in small studies of patients with cirrhosis. Although a small, open-label study found significant improvement in cramping with vitamin E at 200 mg three times a day used over 4 weeks, a subsequent pilot randomized, crossover study of 9 patients with cirrhosis found no significant improvement over placebo. In the absence of larger efficacy trials, these agents can be considered, given their favorable safety profiles (Table 6).

Guidance statements

40. Checking serum electrolyte levels and repleting potassium, magnesium, and zinc is a first step in the management of muscle cramps in patients with DC.

41. Taurine (2–3 g daily), vitamin E (200 mg three times a day), and baclofen (5–10 mg three times a day) have preliminary supportive data and can be considered in patients with cirrhosis and significant muscle cramps.

Sleep disturbances

Sleep disturbances, which include insomnia (poor sleep quality), excessive daytime sleepiness, and sleep-wake inversion, affect 50%–80% of patients with cirrhosis. Although encephalopathy is associated with sleep-wake inversion and daytime sleepiness, up to half of patients with cirrhosis without encephalopathy experience sleep disturbances, associated with melatonin metabolism changes, immune mechanisms, and impaired thermoregulation, which may disturb circadian rhythms. Patients with cirrhosis also have a higher prevalence of sleep-related movement disorders, such as restless leg syndrome, compared with the general population. Complications of LD, such as ascites and edema, and disease-specific symptoms (e.g., pruritus in primary biliary cholangitis, obstructive sleep apnea in patients with metabolic-associated fatty liver disease) may also contribute. Sleep disturbances are associated with significantly decreased frequency and duration of cramps in 100 patients with hepatitis C–related cirrhosis, who experienced minor side effects of dry mouth and drowsiness. Orphenadrine improved muscle spasms in patients with cirrhosis after 4 weeks of treatment. However, the long-term effectiveness of these agents requires further evaluation.

Small studies have demonstrated preliminary effectiveness for albumin infusion, L-carnitine, and zinc in managing muscle cramps. Intravenous albumin (100 ml of 25% albumin) used once-weekly for 4 weeks significantly decreased cramp frequency and improved mean arterial pressure in patients with cirrhosis in a small crossover study, though this is a less-feasible solution for most patients. L-carnitine at the dose of 300 mg, three to four times a day for 8 weeks, was associated with improvement in symptoms in a recent study. Although zinc levels are lower in patients with cirrhosis versus healthy controls, zinc level is not directly correlated with muscle cramps in this population. However, oral zinc sulfate 220 mg twice-daily for 12 weeks significantly decreased cramp frequency. Recommendations for the management of muscle cramps are summarized in Table 6.

38. Onset of encephalopathy can be an opportunity to provide education, elicit preferences, and discuss the overall trajectory of LD with a focus on ACP.

39. Approaches to the treatment of encephalopathy may depart from standard care at the end of life to align with patient goals and values.
with fatigue, depression, anxiety, and poor quality of life in patients with cirrhosis.\textsuperscript{[201,203,204]}

The evaluation of sleep disturbances in cirrhosis should include an assessment of sleep-wake timing, nighttime sleep quality, and daytime sleepiness.\textsuperscript{[204]} Clinicians should perform a thorough assessment of the timing of physical activity, meals, and medications to promote good sleep hygiene; for example, late administration of diuretics and lactulose during the evening hours may lead to nocturnal awakenings and contribute to poor sleep.\textsuperscript{[204]} Encephalopathy, sleep apnea, restless leg syndrome, and pruritus should be treated, if present, because these conditions can impair sleep.\textsuperscript{[204,211,212]}

There are several potential treatments for patients with cirrhosis who suffer from sleep disorders (Table 6). Evidence-based behavioral treatments for primary sleep disorders in general populations include cognitive behavioral therapy for insomnia, which has little downside.\textsuperscript{[213]} In patients with cirrhosis, a 4-week trial of mindfulness-based stress reduction led to significantly improved sleep quality.\textsuperscript{[61]} Light therapy has also been evaluated. Among 12 inpatients with cirrhosis and significantly impaired sleep, light therapy did not impact sleep quality; however, because light therapy is low risk and helpful in other populations, some researchers still favor a trial of light therapy in outpatients with cirrhosis.\textsuperscript{[202,214,215]}

There are few pharmacological options for sleep disturbance in patients with cirrhosis, especially those with DC, beyond agents that treat contributing encephalopathy. Melatonin 3 mg nightly for 2 weeks and zolpidem 5 mg nightly for 4 weeks have each been tested in randomized trials of patients with Child-Pugh A and B cirrhosis and found to be effective for improving sleep quality, but these medications have not been trialed in more-advanced disease or for longer duration.\textsuperscript{[216,217]} Despite these preliminary data, zolpidem should generally be avoided in patients with DC, because of impaired hepatic clearance, minimal data, and potentiation of encephalopathy.\textsuperscript{[111]} Hydroxyzine 25 mg at bedtime was tested (vs. placebo) in a trial of 35 patients with cirrhosis and minimal encephalopathy, with significantly improved subjective and objective sleep measures in the hydroxyzine group.\textsuperscript{[218]} Benzodiazepines should generally not be used for sleep in this population given the risk for sedation, respiratory depression, cognitive impairment, and falls.\textsuperscript{[139,219]} However, there are potential, limited indications for benzodiazepines in this population at the end of life, as discussed in the Dyspnea section above.

### Guidance statements

42. Clinicians should first evaluate and treat underlying causes for insomnia such as HE, pruritus, obstructive sleep apnea, and restless leg syndrome.

43. Clinicians should perform a thorough assessment of the timing of physical activity, meals, and medications to promote good sleep hygiene.

44. Mindfulness-based stress reduction therapy and cognitive behavioral therapy approaches can be considered in patients with cirrhosis and disturbed sleep.

45. Short-term use of melatonin 3 mg or hydroxyzine 25 mg nightly can improve sleep quality in patients with Child-Pugh A and B cirrhosis, but data on long-term use of these medications are limited.

46. Although chronic use of benzodiazepines should be generally avoided in patients with DC, specific clinical circumstances may warrant their use, such as anxiety at the end of life when comfort is the stated priority.

### Fatigue

Fatigue is among the most frequent, debilitating, and distressing symptoms in patients with cirrhosis, with a prevalence of 50%–86%.\textsuperscript{[105,220]} Fatigue is a complex, subjective sensation, with complex physiological, psychological, behavioral, and social underpinnings.\textsuperscript{[220]} LD is associated with disturbances in homeostasis, inflammation, and metabolism that can contribute to central and peripheral fatigue.\textsuperscript{[221]} Central fatigue develops as a result of changes in neurotransmission, whereas peripheral fatigue is associated with neuromuscular dysfunction that results in muscle wasting and weakness.\textsuperscript{[222]} Fatigue has been associated with disease severity, ascites, encephalopathy, level of physical activity, poor sleep quality, decreased quality of life, mood disturbance, anxiety, depression, and job performance in cirrhosis and with age, sex, diet, mental status, and personality type in general populations.\textsuperscript{[220,223–226]} The evaluation of fatigue should include a comprehensive assessment of other potential contributing factors, such as hypothyroidism, depression, adrenal insufficiency, anemia, vitamin deficiency, and medication side effects (e.g., beta-blockers).\textsuperscript{[222,226,229,230]}

Nonpharmacological management of fatigue includes education, recommendations about energy-conserving and -restoring activities, and referral to physical and occupational therapy. A structured four-component behavioral approach, called Treat, Ameliorate, Cope, and Empathize, focuses on treating what is treatable, addressing ameliorating factors (e.g., sleep disturbances), providing coping skills, and empathizing with patients.\textsuperscript{[230,231]} Several studies in patients with Child Class A and B cirrhosis have found that physical exercise can reduce fatigue.\textsuperscript{[227,232,233]} Stimulants, including modafinil and methylphenidate, have been successfully used for fatigue in other populations.\textsuperscript{[234,235]} However,
although modafinil was successfully used in patients with HIV and HCV coinfection and initial open-label trials in primary biliary cholangitis were promising, an RCT of modafinil in patients with primary biliary cholangitis found no significant impact on fatigue.\[229,236,237\] Thus, there are not data to support the use of stimulants in patients with DC.

Guidance statements

47. A multidisciplinary approach to addressing fatigue includes evaluation and treatment of contributing factors (e.g., encephalopathy, hypothyroidism, adrenal insufficiency, depression, and medications), providing behavioral education, and recommending physical activity.

48. There are insufficient data to support the use of stimulants to treat fatigue in patients with cirrhosis.

Pruritus

Pruritus is a common symptom in patients with cirrhosis of all etiologies, although it disproportionately affects patients with cholestatic LDs. As such, most of the existing studies have been conducted in patients with primary biliary cholangitis and other cholestatic LD.\[238,239\] Although the pathophysiology of pruritus is incompletely understood, the presentation of pruritus varies in distribution, frequency, and correlation with the severity of LD. Initial treatment includes moisturizing creams, avoidance of hot baths and rubbing of the skin, minimizing use of harsh soaps and detergents, and using loose-fitting clothing and cool humidified air (Table 6).\[240\] Antihistamines, which are often used for pruritus, may have sedating effects or exacerbate encephalopathy and are generally not efficacious for pruritus attributable to cholestasis.\[238\] However, the sedating properties of antihistamines may render them helpful for addressing pruritus-mediated sleep disturbances, and antihistamines are efficacious for certain skin conditions (e.g., urticaria).\[238,241\]

Pharmacological treatments for cholestasis-associated pruritus include cholestyramine (or colestipol), RIF, naltrexone, and selective serotonin reuptake inhibitors (SSRIs), as presented in Table 6. Cholestyramine, a bile acid sequestrant, was shown to be effective in randomized studies with small numbers of patients (n = 8 and n = 10).\[242\] It is generally considered as the first-line treatment for pruritus; however, given the potential for drug interactions, consultation with a pharmacist and thoughtful spacing from other medication administration are often required. The recommended starting dose for cholestyramine is 4 g/d, with titration up to 16 g/d as needed and tolerated.\[238\] An alternative to cholestyramine use is colestipol, which some patients may find more palatable.

A meta-analysis of five trials showed that RIF was effective in treating chronic pruritus.\[243\] Although safe as short-term treatment, longer-term use of RIF can be associated with hepatotoxicity.\[152\] Therefore, RIF should be initiated at a quarter dose and titrated slowly to 150–300 mg twice-daily with careful monitoring of liver biochemistries. RIF should not be used in patients with bilirubin levels >2.5 mg/dl, making it impractical for many patients with DC.\[238,244\]

Naltrexone, an opioid antagonist, was effective in treating cholestatic pruritus in prospective placebo-controlled trials.\[244–248\] Naltrexone for this indication requires a low dose, starting with 12.5 mg daily and up-titrating every 3–7 days to reach the maximum dose of 50 mg/d.\[246,247\] Although uncommon, naltrexone-related hepatotoxicity can occur and necessitates close follow-up of liver biochemistries.\[152\] Naltrexone use is also often inappropriate in persons receiving opioids for pain because it can block opioid binding, thus reducing analgesia and potentially causing opioid withdrawal.\[249\]

Sertraline, an SSRI, has been shown to reduce cholestatic pruritus symptoms at 75- to 100-mg doses.\[250–252\] Sertraline was well tolerated and showed moderate antipruritic effects in a randomized trial with a small number of patients with liver-associated pruritus.\[250\] Notably, the antipruritic effect was independent from an improvement in depression.\[250\] Because sertraline is largely metabolized in the liver, it requires careful administration (e.g., a starting dose of 25 mg with titration) in patients with DC. Paroxetine, another SSRI, may also be beneficial for pruritus, and other agents, such as ileal bile acid transporters, are undergoing investigation.\[249,253\]

Guidance statements

49. Our suggested approach to pruritus in patients with DC includes starting with nonpharmacological options, including using moisturizing creams, avoiding hot baths and harsh soaps, and using loose-fitting clothes and cool humidified air.

50. Cholestyramine (4 g/d with titration to 16 g/d) is first-line treatment for pruritus.

51. Alternative agents include low-dose naltrexone, RIF (in anicteric patients), and sertraline, but these agents require careful titration in the context of DC.

Sexual dysfunction

Recent AASLD guidelines address reproductive concerns for women with cirrhosis, so we have focused on the palliative aspects of sexual dysfunction management for patients with DC.\[254\] Approximately two thirds of men...
and 80% of women with cirrhosis suffer from sexual dysfunction, which leads to impaired HRQoL. Sexual function is one of the least evaluated symptoms in medical encounters and is often under-reported because of cultural norms about discussing sexuality. Thus, asking patients is the most important first step toward addressing sexual symptoms (e.g., “Are you sexually satisfied?” and “Are you able to achieve orgasm?”). Evaluation should include first a search for reversible contributors, such as underlying medical comorbidities, including diabetes or hypertension, medications (such as beta-blockers), alcohol, and psychiatric conditions, such as depression. Sexual dysfunction can result from cirrhosis because of associated hypogonadism, low testosterone, and altered circulation.

Treatment of sexual dysfunction includes pharmacological and nonpharmacological approaches. First, medications (e.g., beta-blockers) and substances (e.g., alcohol, tobacco) that can cause sexual dysfunction should be removed, where appropriate. Second, underlying conditions that contribute to sexual dysfunction, such as depression and diabetes, should be medically managed. Third, one can consider using phosphodiesterase inhibitors. One small study of tadalafil in 25 men with cirrhosis, erectile dysfunction, and a mean MELD of 13 ± 4 found that 10 mg over a 4-week period was a safe and efficacious approach.

Although 55% of the men studied had decompensated disease, the trial excluded those with encephalopathy. Three patients had adverse events, including dyspepsia (n = 2) and headache (n = 1), but these were not dose limiting. Studies of portopulmonary hypertension treatment using these agents have been successful, though in the setting of hypotension such medications are contraindicated. There is an ongoing trial of tadalafil for patients with cirrhosis that should add to this literature.

Nonpharmacological treatments, including sex therapy or vacuum devices, have not been tried in patients with cirrhosis, but may be a safe alternative. Furthermore, a small study found that sexual satisfaction and erectile dysfunction improved after LT. More research is needed to determine how to manage sexual dysfunction in this population, particularly among women.

Guidance statements

52. Sexual dysfunction is often important for quality of life of patients with DC and should be assessed.
53. There are sparse data about management of erectile dysfunction treatment in this population, though tadalafil may be a safe short-term option in select patients and is undergoing further evaluation.
54. There is a notable lack of research regarding the assessment or management of sexual dysfunction in women with cirrhosis.

Depression and anxiety

Depression and anxiety are common among patients with cirrhosis, with a prevalence of 30%–60%. Untreated depressive symptoms are associated with pain, disability, worse HRQoL, increased health care use, and increased mortality. A recent report found that patients with new cirrhosis diagnoses were at increased risk of suicide, highlighting the importance of identifying and treating mental health symptoms in this population. Mental health symptoms can have organic causes (e.g., vitamin deficiency) and can mimic encephalopathy and dementia, such that a high index of suspicion is required to distinguish mental health symptoms from other related disorders. Evaluation can include validated screeners. For example, the Patient Health Questionnaire-2 is a two-question screening tool that asks patients to rate (1) interest in activities and (2) feeling down, depressed, or hopeless over the past 2 weeks on a 4-point scale, where a score of 3 triggers further evaluation.

A thorough exploration of evidence-based mental health treatments is beyond the scope of this Guidance. However, having a low threshold for referral to mental health specialists is recommended, and efforts should be made to combat stigma about seeking mental health care. Treating contributors, such as vitamin B12, iron, or folate deficiency, sleep disorders, and encephalopathy, is an important aspect of managing mental health symptoms. The backbone of primary management of mental health symptoms should be cognitive behavioral therapy with or without pharmacotherapy. Although SSRIs are generally considered to be efficacious and safe, selection requires consideration of other symptoms, and presence of sexual dysfunction, somnolence, and/or weight loss should guide the selection of specific SSRIs. These nuanced treatment considerations are often best managed by a mental health professional, who can also provide evidence-based behavioral therapies. Regardless of the type of treatment, psychosocial support is part of a key component of primary palliative and hepatology care.
health professionals, particularly when considering pharmacotherapy.

Nausea and vomiting

Nausea is experienced by over half of patients with cirrhosis attributable to a number of potential etiologies, including medications (e.g., lactulose, opioids), adrenal insufficiency, electrolyte imbalance (e.g., hyponatremia, hypercalcemia), uremia, reflux, and constipation. LD can also be associated with gastroparesis and increased intra-abdominal pressure (e.g., with tense ascites). Thus, nonpharmacological approaches to the management of nausea and vomiting can include behavioral avoidance (e.g., avoiding triggering smells and tastes), removal of triggering medications, treatment of underlying physiological causes, use of ginger, guided imagery or relaxation techniques, and acupuncture (Table 6).

First-line pharmacotherapy for nausea and vomiting in patients with cirrhosis may include a trial of a histamine H2 antagonist or proton pump inhibitor in patients with suspected reflux-associated nausea. Ondansetron (a serotonin 5-HT3 antagonist) can be used in patients with liver impairment at a dose of up to 8 mg/d, though patients should be monitored for constipation and QTc prolongation. A small, randomized trial of 8 patients with cirrhosis and mild encephalopathy were treated with metoclopramide (up to 60 mg daily) versus placebo for nausea over a period of 2 weeks; all patients also received neomycin. Although metoclopramide was associated with reduced nausea and heartburn in this small study, the risk of extrapyramidal side effects limits its long-term use, and a 50% dose reduction is recommended for patients with hepatic impairment. Other medications for the palliative treatment of nausea may include olanzapine, haloperidol, or prochlorperazine; however, all have significant side-effect profiles (Table 4); prochlorperazine should be avoided in the setting of jaundice given case reports of cholestatic liver injury.

Cannabinoids are another potential treatment for nausea and vomiting. Because of media coverage and conflicting data, clinicians should be prepared to discuss the benefits and potential harms of medical marijuana and other cannabinoids with patients with cirrhosis and their caregivers. The strongest supportive data for the use of medical marijuana are for nausea and vomiting. However, although one meta-analysis found that cannabinoids were associated with a reduction of nausea and vomiting of >50%, the data, particularly in cirrhosis, are limited. Adverse effects of cannabinoids in the general population include dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination. Some observational studies identified associations between cannabis and accelerated hepatic fibrosis, encephalopathy, and ascites in patients with chronic LD attributable to HCV and fatty liver disease. However, other observational studies, including two meta-analyses of marijuana use and HCV, did not find a significant association between cannabis and hepatic fibrosis. Trials of medical cannabinoids/marijuana have generally excluded patients with cirrhosis, given their vulnerability to neuropsychiatric symptoms. Thus, cannabinoids should be used with caution and with attention to institutional protocols for its use. When cannabinoids are used, edible formulations are favored over inhaled because of the potential infectious and respiratory effects of smoking.

Guidance statements

58. For patients with cirrhosis who suffer with nausea and/or vomiting, an evaluation should include assessment of electrolytes, adrenal insufficiency, and pharmaceutical causes as well as assessment for and treatment of gastroesophageal reflux disease.

59. First-line pharmacotherapy for nausea and vomiting is ondansetron (maximum 8 mg/d), using caution given constipating effects; most antiemetics require monitoring for QTc prolongation.

60. Medical marijuana is not first-line management for any symptom for patients with DC. However, providers should be able to engage in an educated conversation about its risks and benefits.

END-OF-LIFE CARE

The burden of symptoms and distress that patients with DC experience at the end of life is comparable to that of patients with advanced colorectal and lung cancer. Symptoms commonly include pain, lack of energy, drowsiness, insomnia, and difficulty concentrating. Eliciting treatment preferences for EoLC and addressing palliative needs based on priority are critical to ensuring that care at the end of life is patient and caregiver centered.

Patients and caregivers often want to know what to expect nearing the end of life; thus, health care teams should provide education about prognosis and help them develop plans for addressing infection, hemorrhage, and encephalopathy, which are the most common scenarios leading to death. Care plans developed based on these discussions may often require balancing goals that are simultaneously aggressive and nonaggressive. This can be a particular challenge for patients and caregivers who wish to pursue EoLC at home or in the community, though the majority of patients with cirrhosis die in a health care facility.
discuss and difficult to address. For example, patients with variceal hemorrhage may be managed with endoscopic treatment to preserve the time left or may elect to manage bleeding at home with dark towels and sedation if dying at home is prioritized. Another common scenario is managing encephalopathy when patients are unable to swallow and decisions regarding nasogastric tube placement are being considered. Conversely, in some cases, patients may continue LD-focused care even on hospice if it is for palliation (e.g., paracentesis for tense ascites), in collaboration with the hospice agency. Thus, developing plans that address preferences around hospital readmission are crucial.

Clinical decision making may shift when death is imminent, as discussed throughout this document. For example, whereas past opioid use disorder is a relative contraindication for chronic opioid analgesia, EoLC should prioritize analgesia, comfort, and compassionate care over concerns about long-term comorbidities or adverse medication effects. Consequently, medications that may be generally contraindicated for patients with DC (e.g., benzodiazepines) can be considered in the context of EoLC. Because prognostic information may impact caregivers’ decision making around difficult issues, it is critical that hepatology team members engage in frequent prognostic conversations and shared decision making with families.

Hospice is comfort-focused EoLC that, in the USA, is covered by Medicare Part A. It is typically provided in the home and is focused on symptom management, psychosocial support, and counseling by an interdisciplinary team. Generally, the hospice team continues to follow bereaved family members for up to a year after death. Bereavement services are an important part of the hospice benefit that are not consistently provided by routine medical care and should be considered a potential benefit in the decision-making process. Hospice is generally appropriate for patients who prioritize comfort-focused care and are no longer pursuing disease-directed therapies and whose prognosis is <6 months. Hospice has been associated with improved control of physical and psychological symptoms, quality of life, and caregiver bereavement. Evidence shows that hospice is provided infrequently and, when provided, is very close to the end of life for patients with DC. Likely factors responsible for this observation include infrequent and delayed discussions about EoLC, defaulting to aggressive, disease-directed care, the unpredictability of decompensating events, and clinician discomfort with end-of-life conversations. Centers for Medicare & Medicaid Services (CMS) eligibility criteria for hospice in the USA are shown in Table 7; MELD score >21 or Child-Pugh score ≥12 are also associated with an ~6-month life expectancy, which can be useful prognostic information for patients and caregivers.

A significant policy-level barrier to hospice for patients with cirrhosis is that the Medicare hospice benefit does not financially cover disease-directed care. That said, it is possible (though uncommon) for patients to remain on the transplant list and receive hospice benefits. There are alternative models that have been piloted for patients with LD at the end of life. A feasibility study provided hospice care to 157 patients who were being evaluated or listed for LT; 6 study patients ultimately received transplantation. To date, such models have not been widely implemented in the USA, owing, in part, to the complexities of payment models that would be needed to support a hybridized hospice/transplant approach. In general, when people elect to enroll in hospice, the agency generally assumes management of their medical care. Consultants may follow and bill for services; however, this is best arranged with the hospice agency on a case-by-case basis. Evidence from the oncology literature suggests that patients and families may feel a sense of abandonment by their treating teams at the time of hospice transition; however, no such studies have been conducted among patients with cirrhosis. Nonetheless, hospice remains the standard of high-quality EoLC. More information about how to best tailor hospice services to the needs of this population, and to better understand contributors to complicated grief among caregiver members, is needed.

### Table 7: Hospice criteria for patients with DC

Patients will be considered to be in the terminal stage of LD (life expectancy of ≤6 months) if they meet the following criteria (criteria 1 and 2 should be present; factors from criterion 3 will lend supporting documentation):

1. The patient should show both a and b:
   a. Prothrombin time prolonged >5 s over control or international normalized ratio >1.5;
   b. Serum albumin <2.5 g/dl.
2. End-stage liver disease is present and the patient shows at least one of the following:
   a. Ascites, refractory to treatment or patient noncompliant;
   b. SBP;
   c. Hepatorenal syndrome (elevated creatinine and blood urea nitrogen with oliguria);
   d. HE, refractory to treatment or patient noncompliant;
   e. Recurrent variceal bleeding, despite intensive therapy.
3. Documentation of the following factors will support eligibility for hospice care:
   a. Progressive malnutrition;
   b. Muscle wasting with reduced strength and endurance;
   c. Continued active alcoholism (>80 g of ethanol per day);
   d. HCC;
   e. HBsAg positive;
   f. Hepatitis C refractory to interferon treatment. Patients awaiting LT who otherwise fit these criteria may be certified for the Medicare hospice benefit; but if a donor organ is procured, the patient should be discharged from hospice.


![Table 7](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34538)
Guidance statements

61. Addressing palliative needs at the end of life involves eliciting end-of-life treatment preferences, creating care plans, and providing education about possible scenarios, including infection, bleeding, and HE.

62. Hospice is a patient- and caregiver-centered option for EoLC that is underused by patients dying with cirrhosis.

63. In addition to current criteria, hepatology teams may consider using MELD >21 and Child-Pugh >12 to determine whether patients are prognostically appropriate for hospice (i.e., have estimated survival of ≤6 months).

64. Providing caregivers with information about imminent death may help support decisions aligned with the patient’s prognosis (e.g., providing pain medications despite past substance use disorder at the end of life).

FUTURE CLINICAL AND POLICY IMPLICATIONS

To successfully weave the principles of palliative care into hepatology care requires substantial research, clinical innovation, culture change, and health policy advocacy. A critical first step is workforce training and programmatic development to support palliative care. Although not every hepatology trainee or team member requires expert-level palliative care skills, there is a growing consensus that clinicians across all medical and surgical specialties need to develop core competencies in providing PPC and then engage with specialists as needed. This is even more critical in light of palliative care workforce shortages. Palliative care is a growing field, but its penetration is uneven across the USA, with the largest gaps existing in ambulatory and community palliative care services. Several societies have developed key competencies in PPC for nonspecialists, including communication, ACP, and symptoms assessment and management skills. For example, competencies for cardiologists include, but are not limited to, communication and shared decision-making skills, pain and symptom management, caring for caregivers, understanding hospice indications, end-of-life decision making and care, and working with an interdisciplinary team to manage psychosocial, spiritual, and cultural aspects of care. Similarly, some skills that are important for hepatology clinicians include identifying and documenting surrogate decision maker, communicating prognosis, eliciting and documenting goals and values, and delivering care concordant with these goals and values. Offering trainees in hepatology the opportunity to serve on palliative care consultative services and in hospice settings may provide hands-on experience and training that can diffuse into current hepatology practitioners. Resources for further skill development are offered in Table S2.

In addition to training opportunities, there are other potential opportunities to increase palliative care implementation in clinical hepatology settings. For example, specialty palliative care providers can round on inpatient hepatology services or have colocated clinics with hepatology. Alternatively, palliative care consultation can be automated based on trigger criteria (e.g., intensive care unit admission, removal from the transplant list). Simply offering information about palliative care in hepatology settings can help caregivers and patients become more aware of their options. Routine symptom assessment in hepatology can increase providers’ expertise with triaging and managing symptoms that are often underaddressed for patients with cirrhosis.

Policy and infrastructure changes can also facilitate palliative care implementation in hepatology. Advocating for payers and hospice agencies to innovate to best meet the needs of patients with cirrhosis will ensure that the specific issues facing our patients are addressed. For example, policies supporting reimbursement for specialty palliative services should be considered. Providing palliative care training to social workers, psychologists, and other members of multidisciplinary liver teams or seeking out palliative care–trained specialists in these disciplines can extend the reach of the existing workforce. Developing reimbursement infrastructure around the various aspects of palliative care can also facilitate its implementation. Similarly, formal communication and collaboration between palliative care and hepatology societies could facilitate palliative care implementation in patients with DC. Furthermore, dissemination of information about available supports and benefits is important. For example, many are unaware that patients on the transplant list can receive hospice benefits until a donor organ becomes available. Finally, incorporating measures of hospice and palliative care into cirrhosis quality metrics can demonstrate the importance of these topics to providers and payors.

Clinical research gaps have been highlighted throughout this guidance. These include developing evidence around which interventions work at what times for patients with cirrhosis, delineating the optimal ways to measure and report patient-reported outcomes for patients with cirrhosis, and addressing the high symptom burden of patients with cirrhosis, particularly using nonpharmacological approaches. Thus, fully implementing palliative care for patients with DC requires a multipronged approach to address ongoing training, practice, policy, and research gaps.
Guidance statements

65. Future workforce training is needed, and developing hepatology competencies in primary palliative care is a first step toward this goal.

66. Policy changes, such as funding for multidisciplinary palliative care teams and extended reimbursement for specialty palliative care services, can help to support patients with cirrhosis and their caregivers at the end of life.

CONCLUSIONS

Palliative care is a multidisciplinary approach to addressing the psychosocial, spiritual, and physical needs of patients and their caregivers that is associated with improved health outcomes in the context of cirrhosis and other chronic diseases, but is highly underused in patients with DC. Although palliative care can be provided by specialists, we encourage all members of the hepatology care team to consider providing palliative care to address the symptomatic, spiritual, and psychosocial needs of their patients and their caregivers. The core principles of palliative care are clearly aligned with high-quality, value-based hepatology care: communication; coordinated interdisciplinary care; comprehensive symptom assessment and management; and care plans that align with patients’ values and preferences. Future research is needed to identify the optimal approaches to train medical staff in primary palliative care skills, symptom management, engagement of specialty palliative care, and innovative models of care that successfully blend these currently distinct disciplines. Palliative care should be offered earlier and to more patients with cirrhosis.

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AUTHOR CONTRIBUTIONS

All authors contributed to article conception and design, data interpretation, and drafting, revising, and approving the article.

CONFLICT OF INTEREST

The opinions expressed in this article are the authors’ own and do not reflect the views of the National Institutes of Health or the United States government.

ETHICS STATEMENT

This guidance document does not qualify as human subjects research.

DATA AVAILABILITY STATEMENT

Data are available in the guidance document or the cited references.

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CIRRHOSIS


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189. Kwekkeboom KL, Bratzke LC. A systematic review of relaxation, meditation, and guided imagery strategies for symptom


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