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Nonhospice Palliative Care within the Treatment of End Stage Liver Disease

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Abstract

Palliative care (PC) that has evolved from a focus on end of life care to an expanded form of holistic care at an early stage for patients with serious illnesses and their families is commonly referred to as nonhospice PC (or early PC). Patients with end stage liver disease (ESLD) suffer from a high symptom burden, deteriorated quality of life with uncertain prognosis and limited treatment options. Caregivers of these patients also bear the emotional and physical burden similar to cancer caregivers. Despite proven benefits of nonhospice PC in other serious illnesses and cancer, there are no evidence-based structures and processes to support its

integration within the routine care of ESLD patients and their caregivers. In this article, we review the current state of PC within ESLD, and propose key structures and processes to integrate nonhospice PC within routine hepatology practice.

Results found that PC is highly underutilized within ESLD care, and limited prospective studies are available to demonstrate methods to integrate PC within routine hepatology practices. Hepatology providers reported lack of training to deliver PC along with no clear prognostic criteria on when to initiate PC. A well informed model with key structures and processes for nonhospice PC integration would allow hepatology providers to improve clinical outcomes, ESLD patients' quality of life, as well as reduce healthcare costs. Educating the hepatology providers about PC principles and developing clear prognostic criteria for when and how to integrate PC based on individual patient needs are the initial steps to inform the integration. The fields of nonhospice PC and hepatology have ample opportunities to partner clinically and academically.

Introduction

End stage liver disease (ESLD) is the 12th leading cause of death and claims approximately 66,000 lives each year in the United States (US).¹ Between 2006 and 2016, the prevalence of ESLD increased by 7.9% among men 25-34 years and 11.4% among women in the same age group due to increasing burden of non-alcoholic steatohepatitis (NASH), alcohol-related liver disease, and advanced hepatitis C virus (HCV).² In parallel, mortality due to ESLD increased by 65% from 1999 to 2016.³

ESLD is also associated with functional and cognitive impairment, often with concomitant mental health and substance use disorders. The physical and psychological symptom burden and social role consequences of ESLD is often worse than many non-liver cancers.⁴ The most frequently reported symptoms include pain, breathlessness, muscle cramps, sleep disturbance, fatigue, pruritus, anxiety, depression, and erectile dysfunction.⁴ In addition to its direct effects on patients, ESLD is linked with substantial caregiver emotional and physical burden, mirroring that observed in caregivers of patients with cancer.⁵ However, interventions to improve patients' with ESLD and their caregivers' quality of life (QOL) are under-developed.

Palliative care (PC) is the most promising solution to address the physical, psychological, and caregiver burden of ESLD. The aim of PC is to provide holistic care for patients with serious illnesses and their families, focusing on symptom management, goals of care discussions,

advance care planning (ACP) and end-of-life care or hospice. Whereas hospice is considered for patients with projected life expectancy of less than 6 months, nonhospice PC is inclusive of all the other elements of PC applicable from the time of diagnosis onwards, for any serious illness.⁶ Nonhospice PC has been clearly defined recently (**Table 1**). Unfortunately, there is suboptimal understanding of the structures and processes required to integrate nonhospice PC within hepatology. The goal of this review is to synthesize recent literature regarding the current state of PC for patients with ESLD, and propose key structures and processes required to integrate nonhospice PC within hepatology practice.

Palliative Care Overview

Palliative care is a subspecialty focusing on patients' individual needs (including physical, psychosocial and spiritual). Early PC has been shown to improve patient symptoms, QOL, patient satisfaction, advance care planning (ACP) discussions, reduce health care costs/utilization particularly intensive medical care and caregiver burden (**Table 2**).⁷ More recently, several non-cancer societies have recommended early introduction of PC for chronic illnesses such as end stage renal disease, heart failure and lung disease⁸; however, no such guidelines exist in the liver disease literature.⁹

Current state of Palliative Care in ESLD

Several studies within the past 5 years identified limited availability of PC services for liver disease patients, leading to limited and late involvement of PC specialists, by which many potential benefits of PC may be lost.¹⁰ In an analysis of the nationwide inpatient sample, Rush et al found only 4.5% of all ESLD-related admissions received PC consult, although this increased from 1.0% in 2006 to 7.1% in 2012.¹¹ Barnes et al found only 19% of eligible patients (defined as ≥ 2 admissions within 6 months for decompensated cirrhosis, excluding those who were listed for liver transplantation) received "early PC" (i.e. PC received >30 days prior to death), with hospitalizations costs significantly reduced in those with early PC due to a lower number of endoscopies and blood transfusions.¹² Similarly, studies have shown that less than 20% of patients removed from the liver transplant (LT) waiting list receive PC consult, and most of those occur within 72 hours of death in an inpatient setting.¹³ A provider survey conducted among Veterans' practices found that despite 82-88% practices having PC available on site, less than 25% of ESLD patients were referred for PC consultation.¹⁴ Commonly reported barriers were insufficient staff knowledge about PC, uncertainty of timing to make PC referrals, and patient refusal to received PC (potentially due to the misconception of PC being equivalent to end-of-life

care). A study from Canada reported less than 20% of patients with cirrhosis had ACP documented, despite a public awareness campaign raising awareness of ACP within the province, and almost 66% of patients were listed as being full code despite a dismal prognosis.¹⁵ However, patients preferred to have ACP discussions when they were still well, not wait till their health completely declines, and with the physicians they have ongoing relationships such as their hepatologists.

Few prospective studies have tested nonhospice PC for ESLD, and some are ongoing (**Table 3**). Of the few prospective studies, 50% are single arm uncontrolled studies. Only 1 RCT has been completed, but that was terminated due to under enrollment. However, all studies have supported feasibility, and positive patient outcomes.

Barriers to Implementing PC

Barriers to include PC within routine hepatology practice can be categorized into those related to patients, providers and health systems.

1. For *patients*, many see PC being synonymous with end-of-life care. The fear that PC may exclude them from liver transplant candidacy makes patients and their caregivers less willing to receive PC consultation. Hepatic encephalopathy can make the patients unable to participate in PC discussions such as goals of care or ACP.¹⁶
2. For *providers*, barriers include uneasiness in including PC consultants, misperception of PC being just end-of-life care, insufficient guidelines for PC integration, inadequate access to PC providers coupled with deficiency in PC provider workforce, insufficient time during routine clinical care for complex discussions, inadequate training in goals of care discussions or psychological/ symptom management, and a preferential focus on life-saving interventions.¹⁷ Fear of upsetting patients, not wanting to abandon them, considering PC referral as an admission of failure/ no hope, impaired patients' cognitive capacity to participate in provider-led discussions, and providers not completely understanding the benefits of PC are other reasons.⁴
3. For *health systems*, implementation and policy barriers have been identified.¹⁸ Implementation barriers include limited number of providers with PC training, challenges of identifying patients for appropriate PC referral at the systems level, and the need for a culture change across settings. Policy barriers include fragmented healthcare systems, lower profit margins in reimbursements for PC services, need for a pre authorization in some states and insurance carriers, inability to cover the uninsured, and lack of complete evidence to drive this change. However, given the move of US healthcare

towards patient-centered care, health systems are looking for options to improve patient satisfaction, and PC has proven to be one of them.

Structures and Processes required for integrating Nonhospice PC in ESLD

Models of nonhospice PC differ in their level of integration (e.g. freestanding or embedded PC clinics, inpatient PC consultation or a dedicated inpatient PC unit) and place of delivery of palliative care (e.g. inpatient, outpatient, home based or remote/using telehealth). **Table 4** outlines the model structures and their potential strengths and weaknesses. Timely, integrated PC requires contact at a time when the patients are functional, independent, and have supportive care needs. This is not a prognosis-based decision but rather a patient or family caregiver based decision. This type of care has been shown to be most effective at the time of outpatient visits, making outpatient clinics an ideal setting for nonhospice PC.¹⁹ However many different models exist that are tailored to overcome geographic barriers, work force shortages, etc. (e.g., virtual clinics, telehealth).

The structures and processes to enable the heterogeneous PC models may vary. However there are basic elements which must be the part of a PC intervention.²⁰ These elements include:

1. Patient- and family-centered care: Patient centered care, defined as health care which is inclusive of informed, respected and involved patients, is one of the six key elements of high quality care according to the Institute of Medicine.²¹ Optimal nonhospice PC engages patients and caregivers in decision making, prognosis understanding and preparedness for acute decompensation events. An example is the ENABLE model (Educate, Nurture, Advise, Before Life Ends) which has demonstrated effectiveness in oncology and heart failure.²² The intervention included an in-person PC assessment, weekly telehealth coaching sessions with advance practice nurses for 6 weeks for patients and 4 weeks for caregivers on select topics such as problem solving, symptom management, communication and decision making. The qualitative programmatic evaluation found that participants gained illness management and decision making skills while continuing with curative treatments, and reported feeling empowered and experienced better care planning.²³

2. Inter-professional team: PC assessments target physical, psychological, social, spiritual and cultural needs of patients. An interprofessional team, usually comprised of a PC physician, nurse practitioner, registered nurse, social worker, psychologists, and chaplains, is needed to

tackle the multidimensional needs of patients and caregivers.²³ Team efficiency is featured by good leadership, effective decision making, and communication among team members. There is no evidence available to support which discipline optimizes the efficacy of PC. Interprofessional PC teams have improved patient's health outcomes (such as symptoms and survival); however, no study has compared interprofessional teams with a solo practitioner approach.²⁴

3. Provider characteristics: Conventionally, a trained PC specialist provides PC when consulted, often referred to as "*specialist/ consultative PC*". However, given the shortage in PC providers, high value and demand of PC, and the need to reduce care fragmentation, the concept of *primary PC* has gained importance. This includes basic skills that all clinicians should have i.e. basic management of pain and symptoms; depression and anxiety; basic discussions on prognosis, goals of care, suffering and code status.²⁵ Web-based online PC training has been described as a pragmatic approach, given the time constraints of most providers, and has demonstrated enhanced patient care.²⁶ A study testing an online curriculum demonstrated improved confidence, knowledge and satisfaction of primary care providers in offering PC to their patients.²⁷ A randomized controlled trial demonstrated improved patient symptoms in the group receiving PC from primary care physicians trained in PC versus primary physicians not trained in PC.²⁸ Similar results have been seen in specialists trained in PC. For example, a nephrologist-led PC study showed significant increase in documentation of patient preferences for cardiopulmonary resuscitation and limits on life-sustaining treatment.²⁹

It is expected that hepatologists are aware of patient prognosis and treatment options, whereas PC specialists may not be fully aware of those including transplant eligibility, which can change over time. With appropriate training, hepatologists can provide evidence-based PC to their patients with supportive care needs (e.g., advanced care planning, goals of care communication, symptom management) in addition to offering all appropriate advanced therapies for patients with ESLD as routine practice.

4. Screening tools to aid PC intervention at an early stage of ESLD: It is important to identify ESLD patients who may benefit from nonhospice PC early in their disease trajectory. Screening tools have been developed and validated to help identify patients for whom PC can be triggered in other settings such as emergency departments. However, few tools exist to identify unmet needs among ESLD patients. One such tool for ESLD inpatients at high risk of dying within 1 year includes 5 criteria: Child-Pugh class C, more than 1 liver-related admissions within prior 6 months, ongoing alcohol use in the context of known alcohol-related liver disease,

unsuitability for liver transplantation and WHO performance score 3 or 4; a cumulative score > 3 can be used to trigger PC referral.³⁰ Other more general screening tools can be applied to ESLD patients such as ED-PC (Emergency Department- Palliative Care), which includes three simple criteria: 1) presence of a life-limiting illness, 2) unmet PC needs (e.g. symptoms, functional decline, frailty, new onset of complications, limited social support) and 3) hospital admissions.³¹

To intervene at an early stage of illness, it is important to use screening tools as standard practice. However, feasibility of including these screening tools within Hepatology practices needs further evidence. Instruments such as ESAS (Edmonton Symptom Assessment Score) for symptoms, PHQ-9 (Patient Health Questionnaire) for depression, and DT (Distress Thermometer) for distress can also be utilized. ESAS assesses pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, feeling of wellbeing, shortness of breath and others (including disease specific symptoms such as muscle cramps, itching, sexual function, and sleep). PHQ-9 includes 9 questions assessing depression, with higher scores reflecting greater severity of depression. DT is a brief valid instrument to assess the severity of psychosocial distress in patients with serious illnesses, and helps initiate conversations about the wide range of difficulties, services and resources that may help address them.

5. Goals of care discussions: Effective communication is the key to eliciting patient's personal goals and preferences, and aligns those with their care management plans. Research has shown that communications about goals of care lead to improved patient's health outcomes and reduced intensity of end of life care acts. These should be conducted at an early stage of illness, such as once a diagnosis of cirrhosis is made, but can change over time so must be revisited. The hepatology team can play a pivotal role in eliciting these goals.³² However, clear evidence on how much of these discussions happen during routine hepatology consultations remains unclear. There are standard educational courses available to learn about goals of care such as VitalTalk and OncoTalk, which have been widely used to improve communication skills among providers.³³ These are based on effective communication strategies to elicit and deliver personalized care. These can be a part of faculty development within Hepatology. Furthermore, a framework such as REMAP tool (Reframe, Expect emotion, Map out patient goals, Align with goals, and Propose a plan) can be utilized by the hepatology team to improve goals of care discussions.³⁴

6. Advance care planning is a mechanism of developing future health care goals, to be inclusive of personal values and preferences. Discussions around ACP provide moments to

explain the patients' current health situation in a broader context of overall trajectory of liver disease, treatment options and potential outcomes associated with each (disease and treatments). In addition, these discussions ameliorate surrogate decision makers anxiety and depression, and reduce unwanted care acts towards end of life. A framework tailored to cirrhosis outlining the best practice tools for ACP has been published by Brisebois et al.³⁵ They outline the key elements of ACP process as 1) elicitation of patient's perspectives, 2) assess readiness to discuss ACP and choose a surrogate person, 3) educating patients (using educational resources on cirrhosis and its complications), 4) describing the focus of care to be inclusive of curative therapy and symptom management, 5) discuss prognosis using tools which include comorbidities, 6) review liver disease complications, 7) review available local resources for patients and their families, and 8) document goals of care. For compensated cirrhosis, eliciting patients' health goals are important. As they enter decompensated phase, in depth discussions on prognosis, treatment options and symptoms is warranted. Brisebois and colleagues recommend these discussions to occur irrespective of LT eligibility.

7. Concurrent care models

In 1990 the World Health Organization was the first to propose a concurrent care model in which PC was offered from the time of diagnosis of cancer.³⁶ This was without evidence until the 2000s when multiple studies in cancer have demonstrated PC effectively improved patients QOL, symptoms, and surprisingly, survival.⁷ Similarly, although PC and liver transplantation are often viewed as mutually exclusive a concurrent care model may prove beneficial.³⁷ Especially for ESLD patients who have the hope for transplant but risk of surgery, organ rejection, infection, and post-transplant morbidity in the setting of already diminished QOL pre-transplant, PC can optimize care. A quality improvement study in a VA setting, designed to proactively identify patients with a MELD ≥ 14 , and/or HCC were referred for a PC consult through a care coordinator.³⁸ The results showed that PC consults improved the likelihood for considering for LT and the likelihood of completing the transplant evaluations. Telehealth could potentially be utilized to integrate PC within LT care, as has shown to work within liver practices.³⁹

Another prospective study conducted in a surgical ICU for LT patients, tested a 2-part intervention of interdisciplinary communication between providers and patients/ families: family support, goals of care discussion and prognosis at admission and a follow-up interdisciplinary family meeting 72 hours later.⁴⁰ The intervention increased goals-of-care discussions (2% to 38%), increased DNR status (52 to 81%), and decreased SICU length of stay without affecting

mortality. The authors concluded that concurrent PC can be delivered in a surgical ICU setting, and can potentially improve end-of-life care. However, there is a high need to educate LT providers on PC benefits for patients and their caregivers.

8. Caregiver support: Caregivers of ESLD patients have high rates of undiagnosed clinical depression; and higher burden is observed among those who care for patients with frequent hospitalizations, hepatic encephalopathy, or active alcohol use.⁴¹ Bajaj and colleagues reported increased caregiver burden, especially for those whose liver disease severity was high.⁴² This increased burden in general has been linked to increased mortality in addition to depression and anxiety. Research shows that caregivers who received PC were less likely to have depression or grief.⁴³ Through nonhospice PC, caregivers can be evaluated for burden and distress, and linked to additional supportive resources. This may prove to be beneficial for both caregivers and their patients.

Key steps to integrate nonhospice PC into ESLD care

Based on the above described structures and processes, and the current situation of nonhospice PC, there are 5 things which can be applied to improve PC integration within the treatment of ESLD:

- 1) Provider education on nonhospice PC, as brief courses or an integral part of their fellowship training.
- 2) Universal use of prognostic tools and screening of symptoms, depression, and distress within routine care, coupled with predetermined alerts to promote PC service.
- 3) Develop clear criteria for PC referrals such as MELD (Model for End Stage Liver Disease) score, occurrence of an acute decompensation event, development of HCC beyond an early stage, number of hospitalizations and presence of comorbidities.
- 4) Include goal of care and advance care planning discussions as a part of routine ESLD care including at the time of transplant evaluation, wait-listing or delisting, or when no other curative options exist.
- 5) Identifying methods to assess and address caregiver burden, QOL and distress separately from patients, coupled with referrals made based on the evaluations

PAL LIVER study (Introducing PC within the treatment of ESLD)

PCORI has invested in large scale comparative effectiveness trials testing PC models and

advance care planning approaches. One of these is targeting ESLD population. The PAL LIVER study (**P**alliative Care for **L**iver Diseases) aims to compare a Consultative PC model to trained hepatologist-led PC delivery. It is a multi-center cluster randomized study, with clinical centers as the unit of randomization.⁴⁴ The primary hypothesis is that the trained hepatologist led PC model will have better improvement in QOL (from baseline to 3 months) than the Consultative model. Delivering PC in the context of routine hepatology care will build upon an established relationship between the patient and his/her hepatologist. Furthermore, it will be more pertinent given the hepatologists' understanding of the disease process; that includes the prognosis and ramifications of each complication.

A PC training program tailored to liver diseases has been developed to formally train hepatology providers in the Model 2. The study is currently enrolling (ClinicalTrial# NCT03540771), and recruits dyads (i.e. patients and caregivers together). The intervention is tailored towards both patients and caregivers, and utilizes a PC checklist for all study visits. The visits are billed to insurance, given the pragmatic nature and an aim to inform real world practice. The study has brought the two specialties: palliative care and hepatology together, to partner and improve the care of ESLD patients and their caregivers. Through this collaboration, the study has been able to implement both models in distinct settings. The results are projected to improve understanding of optimal integration of PC into clinical workflow. However, conducting PC research has its own inbuilt challenges. Some ongoing challenges to recruitment include: *Patient factors*- health related (such as uncertain prognosis/ complications, physical and mental challenges, patient not too sick, or doesn't understand the value of PC) and social barriers (fear, resistance, additional time and travel); *Caregiver factors*- such as mistrust, limited information, beliefs, fear of intrusion, false hopes; and *Provider factors*- such as time sensitivity, work load, and other competing priorities.

Conclusions

Nonhospice PC is underutilized in ESLD care, despite a great need and potential to improve patient and family members' QOL and reduce costs. Significant barriers exist with an unclear understanding of how to integrate PC within the treatment of ESLD. The structures and processes described in this review can guide the development of programs and interventions to improve nonhospice PC integration within ESLD care. The provision of training on PC for hepatology trainees and established practitioners will facilitate the implementation of this important integration. The ongoing PAL LIVER study aims to prove that early integration of PC

in the care of ESLD can lead to an improvement in patients' quality of life and demystify some of the key challenges to support PC integration.

Future Research:

Future collaborative research needs to continue between nonhospice PC and hepatology to test effective PC education approaches for hepatologists'; delineating clinical criteria which can trigger PC services for ESLD patients, advanced practice providers delivering PC within Hepatology offices given the busy schedules and limited time with hepatologists, or using telehealth based PC approaches. Furthermore, it will be important to identify which ESLD subgroups benefits the most from PC, how much PC can be delivered by hepatologists, and the optimal methods of conducting routine assessments of symptoms, depression, and distress within routine hepatology practices. Finally and critically, it is important to understand the financing of additional PC services within hepatology practices, supporting value-based medicine as opposed to a fee-for-service approach.

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