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# Integration of Palliative Care in End-Stage Liver Disease and Liver Transplantation

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## Abstract

***Background:*** Patients with end-stage liver disease (ESLD) have a life-limiting illness that causes multiple distressing symptoms and negatively affects quality of life (QOL). This population traditionally has not had much attention within the palliative care community.
***Discussion:*** This article provides an evidence-based review of palliative care issues that patients with ESLD and those awaiting liver transplant face, including approaches to prognosis, symptom management, advance care planning, and end-of-life care.
***Conclusion:*** Tremendous opportunity exists to integrate palliative medicine into the care of these patients.

## Introduction

End-stage liver disease (ESLD) is a term synonymous with advanced liver disease, liver failure, and decompensated cirrhosis. It is a progressive illness that develops after inflammatory changes in the liver lead to fibrosis and disruption of liver structure and function. The only existing cure is liver transplantation, an option that only a minority of patients will receive. Remaining therapies are palliative in nature. ESLD is a terminal diagnosis, one that may cause symptoms such as pain, fatigue, abdominal pain secondary to ascites, and confusion. Quality of life (QOL) is often negatively impacted by such physical symptoms, as well as by the psychological complications of the illness. In accordance with the relatively poor prognosis, symptom burden, and prevalent mental health issues that ESLD patients face, this group would greatly benefit from improved collaboration between palliative care clinicians, hepatologists, and transplant surgeons. To date, ESLD has received relatively little attention within the palliative care community.

Meanwhile, ESLD is becoming increasingly prevalent in the United States; an estimated 5.5 million people, 2% of the population, are affected. Annually it results in over 2 million clinic visits, 500,000 hospitalizations, and 40,000 deaths.[1–3] These statistics, culled from *International Classification of Disease, 9th edition* (*ICD-9*) codes, likely underestimate the true burden of disease. The most common causes of ESLD in the United States are alcoholic liver disease and hepatitis C. Obesity is associated with a spectrum of liver disease from hepatic steatosis (fatty liver) to more serious liver damage known as nonalcoholic steatohepatitis; both may lead to cirrhosis and ESLD. This problem is on the rise and expected to become the primary reason for liver transplant between 2015 and 2030.[4] Liver transplantation leads to a significant survival advantage but is attainable for a minority of patients. Of the 16,000 patients on the waiting list, 6500 are transplanted annually[5] while 1600 patients will die yearly awaiting transplant. Many more are removed from the waiting list as they become too ill for transplantation.

This article summarizes the available evidence-based literature regarding palliative care and ESLD. A MEDLINE database search was conducted with the subject headings ''end-stage liver disease,'' ''cirrhosis,'' or ''liver transplantation,'' and ''palliative care,'' ''prognosis,'' ''symptom management,'' or ''supportive care.'' Additional studies were located by manual search using references from retrieved articles.

## Patient Experience of ESLD

Patients with ESLD may present in a variety of ways. Commonly, an asymptomatic phase of compensated cirrhosis progresses to portal hypertension followed by decompensation to ESLD. Complications of portal hypertension include ascites, spontaneous bacterial peritonitis, esophageal and gastric varices, hepatic encephalopathy, renal failure, and coagulopathy. Symptoms often include fatigue, abdominal bloating and pain, spontaneous bruising, gastrointestinal bleeding, and confusion.

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### *Symptom experience and QOL*

There are few studies examining the perspective of patients living with ESLD and those undergoing liver transplantation. A Korean questionnaire-based study of 129 cirrhotic patients identified fatigue, abdominal distention, peripheral edema, and muscle cramps as the symptoms most often needing management.[6] One hundred eighty-eight Australian patients with chronic hepatitis C were surveyed and 83% reported 6 or more symptoms in the past 3 months, with physical and mental fatigue, irritability, depression, and abdominal pain being the most frequently reported.[7] The SUPPORT Study reported that 60% of ESLD patients identified experienced pain.[8] This was rated at least moderately severe most of the time in 1 of 3 patients.[9] There is often a discrepancy between patient-reported symptom burden and physician awareness of such symptoms, for example, muscle cramps, which occurred in 52% of 92 cirrhotic patients in a 1996 survey, are not often identified as an issue by physicians.[10]

Multiple questionnaire-based studies have shown a decrease in all aspects of QOL in ESLD patients compared with controls.[11–14] Younger age, muscle cramps, and hepatitis C have each been associated with worse QOL, while disease severity has not been shown to correlate.[12–14] The worse QOL experienced by ESLD patients is comparable to those with advanced chronic obstructive pulmonary disease (COPD) or heart failure. Patients awaiting liver transplant have a perceived QOL similar to those awaiting heart transplantation.[15] In a study of 67 French patients assessed before and after transplant, patients reported fewer disease related symptoms and a lower overall level of distress afterwards. QOL after transplantation approached but did not equal that of the general population.[16]

### *Psychiatric factors*

Psychiatric comorbidities are thought to be quite common in patients with ESLD. An Italian survey of 156 patients with cirrhosis found greater than 50% had a Beck Depression Inventory score indicative of a depressed mood.[17] Those with depression experience more physical symptoms, have worse QOL, and are more likely to die while awaiting transplant. This discrepancy is not explained by illness severity. Similarly to patients with cancer, diagnosing depression may be challenging due to the frequent overlap of somatic symptoms such as fatigue, lethargy, and insomnia. Anxiety is also prevalent, with estimates in pretransplant patients ranging from 27%–44%. A survey of Brazilian patients found 19% to have moderate–severe levels of anxiety, while 27% of those with autoimmune cirrhosis had severe anxiety.[18,19]

### *Prognosis*

Patients with compensated cirrhosis have a median survival of 6–12 years. Decompensation occurs in 5%–7% annually; median survival then declines to 2 years.[20,21] Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores are the most widely used tools for prognostication. CTP uses total bilirubin, albumin, and international normalized ratio (INR) values, as well as the degree of encephalopathy and ascites. Categories A, B, and C indicate increasing severity of liver disease. CTP score was first utilized in prognostication and listing of liver transplant candidates; its use has now been validated in patients with liver disease of varying severity. MELD utilizes INR, bilirubin, and creatinine to predict survival; higher scores reflect more significant liver disease. The United Network for Organ Sharing (UNOS) now uses MELD for allocation of liver transplants. Table 1 shows rates of 6-, 12-, and 24-month survival in ESLD comparing CTP and MELD scores. Clinical judgment, patient comorbidities, rate of decline, and likelihood of transplantation should also affect prognostication in ESLD.[21]

Prognosis in ESLD is comparable to patients with other types of organ failure. Those with heart failure have a 50% 5-year survival; class IV heart failure carries 30%–40% 1-year mortality.[22] Ambulatory COPD patients with the lowest lung function scores have 25% 2-year and 55% 4-year mortality.[23]

Ascites is often the earliest complication of ESLD; when present it indicates 50% 2-year mortality. Median survival is 6 months when ascites becomes refractory. Encephalopathy that is severe or refractory has a 12-month average survival. In an analysis of 178 studies, 30% of ESLD patients with infections died within 30 days, another 30% within 1 year.[24] Renal failure portends the worst outcome; hepatorenal syndrome (HRS) equals a rapid deterioration in kidney function in cirrhotic patients with ascites. Declining liver function is thought to cause changes in renal blood flow and blood vessel tone rather than direct kidney damage. Type 1 HRS is rapidly progressive, with a four-week median survival.[25] Type 2 HRS is more insidious, with a 6-month life expectancy.[26] Figure 1 outlines median survival according to presence of several common ESLD complications.

## Transplantation

The experience of waiting for a transplant impacts patients considerably.[13] Most patients interviewed in qualitative studies experience suffering of a physical and psychological nature. They identify difficulty coping, loss of trust in physicians, and medical, personal, and social uncertainties.[29–31] There is sparse literature on the experience of patients not

Table 1. Survival of End-Stage Liver Disease Patients Based on Child-Turcotte-Pugh/Model for End-Stage Liver Disease Scores

| *CTP score* | *6 months* | *12 months* | *24 months* | *MELD score* | *6 months* | *12 months* | *24 months* |
|---|---|---|---|---|---|---|---|
| Class A | n/a | 95% | 90% | 0–9 | | | |
| Class B | n/a | 80% | 70% | 10–19 | 92% | 86% | 80% |
| | | | | 20–29 | 78% | 71% | 66% |
| Class C | n/a | 45% | 38% | 0–39 | 40% | 37% | 33% |

CTP, Child-Turcotte-Pugh; MELD, Model for End-Stage Liver Disease.

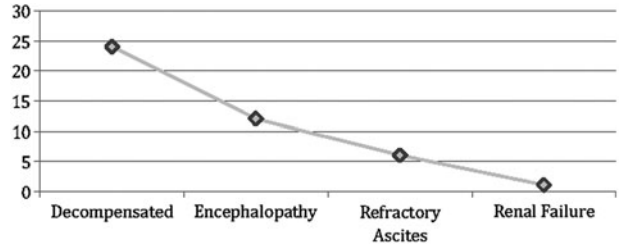


**FIG. 1.** Median survival in months for end-stage liver disease (ESLD) patients.[26]

eligible for transplant. A recent retrospective chart review was performed of 102 patients removed from transplant list or denied listing who were cared for at a single Canadian institution. This study found that while a majority of these patients had symptoms including pain and nausea, only 10% of patients were referred for palliative care consultation, and 28% had documentation of a do-not-resuscitate status (DNR).[32] This highlights the discrepancy between palliative care needs and utilization. Underserved groups that have not had equal listing for transplant, such as women, minorities, and obese patients with comorbidities, may also represent areas of opportunity for palliative care. Substance abuse is prevalent and transplant programs require abstinence before listing. Patients in methadone maintenance programs are at high risk for relapse after transplant.[33] Caring for this population with coexisting substance abuse may be challenging and requires close collaboration among clinicians.

### Symptom Management

Intensive symptom management is an integral role for palliative care in many illnesses. Appropriate medication selection and dosing in ESLD is often difficult. A majority of drugs are metabolized in the liver and liver failure may lead to accumulation of medications or toxic metabolites. Decreased hepatic blood flow leads to slower drug metabolism and higher bioavailability. This amounts to a higher risk of adverse effects and often leads to less aggressive symptom management. Clinical trials routinely exclude patients with liver dysfunction, making it difficult to apply results to ESLD patients. A review of Food and Drug Administration (FDA)-approved medications in 2005 found only 23 medications with recommended dose adjustments for hepatic impairment based on Child-Pugh scores.[34]

ESLD patients report similar pain levels as patients with lung and colon cancer.[9] However, undertreatment of pain is common. No randomized trials or large epidemiologic studies of pain management in ESLD have been conducted, and data is limited to small case series and preclinical data. Physicians may be reluctant to prescribe opioids for those with a history of substance abuse. Opioids may precipitate or worsen hepatic encephalopathy and some sources recommend against using any opioids in patients with a history of encephalopathy. Constipation is a common side effect of opioids and may exacerbate encephalopathy.[35] Despite these limitations, opioids may be required for management of moderate-to-severe pain particularly at the end of life. When utilized, initiation at low doses and slow uptitration of dosing is generally recommended.

Morphine clearance in cirrhotic patients is delayed by 35%–60% in studies utilizing single-dose administration. Administered orally, there is increased bioavailability due to decreased first pass metabolism. Dose reduction and increased dosing intervals are recommended. Morphine should be avoided in patients with concomitant renal dysfunction due to risk of neurotoxicity from accumulation of toxic metabolites. Similarly, oxycodone and hydromorphone have impaired elimination profiles in ESLD. One study of single-dose fentanyl administration in cirrhotic patients did not lead to altered pharmacokinetics. It therefore has been recommended by some to be the opioid of choice in ESLD. Methadone was not shown to have altered kinetics in a study of 14 patients enrolled in methadone maintenance, however, it has not been investigated for use as analgesia in patients with liver impairment.[35–37]

Over-the-counter pain medications are widely used, although guidelines for patients with liver impairment are not available. Short-term use of acetaminophen at a dose of 4 g/d for 13 days showed no adverse effects when given to 20 patients with stable liver disease including 8 with cirrhosis.[38] For longer term use, experts recommend doses no higher than 2–3 g/d.[35] Nonsteroidal anti-inflammatorie drugs (NSAIDs) have many adverse effects including increased risk of renal failure and hepatorenal syndrome due to inhibition of prostaglandins. NSAIDs may also increase risk of mucosal bleeding and interfere with the effect of diuretics, and are therefore best avoided.[36] The controversy over appropriate strategies for pain management in ESLD is an area that palliative care may be able to help reconcile.

Ascites is the most common complication of cirrhosis and most common reason for hospitalization in patients with ESLD; management involves sodium restriction and the use of oral diuretics. Dietary sodium restriction to under 2 g/d and a diuretic regimen of spironolactone and furosemide was shown to be effective in more than 90% of patients in reducing ascites to acceptable levels in a randomized study comparing medical therapy to peritoneovenous shunting in 299 patients.[39] Some patients become refractory to diuretics and require repeated paracenteses or transjugular intrahepatic portosystemic shunting (TIPS). Five meta-analyses on available randomized controlled trials including up 305–330 patients concluded that TIPS led to lower rates of ascites recurrence but higher rates of encephalopathy. One meta-analysis demonstrated a trend toward improved survival and a second showed a survival advantage for TIPS.[40] For patients who do not undergo TIPS, repeated large volume paracenteses are often required. Indwelling peritoneal catheters are sometimes used for patients with malignant ascites, retrospective studies have shown a low median infection rate of 5.9%.[41] However, such catheters are less often used in ESLD because there is a theoretically increased risk of peritonitis. A retrospective review of 12 ESLD patients undergoing catheter placement for refractory ascites yielded a 16% infection rate.[42] The technique of continuous peritoneal drainage of ascites was studied in 40 patients with ESLD and refractory ascites. When limited to 72 hours of drainage, there were no cases of infection seen.[43]

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome ranging from subtle personality or sleep disturbances to confusion and coma. Precipitants include gastrointestinal hemorrhage, infections, renal and electrolyte disturbances,

constipation, and medications, particularly benzodiazepines. Treatment involves correction of underlying causes and the use of medications aimed at decreasing intestinal toxins, particularly ammonia. Nonabsorbable disaccharides such as lactulose have traditionally been the mainstay of treatment. A Cochrane Review of 10 studies of lactulose versus placebo found that only nonrandomized, controlled trials showed a benefit for lactulose in the acute treatment of HE.[44] An open-label randomized controlled trial of lactulose versus placebo for secondary prophylaxis in 140 patients with a history of HE showed a decrease in recurrent HE from 46.8% to 19.6%.[45] Nonabsorbable antibiotics such as rifaximin may also be used for HE. A meta-analysis of 8 studies comparing rifaximin versus nonabsorbable disaccharides showed that rifaximin was at least as efficacious at treating HE, with better results in serum ammonia levels, mental status, asterixis, and improved safety.[46] However, rifaximin is a more costly option, an important consideration in the care of hospice patients.[47]

#### *Advance care planning/social support*

While data are scarce, goals of care and advance care planning seem to be discussed less frequently with ESLD patients compared with cancer patients. In SUPPORT, 66% of ESLD patients preferred cardiopulmonary resuscitation (CPR) when asked about resuscitation status.[9,48] In a separate study conducted at three teaching hospitals, 16% of ESLD patients had DNR orders compared with 47% of patients with metastatic lung cancer. Housestaff were less likely to discuss these issues with ESLD patients despite awareness of their poor prognosis.[49] There is an inherent difficulty in discussing advance directives with patients pursuing curative therapies and DNR orders are often considered controversial for patients awaiting transplantation. Bramstedt,[50] a transplant ethicist, argues that in certain patients with ESLD, resuscitation may be futile and not in a seriously ill patient's best interest. It is imperative to discuss goals of care and identify health care proxy agents promptly, as encephalopathy can impact decision making.

Caregiver support is crucial for transplant candidates and lack of a reliable caregiver may preclude transplant. Qualitative studies reveal that caregiver burden is high, with a significant percentage of both pretransplant and post-transplant patient caregivers reporting decreased QOL, low life satisfaction, and a high amount of caregiving strain.[51] Women caregivers in particular report higher perceived overload and higher levels of depression than men.[52] In a survey of 61 caregivers, there were higher rates of depression and overall burden scores when caring for patients with alcoholic liver disease compared with other etiologies.[53]

### Opportunities for Collaboration between Palliative Care and Liver Transplant Teams

Best practices for the role of palliative care in ESLD patients and transplant candidates have not been defined. The fourth edition of the *Oxford Textbook of Palliative Medicine* contains only three references to liver transplantation and one paragraph on palliative care in liver disease.[54] The Gold Standards Framework in the UK, a guideline for care of patients with end-stage illnesses including cardiac, pulmonary, renal, and neurologic diseases, omits liver disease.[55] In a survey of U.K. gastroenterologists, most had access to palliative care, but less than half referred a patient within the previous 3 months. The most common reasons for referral were end-of-life care and symptom management.[56] Similarly, lung transplant clinicians favor the idea of integrating palliative care after transplantation but few make referrals.[57] Palliative care interest in the liver disease population does seem to be increasing. The recently published book, *Evidence-Based Practice of Palliative Medicine,* contains two chapters on liver disease detailing clinical course, symptomatology and treatment considerations.[58,59]

#### *Upstream integration of palliative care into hepatology and transplant care*

Introduction of palliative care for patients with ESLD and those awaiting transplant can be challenging. Many patients feel well for years after diagnosis and develop symptoms of ESLD abruptly. This allows less time to acquire coping skills needed to face progressive illness and approach the end of life. End-of-life discussions can be difficult as patients often focus their hope on obtaining a life-saving transplant.[60] Many surgical specialists, like other clinicians, may think of palliative care as synonymous with end-of-life care. In 2005, the American College of Surgeons released a statement extending the palliative care needs of surgical patients to include those at all stages of disease.[61] There has been increased support in the transplant community for integration of palliative care as evidenced by this statement in *Surgical Clinics of North America:* ''The fields of transplantation and palliative care have a treasure trove of experience that is lacking in the other that could be exchanged profitably with a great sense of satisfaction for all.''[62] Such a statement suggests an opening in the transplant community to start a dialogue with palliative care specialists.

Currently, palliative and hospice care are offered to patients rarely after removal from the transplant list. This event is often associated with withdrawal of specialty care, feelings of abandonment in patients, and death within a few days, without a chance for end-of-life care to be optimized.[63] A strategy of providing palliative care alongside disease-directed therapy while awaiting transplant has the potential to improve QOL, patient satisfaction and reduce hospital admissions without decreasing chances of transplantation.

Palliative care involvement after transplantation is another topic gaining interest. A recent pilot study assessed early palliative care intervention for patients after liver transplant that required admission to the surgical intensive care unit (SICU). This intervention involved 104 patients and 31 deaths. Goals of care discussions and DNR rates increased, and SICU lengths of stay decreased. There was improved communication and family satisfaction as well as earlier consensus around goals of care without impacting patient mortality.[64]

There are several barriers that may need to be addressed for this integration to be successful. There may be a misunderstanding that palliative care is end-of-life care and education of transplant clinicians is essential. Education of trainees in related fields would also likely increase the involvement of palliative care in the management of ESLD patients.[65,66] Consideration could be given to development of clinical triggers for palliative care consultation such as development

of refractory ascites, spontaneous bacterial peritonitis, or HE that each portend a poor prognosis. Use of certain clinical factors to trigger palliative care consultation has been investigated in many disease groups such as in heart failure, and has been shown in the ICU setting to lead to improved outcomes as noted previously.[66,67]

### *Hospice care*

Few patients with end-stage organ failure are discharged from the hospital with hospice.[68] In 2003, ESLD was the fifth ranking noncancer diagnosis for hospice enrollment, representing 1.6% of patients.[69] Possible reasons for underutilization of hospice include the belief that transplantation and hospice are mutually exclusive, and the lack of referral guidelines. Patients with ESLD are referred late, with an average survival of 29 days compared with overall mean length of hospice stay of 59 days. Late hospice referral puts patients at risk for decreased quality of care at the end of life.[70] Unfortunately, using National Hospice Organization guidelines to identify hospice-eligible ESLD patients did not accurately identify patients who died within 6 months.[68] MELD has been used to estimate 30-day mortality in a cohort of 50 ELSD patients discharged to hospice with moderate correlation between MELD and survival.[71] MELD may therefore be used to estimate 6 month mortality, and hospice eligibility as well. This has not yet been accomplished in practice.

Hospice eligibility for patients on the transplant list remains controversial. Those in support of this approach cite the inability to know which patients will ultimately receive a transplant, that patients at the top of the list have the greatest need for monitoring and preparation for end of life, and that hospice services can provide support to patients and families and improve QOL. Others feel that patients awaiting transplant should not benefit from hospice care since they are pursuing curative therapies, hospice services may not cover expensive treatments these patients often need, and according to Health Care Financing Administration guidelines, more than 80% of care days provided by hospice must be in the home.[72] If patients on the waiting list are to be enrolled on hospice, hospice teams would need to recognize that patients are likely to remain full code and may require hospitalizations for acute decompensation.

A recent retrospective review demonstrates an example of successful comanagement of patients awaiting transplant. In 2000, hepatology and hospice services at UC Davis jointly introduced the concept of comanaging patients. One hundred fifty-seven patients with ESLD were admitted to hospice under this innovative program; of these patients, 122 died. Patients had a mean length of stay of 38 days. Six patients on hospice went on to successful liver transplant, and 4 of these had improvements in MELD scores during this time. The hospice staff was successfully trained to manage complicated symptoms at home.[73,74] In this group, average MELD score at time of hospice admission was 21 and almost all patients with MELD over 18 died within several months. This study highlights that only 5% of the listed patients in this program actually went on to transplant.

### *Areas for further research*

Palliative care clinicians should aim to assist in better defining the needs and expectations of ESLD patients and assist in development of appropriate symptom management strategies.[73] Identification of potential triggers for palliative care consultations and hospice referrals is another opportunity to improve care of these patients. Finally, even when patients do make it to transplantation, many are left with a new set of chronic issues and will face mortality once again. Early involvement of palliative care in the management of patients pretransplant would thus provide continuity posttransplantation and may lead to improved outcomes for patients and families. Early integration of palliative care may also lead to improvement in symptoms and QOL, and potentially improve a patient's chance at transplantation.

## Summary

Patients with ESLD have significant palliative care needs in regards to physical symptoms and psychosocial aspects of care. These needs are often unrecognized among caregivers and subsequently unmet. High-quality data addressing many palliative care treatment aspects in ESLD are lacking. This patient population represents a unique opportunity for further research, education, and collaboration between palliative care clinicians and transplant providers. Integration of care between these groups will hopefully lead to significant benefit among patients, caregivers, and transplant teams.

## Author Disclosure Statement

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## References

1. Shaheen NJ, Hansen RA: The burden of gastrointestinal and liver disease, 2006. Am J Gastroenterol 2006;101:2128–2138.
2. Everhart JE. Ch. 21: Liver Disease. In: Everhart JE (ed): *The Burden of Digestive Diseases in the United States.* Washington, D.C.: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. US Government Printing Office, NIH Publication No. 09-6443, 2008, pp. 111–114.
3. Centers for Disease Control: National Center for Health Statistics. Fast Stats. www.cdc.gov/nchs/fastats/liverdis.htm (Last accessed June 8, 2010).
4. Charlton M: Nonalcoholic fatty liver disease: A review of current understanding and future impact. Clin Gastroenterol Hepatol 2004;2:1048–1058.
5. Freeman Jr RB, Steffick DE: Liver and intestine transplantation in the United States, 1997–2006. Am J Transplant 2008;8:958–976.
6. Kim SH, Oh EG: Symptom experience in Korean patients with liver cirrhosis. J Pain Symptom Manage 2006;31:326–334.
7. Lang CA, Conrad S: Symptom prevalence and clustering of symptoms in people living with chronic Hepatitis C infection. J Pain Symptom Manage 2006;31:335–344.
8. Desbiens NA, Wu AW: Pain and satisfaction with pain control in seriously ill hospitalized patients: Findings from SUPPORT research investigators. Crit Care Med 1996;24: 1957–1961.
9. Roth K, Lynn J: Dying with end stage liver disease with cirrhosis: Insights from SUPPORT. J Am Geriatr Soc 2000; 28:S122–130.
10. Abrams GA, Concato J: Muscle cramps in patients with cirrhosis. Am J Gastroenterol 1996;91:1363–1366.

11. Younossi ZM, McCormick M: Impact of liver transplantation on health-related quality of life. Liver Transpl 2000;6:779–783.
12. Saab S, Ibrahim AB: MELD fails to measure quality of life in liver transplant candidates. Liver Transpl 2005;11:218–223.
13. Kanwal F, Hays RD: Are physician-derived disease severity indices associated with health-related quality of life in patients with end-stage liver disease? Am J Gastroenterol 2004;99:1726–1732.
14. Marchesini G, Bianchi G: Factors associated with poor health-related quality of life of patients with cirrhosis. Gastroenterology 2001;120:170–178.
15. Diaz-Dominguez R, Perez-Bernal J: Quality of life in patients with kidney, liver, or heart failure during the waiting list period. Transplantation Proc 2006;38:2459–2461.
16. Karam V, Castaing D: Longitudinal prospective evaluation of quality of life in adult patients before and one year after liver transplantation. Liver Transpl 2003;9:703–711.
17. Bianchi G, Marchesini G: Psychological status and depression in patients with liver cirrhosis. Dig Liver Dis 2005;37:593–600.
18. Singh N, Gayowski T: Depression in patients with cirrhosis: Impact on outcome. Dig Dis Sci 1997;42:1421–1427.
19. Santos GR, Boin IF: Anxiety levels observed in candidates for liver transplantation. Transplant Proc 2010;42:513–516.
20. D'Amico G, Garcia-Tsao G: Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol 2006;44:217–231.
21. Dolan B, Arnold R: Prognosis in decompensated chronic liver failure. Fast Facts and Concepts. September 2007;189. www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_189.htm (Last accessed March 31, 2014).
22. Reisfield GM, Wilson GR: Prognostication in heart failure. Fast Facts and Concepts. October 2005;143. www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_143.htm (Last accessed March 31, 2014).
23. Childers JW, Arnold R: Prognosis in end-stage COPD. Fasts Facts and Concepts. August 2005;141. www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_141.htm (Last accessed March 31, 2014).
24. Arvaniti V, D'Amico G: Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010;139:1246–1256.
25. Gines A, Escorsell A: Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229–236.
26. Sanchez W, Talwalkar JA: Palliative care for patients with end-stage liver disease ineligible for liver transplantation. Gastroenterol Clin North Am 2006;35:201–219.
27. Cardenas A, Gines P: Management of complications of cirrhosis in patients awaiting liver transplantation. J Hepatol 2005;42:S124–133.
28. Roberts MS, Angus DC: Survival after liver transplantation in the United States: A disease specific analysis of the UNOS database. Liver Transpl 2004;10:886–897.
29. Bjork IT, Naden D: Patients' experiences of waiting for a liver transplantation. Nurs Inq 2008;15:289–298.
30. Brown J, Sorrell JH: Waiting for a liver transplant. Qual Health Res 2006;16:119–136.
31. Martin SC, Stone AM: Medical, personal, and social forms of uncertainty across the transplantation trajectory. Qual Health Res 2010;20:182–196.
32. Poonja Z, Brisebois A: Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. Clin Gastroenterol Hepatol 2014;12:692–698.
33. Koch M, Banys P: Liver transplantation and opioid dependence. JAMA 2001;285:1056–1058.
34. Spray JW, Willett K: Dosage adjustment for hepatic dysfunction based on Child-Pugh scores. Am J Health Syst Pharm 2007;64:690–693.
35. Chandok N, Watt KD: Pain management in the cirrhotic patient: The clinical challenge. Mayo Clin Proc 2010;85:451–458.
36. Rhee C, Broadbent AM: Palliation and liver failure: Palliative medications dosage guidelines. J Palliat Med 2007;10:677–685.
37. Verbeeck, RK: Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008;64:1147–1161.
38. Benson GD, Koff RS: The therapeutic use of acetaminophen in patients with liver disease. Am J Ther 2005;12:133–141.
39. Stanley MM, Ochi S: Peritoneovenous shunting as compared with medical treatment in patients with alcoholic cirrhosis and massive ascites. Veterans Administration Cooperative Study on Treatment of Alcoholic Cirrhosis with Ascites. N Engl J Med 1989;321:1632–1638.
40. Gines P: EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53:397–417.
41. Fleming ND, Alvarez-Secord A: Indwelling catheters for the management of refractory malignant ascites: A systematic literature overview and retrospective chart review. J Pain Symptom Manage 2009;38:341–349.
42. Kundu S, Bettman MA: The safety and efficacy of tunneled, indwelling peritoneal catheter drainage for refractory, non-malignant ascites. Program No. P1337. ACG 2012 Annual Scientific Meeting Abstracts. American College of Gastroenterology. Las Vegas, NV.
43. Van Thiel DH, Moore CM: Continuous peritoneal drainage of large-volume ascites. Dig Dis Sci 2011;56:2723–2727.
44. Als-Nielsen B, Gluud LL: Non-absorbable disaccharides for hepatic encephalopathy: Systematic review of randomised trials. BMJ 2004;328:1046.
45. Sharma BC, Sharma P: Secondary prophylaxis of hepatic encephalopathy: An open-label randomized controlled trial of lactulose versus placebo. Gastroenterology 2009;137:885–891.
46. Wu D, Wu SM: Rifaximin versus nonabsorbable disaccharides for the treatment of hepatic encephalopathy: A meta-analysis. Gastroenterol Res Pract 2013;2013:236963. doi: 10.1155/2013/236963. Epub 2013 Apr 3.
47. Childers JW, Arnold R: Hepatic encephalopathy in ESLD. Fast Facts and Concepts. September 2007;188. www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_188.htm (Last accessed August 16, 2011).
48. Freeborne N, Lynn J: Insights about dying from the SUPPORT project. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. J Am Geriatr Soc 2000;48:S199–205.
49. Wachter RM, Luce JM: Decisions about resuscitation: inequities among patients with different disease but similar prognoses. Ann Intern Med 1989;111:525–532.
50. Bramstedt KA: Hoping for a miracle: Supporting patients in transplantation and cardiac assist programs. Curr Opin Support Palliat Care 2008;2:252–255.
51. Rodrigue JR, Dimitri N: Quality of life and psychosocial functioning of spouse/partner caregivers before and after liver transplantation. Clin Transplant 2011;25:239–247.

52. Cohen M, Katz D: Stress among the family caregivers of liver transplant recipients. Prog Transplant 2007;17:48–53.
53. Miyazaki ET, Dos Santos R JR: Patients on waiting list for liver transplantation: caregiver burden and stress. Liver Transpl 2010;16:1164–1168.
54. Hanks G, Cherny N, Christakis N (eds): *Oxford Textbook of Palliative Medicine, 4th ed.* New York: Oxford University Press, 2009.
55. Prognostic indicator guidance to aid identification of adult patients with advanced disease, in the last months/year of life, who are in need of supportive and palliative care. Royal College of General Practioners; Gold Standards Framework, PIP 2.24, 2006. www.goldstandardsframework.org.uk (Last accessed June 10, 2010).
56. Kitching M: Physicians' Perceptions of the Palliative Care Needs of Patients with Chronic Liver Disease. Powerpoint. Bolton Research Forum in Health & Wellbeing Conference, 2007.
57. Song MK, Devito Dabbs A: Palliative care referrals after lung transplantation in major transplant centers in the United States. Crit Care Med 2009;37:1288–1292.
58. Hope AA, Morrison RS: ''Advanced Liver Disease, Chapters 53 & 54'' Evidence-Based Practice of Palliative Medicine.
59. Goldstein NE, Morrison RS (eds). Elsevier Saunders, Philadelphia, PA 2012. 300–311.
60. Larson AM, Curtis JR: Integrating palliative care for liver transplant candidates: ''Too well for transplant, too sick for life.'' JAMA 2006;295:2168–2176.
61. American College of Surgeons Committee on Ethics and Task Force on Surgical Palliative Care: Statement on principles of palliative care. www.facs.org/fellows_info/statements/st-50.html (Last accessed June 8, 2010).
62. Molmenti EP, Dunn GP: Transplantation and palliative care: The convergence of two seemingly opposite realities. Surg Clin North Am 2005;85:373–382.
63. Rossaro L, Troppmann C: A strategy for the simultaneous provision of pre-operative palliative care for patients awaiting liver transplantation. Transpl Int 2004;17:473–475.
64. Lamba S, Murphy P: Changing end-of-life care practice for liver transplant service patients: Structured palliative care intervention in the surgical intensive care unit. J Pain Symptom Manage 2012;44:508–519.
65. Adler ED, Goldfinger JZ: Palliative care in the treatment of advanced heart failure. Circulation 2009;120:2597–2606.
66. Stuart B: Palliative care and hospice in advanced heart failure. J Palliat Med 2007;10:210–228.
67. Toevs C: Palliative medicine in the surgical intensive care unit and trauma. Surg Clin North Am 2011;91:325–331.
68. Fox E, Landrum-McNiff K: Evaluation of prognostic criteria for determining hospice eligibility in patients with advanced lung, heart, or liver disease. SUPPORT investigators. JAMA 1999;282:1638–1645.
69. Hospice Facts and Figures. Arlington, VA: National Hospice and Palliative Care Organization, 2003.
70. Christakis NA, Escarce JJ: Survival of Medicare patients after enrollment in hospice programs. N Engl J Med 1996;335:172–178.
71. Antaki F, Lukowski A: The model for end-stage liver disease (MELD) predicts survival of liver cirrhosis patients after discharge to hospice. J Clin Gastroenterol 2007;41:412–415.
72. Abrahm JL, Hansen-Flaschen J: Hospice care for patients with advanced lung disease. Chest 2002;121:220–229.
73. Medici V, Rossaro L: The utility of the model for end-stage liver disease score: a reliable guide for liver transplant candidacy and, for select patients, simultaneous hospice referral. Liver Transpl 2008;14:1100–1106.
74. Iredale J: End-stage chronic liver disease: Time to define a good death. Hepatology June 2008;47:1799–1800.

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