Brief Quality Improvement Report

Benefit of Early Palliative Care Intervention in End-Stage Liver Disease Patients Awaiting Liver Transplantation

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Abstract

Background. Patients with end-stage liver disease have a predictable and progressive decline in their quality of life because of physical symptoms and psychological distress. Early palliative care intervention (EPCI) correlates with better symptom control and mood. We aimed to improve symptomatology and mood in liver transplant candidates by implementing a longitudinal multidisciplinary EPCI.

Measures. Depression level and symptom burden were assessed with Center for Epidemiological Studies Depression Scale and a modified liver-specific Edmonton Symptom Assessment System scale.

Intervention. All patients referred for liver transplant evaluation between July 2013 and May 2014 were scheduled for EPCI.

Outcomes. After EPCI, 50% of moderate-to-severe symptoms improved ($P < 0.05$), and 43% of patients showed improvement in clinically significant depressive symptoms ($P = 0.003$). Notably, patients with more symptoms showed a greater improvement in Center for Epidemiological Studies Depression Scale scores ($P = 0.001$).

Conclusions/Lessons Learned. Implementation of EPCI improved symptom burden and mood in end-stage liver disease patients awaiting transplant. J Pain Symptom Manage 2015;50:882–886 © 2015 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

Key Words
End-stage liver disease, cirrhosis, liver transplant, early palliative care intervention, ESAS, CES-D

Background

End-stage liver disease (ESLD) is associated with high morbidity and mortality, and orthotopic liver transplantation is the only cure. The number of individuals awaiting liver transplantation continues to rise, whereas cadaver donation rates remain stable,$^1$ creating a shortage of available organs and longer wait times for transplantation. While awaiting transplant, ESLD patients suffer from somatic ailments (e.g., muscle cramps) and psychological distress (depression, anxiety, and alexithymia) that significantly decrease their quality of life.$^2,3$ Furthermore, these physical and psychological symptoms progressively worsen with time as the severity of their liver disease increases.$^4$ Irrespective of their worsening condition and high mortality, ESLD patients rarely have end-of-life care addressed, and despite having a similar illness severity and prognosis, are much less likely to have do-not-resuscitate orders when compared with lung cancer patients.$^5$ The current standard of care is primarily focused on getting ESLD patients to transplant, and consequently, it often fails to adequately address these additional needs.

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Despite clear evidence that palliative care improves symptom burden and quality of life in other terminal illnesses, referral of ESLD patients to palliative care specialists is rare and delayed until the very end of life. Only 10% of patients removed from liver transplant waiting lists received palliative care despite their uncontrolled symptoms. We can assume that even less receive palliative care while awaiting transplant. It is likely that early palliative care would provide great benefit for symptom burden, depression level, and quality of life in the ESLD population. Therefore, we implemented a longitudinal, multidisciplinary, and early palliative care intervention (EPCI) with ESLD patients awaiting liver transplant. The aim of this intervention was to determine if EPCI would reduce the symptom burden and depressive symptoms associated with ESLD.

**Measures**

Formal assessment of patients’ symptom burden was conducted using an Edmonton Symptom Assessment System (ESAS) scale, modified to better assess symptomatology specific to ESLD. This liver-specific ESAS had patients evaluate 10 symptoms (pain, fatigue, myalgia, sexual dysfunction, anxiety, sleep disturbance, appetite, well-being, dyspnea, and pruritus) on a 10-point scale (Supplementary Fig. 1, available at jpsmjournal.com). Individual symptom scores greater than 5 were considered moderate to severe. Improvement of each moderate-to-severe symptom was evaluated using a paired t-test.

Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (CES-D). The CES-D is a 20-item assessment of patient mood, with scores ranging from 0 to 60, and a score of greater than 15 indicating clinically significant depressive symptoms. Change in CES-D scores of patients with initial scores greater than 15 was compared using a paired t-test. Change in CES-D scores stratified by symptom burden was compared using a repeated-measures two-way analysis of variance. A change of seven points or more in CES-D scores was considered clinically significant.

**Intervention**

Between July 1, 2013 and May 1, 2014, EPCI was incorporated into the standard one-week pretransplant evaluation process at the Liver Transplantation Center of Albert Einstein Medical Center in Philadelphia. EPCI consisted of outpatient consultation with a nurse coordinator and one board-certified palliative care physician. Patients first met briefly with the nurse coordinator and completed the CES-D and ESAS assessment tools. For patients who were illiterate, the nurse coordinator transcribed their verbal answers to the necessary forms. Palliative care sessions evaluated the whole patient as outlined by the National Consensus Project for Quality Palliative Care. In addition to reviewing the formal assessments of patient depression and liver-specific symptomatology, the provider discussed other symptoms, psychosocial well-being, and spiritual health. If patients needed specialty care, they were referred to the appropriate resource (psychiatry, chaplaincy, etc.) and provided assistance in care coordination. The palliative care encounter followed the hepatology visit and allowed the patient to address fears and concerns about their hepatology treatment plan. Finally, goals of care were introduced and discussed with patients and families. When established by the patient, the health care power of attorney (HCPOA) was documented in the medical record. In addition, advance directive documents were explained and provided to the patients.

At a subsequent visit (on average, three to six months later), the two formal assessments were repeated. Patients who failed to appear at their follow-up appointment were contacted by phone and administered the questionnaires. The nurse coordinator was available in person or by phone to provide any clarification about the survey. Patient-completed advance directives were kept in the patient charts. Patients were studied until transplanted, delisted, death, or conclusion of the study in October 2014.

**Outcomes**

During the study period, 79 patients were referred for liver transplant evaluation. Of these patients, 29 (36.7%) were deemed not appropriate for transplant or failed to complete the transplant evaluation. The remaining 50 (63.3%) patients completed the transplant evaluation including EPCI. Subsequently, 29 of 50 patients completed follow-up assessments within six months, and one patient completed his second assessment after one year. Of the 20 (40.0%) patients who did not complete follow-up assessments, six were transplanted, six were delisted or critically ill, and three expired. Only five patients (10.0%) of the initial cohort were lost to follow-up. There were no significant differences in the demographics, etiologies of cirrhosis, Model for End-Stage Liver Disease (MELD) scores, or hepatocellular carcinoma rates between those who completed just the initial assessment and those who completed both assessments (Table 1). There was also no significant difference between initial clinically significant CES-D scores or initial number of moderate-to-severe liver-specific ESAS symptoms between the two groups.
At the initial palliative care assessment, 23 of 30 (76.6%) patients experienced at least one moderate-to-severe symptom (ESAS individual symptom score >5), and on average, each of these patients suffered from 4.7 distressing symptoms. Fatigue, sleep disturbance, and pruritus were the most common symptoms, whereas dyspnea and myalgia were the least. After EPCI, 50% of these initial moderate-to-severe symptoms significantly improved (pruritus, well-being, appetite, anxiety, and fatigue; Fig. 1a). Pruritus, anxiety, and appetite improved by more than three points in 13, 10, and 9 patients, respectively. Fatigue and well-being had a more modest, yet statistically significant, change (1.79 and 1.96 points, respectively). Pain, myalgia, sexual dysfunction, sleep disturbance, and dyspnea improved after EPCI but did not reach statistical significance.

### Depressive Symptoms Improved After EPCI and Correlated with Overall Symptom Burden

Thirteen of the 30 patients had clinically significant depressive symptoms on initial assessment (CES-D score >15). There was no apparent correlation between the initial CES-D scores and etiologies of cirrhosis or MELD scores ($R^2 = 0.016, P = 0.664$). Interestingly, only three patients were receiving pharmacologic treatment for their depression on initiation.

<table>
<thead>
<tr>
<th>Improvement in Symptomatology After EPCI</th>
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#### Table 1

<table>
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<tr>
<th>Patient Demographics: Initial Assessment vs. Initial and Follow-Up Assessments</th>
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<tr>
<td>Demographics</td>
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<tr>
<td>Age, mean ± SD</td>
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<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Etiology, n (%)</td>
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<tr>
<td>MELD score, mean ± SD</td>
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<td>Clinically significant CES-D score, n (%)</td>
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<td>At least one moderate-to-severe liver-specific ESAS symptom, n (%)</td>
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<td>Average number of moderate-to-severe liver-specific ESAS symptoms</td>
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NASH = nonalcoholic steatohepatitis; MELD = Model for End-Stage Liver Disease; CES-D = Center for Epidemiological Studies Depression Scale; ESAS = Edmonton Symptom Assessment System.

All data presented as N (%) unless otherwise indicated.

*Other etiologies include primary biliary cirrhosis, primary sclerosing cholangitis, granulomatous, alpha (1)-antitrypsin deficiency, and hemochromatosis.

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Fig. 1. EPCI improves depressive symptoms by minimizing symptom burden. a) EPCI significantly improved five symptoms (pruritus, well-being, appetite, anxiety, and fatigue) with the remaining five symptoms trending toward significance. Error bars represent 95% CI. Square size is proportional to number of patients with initial Edmonton Symptom Assessment System individual symptom score >5 for that symptom. b) EPCI lessened clinically significant depressive symptoms (CES-D >15). c) Patients with higher symptom burden not only had greater depressive symptoms but also showed significant improvement in their depressive symptoms after EPCI. Bar graphs represent mean ± SEM. EPCI = early palliative care intervention; CES-D = Center for Epidemiological Studies Depression Scale.
of the study. After EPCI, the mean CES-D score for patients with significant depressive symptoms improved by 27.8% (7.57 points, \(P = 0.003\); Fig. 1b). Furthermore, there was no correlation between change in CES-D scores and MELD scores (\(R^2 = 0.253, \ P = 0.086\)). Of note, all patients underwent psychiatric evaluation during transplant workup; however, there was no increase in use of antidepressants during the study period.

To further investigate the improvement in CES-D scores after EPCI, a secondary analysis of all patients grouped by number of moderate-to-severe symptoms was performed. Patients with only a few (0–1) distressing symptoms on the modified ESAS had no improvement in mean CES-D scores after EPCI (Fig. 1c). Patients with two to five symptoms showed a 4.5-point improvement in CES-D scores but did not reach statistical significance. Patients with greater than five symptoms showed a dramatic 8.89-point improvement in CES-D scores (\(P < 0.01\)).

**Documentation of HCPOA and Advance Directives**

During the initial EPCI session, 27 (90.0%) patients received HCPOA counseling. Of those, 15 patients (55.6%) established HCPOAs that were documented in the medical record. No patients had advance directives documented in their charts at the onset of the study; however five of the 30 patients (17%) had documented advance directives on completion of the study.

**Conclusions/Lessons Learned**

This is the first description that we are aware of that describes the effects of EPCI on symptom burden and depression level in ESLD patients. We used both a novel assessment tool for liver-specific symptomatology and a well-established survey for depressive symptoms. We demonstrated that EPCI counters the progressive worsening of ailing symptoms and specifically improved pruritus, well-being, appetite, anxiety, and fatigue. Palliative care intervention also decreased depression, likely by alleviating distressing symptoms. Unfortunately, the intervention did not increase documentation of advance directives on study completion.

Palliative care in ESLD may be underused, in part, because of the lack of available measures by which to assess distressing symptoms in liver patients. The well-established Chronic Liver Disease Questionnaire\(^2\) successfully evaluates a patient’s quality of life but does not identify specific treatable symptoms. We chose to create a modified liver-specific ESAS as a tool to better identify liver-specific symptomatology. This measure is useful in conjunction with a depression survey like CES-D, as symptom burden and mood disturbance are interrelated. This also may reveal subclinical levels of depression, not meeting major depression criteria, which can be further addressed. In the future, the modified liver-specific ESAS can be extrapolated to additional studies in the ESLD population and be used alongside a depression survey to better assess physical and psychological symptom burden.

In this quality improvement project, most patients referred for liver transplant evaluation underwent EPCI. By bundling palliative care consultation with other transplant appointments, palliative care was made more accessible. After the initial visit, only 10% were lost to follow-up, likely secondary to our patient-centric treatment model. The modified liver-specific ESAS contributed to this patient-centered approach to addressing symptom burden and helped incentivize patients to complete follow-up assessments.

Prior observation has demonstrated that depression correlates with liver disease severity;\(^4\) however, CES-D scores did not correlate with MELD scores in our cohort. Although this may be a result of the assessment tools used (Psychological General Well-Being Index and Child-Pugh scores vs. CES-D and MELD scores, respectively), it is likely that depression level is also proportional to a patient’s symptom burden, which worsens with progression of liver disease. Conventionally, depression is managed by antidepressants. This may be appropriate for major depressive disorder; however, we suggest that patients with subclinical to mild depression are better managed initially by symptom control. We found that when patients are grouped by their symptom burden, those with more symptoms demonstrate greater improvement in objective markers of depressive symptomatology after EPCI. Although depressive symptoms may not be clinically significant for all patients, it is clear that there is significant correlation between symptom burden and the ability to improve depression. Understanding this relationship will help clinicians better palliate this population.

Although EPCI improved both symptoms and depression scores, it did not significantly increase rates of advance directive documentation. This is starkly different from EPCI in the surgical intensive care unit and oncology settings where EPCI increased family goals of care consensus and advance directive documentation, respectively.\(^10,11\) We hypothesize that the differences are the result of the perceived prognosis. Unlike patients with metastatic lung cancer or those receiving intensive care, patients undergoing outpatient liver transplant evaluation have a more optimistic attitude regarding their prognosis. They are less likely to accept the tentative nature of their disease and address end-of-life issues. A second
difference between the studies was the location of the patient population. In Pennsylvania, health care practitioners are not able to witness advance directives, which forces patients to complete them without the input of the palliative care team or other health care providers. Patients were less resistant to designating an HCPOA to help them with medical decision making, and HCPOA documentation was achieved in more than half of the patients. This documentation is arguably more essential to liver transplant candidates, given the tenuous nature of their condition.

This intervention was designed as a quality improvement project to better address patient symptoms and mood, which may not be optimally treated by the standard of care. As such, it has a small sample size with a limited number of follow-up visits. Given the limited follow-up, it is unclear whether the improvement in symptomatology and depression will persist with time. In addition, future studies are needed to address whether the improvements are a result of EPCI alone or are confounded by other factors such as early establishment of care and hope for transplant. Another flaw of the study was the lack of spiritual health evaluation as a component of depression, which could alter the patient’s perception of disease. Longer follow-up periods also would be useful to determine whether EPCI in ESLD patients is associated with a survival benefit as it has been for other diseases.\(^{19}\)

Most often, referral to palliative care is reserved for ESLD patients who have decompensated to a point where they are no longer transplant candidates. This study clearly shows that palliative care intervention is beneficial early on in the care of liver disease patients awaiting transplant.

**Disclosures and Acknowledgments**

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**References**


Appendix

Einstein Hepatology- Palliative Care Program
Edmonton Symptom Assessment System (ESAS)

Please circle the number that best describes:

No Pain 0 1 2 3 4 5 6 7 8 9 10 Worst possible pain

Not tired 0 1 2 3 4 5 6 7 8 9 10 Worst possible tiredness

No muscle cramps 0 1 2 3 4 5 6 7 8 9 10 Worst possible

Normal sexual function 0 1 2 3 4 5 6 7 8 9 10 Worst sexual function

Not anxious 0 1 2 3 4 5 6 7 8 9 10 Worst possible anxiety

Normal Sleep 0 1 2 3 4 5 6 7 8 9 10 Severe Insomnia

Best appetite 0 1 2 3 4 5 6 7 8 9 10 Worst possible appetite

Best feeling of wellbeing 0 1 2 3 4 5 6 7 8 9 10 Worst possible feeling of Wellbeing

No shortness of breath 0 1 2 3 4 5 6 7 8 9 10 Worst possible shortness of breath

No Itching 0 1 2 3 4 5 6 7 8 9 10 Constant Itching

Patient’s Name: ____________________________ Complete by (check one)

Date: ____________________________ Time: ______________

☐ Patient
☐ Caregiver
☐ Caregiver assisted

Use the Body Diagram on the next page to indicate location of pain and cramps.
Einstein Hepatology- Palliative Care Program
Edmonton Symptom Assessment System (ESAS)

Please mark on these pictures where it is you hurt.