



An update of palliative care in lung transplantation with a focus on symptoms, quality of life and functional outcomes

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Purpose of review

Palliative care (PC) in lung transplantation is increasingly acknowledged for its important role in addressing symptoms, enhancing functionality, and facilitating advance care planning for patients, families, and caregivers. The present review provides an update in PC management in lung transplantation.

Recent findings

Research confirms the effectiveness of PC for patients with advanced lung disease who are undergoing transplantation, showing improvements in symptoms and reduced healthcare utilization. Assessment tools and patient-reported outcome measures for PC are commonly used in lung transplant candidates, revealing discrepancies between symptom severity and objective measures such as exercise capacity. The use of opioids to manage dyspnea and cough in the pretransplant period is deemed safe and does not heighten risks posttransplantation. However, the integration of PC support in managing symptoms and chronic allograft dysfunction in the posttransplant period has not been as well described.

Summary

Palliative care support should be provided in the pretransplant and select peri-operative and posttransplant periods to help support patient quality of life, symptoms, communication and daily function.

Keywords

dyspnea, lung transplantation, opioids, palliative care, quality of life

INTRODUCTION

Lung transplantation (LTx) is an established modality for advanced lung disease that is known to improve health-related quality of life (HRQL), exercise tolerance, and survival [1^a,2]. There have been over 70 000 LTx performed globally over the last three decades with approximately 4500 LTx performed annually [3]. With advances in surgical and medical techniques, the procedure is being undertaken in older individuals and those with increased comorbidities [4]. The most recent consensus document on the selection of LTx candidates suggests that a referral to palliative care (PC) be made to “provide decision support and treatment selection that is consistent with goals of care throughout the transplant evaluation, listing, surgery and posttransplant” periods [2].

The importance of PC in LTx has been highlighted by the American Thoracic Society and American College of Chest Physicians in adopting a comprehensive and holistic approach to improving

symptoms, HRQL and function in patients awaiting LTx [5,6]. Literature suggests increased utilization of PC support in settings such as hospital admissions, those requiring bridging to transplantation, and retransplants [7^a]. Moreover, PC provides an opportunity to increase communication and support for patients and their caregivers during the transplant

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KEY POINTS

- Palliative care (PC) plays an important role in supporting lung transplant programs and aiding their patients through symptom management, enhancing patient function, and providing crucial support to families and caregivers.
- Existing literature underscores the efficacy of integrating PC into the treatment of patients with advanced lung disease undergoing transplantation, showing improvements in symptoms and reductions in healthcare utilization.
- A range of validated assessment tools and patient-reported outcome measures in PC offer valuable support for clinical practice, research endeavors, and initiatives aimed at enhancing quality of care.
- Opioids have emerged as a safe option for effectively managing dyspnea and cough pretransplantation, without increasing posttransplant morbidity or mortality.
- Further investigation is warranted within lung transplant populations, with a specific focus on assessing the impact of PC on patient function, exercise capacity, and posttransplant settings.

process. A recent review in early 2022 highlights the benefits of PC in LTx [7¹¹].

The present narrative review was undertaken to provide an update of PC support in LTx with a focus on recent developments in the last 18 months. This review first addresses symptoms and HRQL in LTx candidates and recipients that may be amenable to PC support, then reviews PC measurement tools, and provides evidence for the benefits of PC for patients with advanced lung disease and LTx. Further, several PC models of care are proposed and considerations for future directions for PC management in LTx are provided.

SYMPTOMS, HEALTH-RELATED QUALITY OF LIFE AND CLINICAL OUTCOMES: OPPORTUNITIES FOR PALLIATIVE CARE SUPPORT

Palliative care support in the pre, peri-operative and posttransplant periods is recognized as an important source of support in managing patient symptoms and HRQL. This section highlights some of the benefits of PC support on symptoms, HRQL, function and clinical outcomes.

ADVANCED LUNG DISEASE

PC has emerged as a valuable intervention in addressing the complex needs of patients with

advanced lung disease. These patients have several distressing symptoms including breathlessness, fatigue, pain, anxiety, and depression, which can significantly diminish their HRQL [8,9]. However, a growing body of evidence has shown PC in both interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) is associated with a reduced risk of hospital admissions, emergency room visits, and hospital duration [10¹²,11¹²,12¹²,13]. Moreover, several studies highlight significant relief of dyspnea following PC [14,15], often the most burdensome symptom in this population [16]. A randomized controlled trial reported that PC moderated the progression of dyspnea in ILD patients, with those receiving PC experiencing a slower progression of dyspnea over 12 months compared to patients receiving usual care [17¹²]. Furthermore, the lack of a significant improvement in symptoms or overall HRQL observed in some PC studies is important to recognize, particularly given the known progression of symptoms in advanced lung disease [11¹²,17¹²,18,19¹²]. Thus, the emerging body of evidence for efficacy of PC in managing the needs of individuals with advanced lung disease highlights its potential for enhancing care in these patients who are often referred for LTx evaluation [2].

LUNG TRANSPLANT CANDIDATES

Lung transplant candidates experience significant symptoms while awaiting transplantation. In a study from our center by Minuk *et al.* [20¹²] the most common symptoms were dyspnea, cough and fatigue observed in both COPD and ILD LTx candidates. ILD candidates had similar symptom scores compared to patients with COPD on all domains of the Edmonton Symptom Assessment Score (ESAS), apart from greater cough symptoms. The ESAS is a scale that evaluates 12 common symptoms domains (i.e. cough, dyspnea, fatigue, etc) with each domain scored on a scale from 0 (no symptoms) to 10 (worse symptoms) [11¹²,20¹²], as shown in Table 1. Furthermore, symptoms assessed with the ESAS were not correlated with the trajectory of exercise capacity, oxygen requirements or respiratory exacerbations pre-LTx while participating in pulmonary rehabilitation [20¹²]. This highlights the potential contribution of PC support in attenuating symptoms in the setting of disease progression while awaiting transplantation.

LUNG TRANSPLANT RECIPIENTS

The majority of LTx recipients have significant improvements in HRQL and psychological well being that are comparable to population normative

Table 1. Patient reported outcome measures applied in chronic lung disease and lung transplant palliative care studies

Instrument	Domains	Items	Scoring	Population and references
<u>HRQL</u> Chronic Respiratory Disease Questionnaire	Dyspnea (breathlessness), fatigue, emotional function, and mastery (control over disease).	20 items, 4–7 items per domain	7-point Likert scale, where higher scores reflect a better quality of life.	PC – COPD [60 [■] ,61]
EuroQol 5-Dimension 5-level	Mobility, self-care, usual activities, pain/discomfort, and anxiety or depression.	5 items	Each dimension is rated on a 5-point Likert scale, where higher scores signify more severe difficulties.	PC - Advanced Lung Disease [60 [■]]
Functional Assessment of Chronic Illness Therapy-Palliative Care	Physical, social/family, emotional, and functional well being, along with additional concerns specific to PC	46 items 2 subscales: 27 item Functional Assessment of Cancer Therapy 19 item Palliative Care Subscale	Total scores range from 0 to 184; higher scores reflect a better quality of life	PC – COPD [36 [■]]
Short Form - 12	Physical functioning, role physical, role emotional, bodily pain, general health, vitality, social functioning, and mental health	12 items	0 to 100 range; higher scores indicate better HRQL	PC - LTx candidates [17 [■]]
St. George's Respiratory Questionnaire	Respiratory symptoms, activity limitations, impacts and total score.	50 items	0 to 100 total score range; higher scores indicate worse HRQL	PC - COPD [11 [■]], ILD [24 [■]]
<u>Dyspnea/Cough</u> Medical Research Council (MRC)/Modified MRC (mMRC) Dyspnea Scale	Degree of disability caused by breathlessness	1 item	5-point scale for MRC, 0–4 scale for mMRC; higher scores indicate more severe disability	PC - Advanced lung disease [18], COPD [11 [■] ,25 [■] ,62 [■]], FILD [10 [■]], ILD [24 [■] ,63 [■]]
COPD Assessment Test	Cough, phlegm, chest tightness, breathlessness, activities at home, confidence leaving home, sleep quality, energy levels	8 Items	Scores range from 0 to 40 on a 5-point Likert scale; higher scores indicate more severe impact	PC - COPD [11 [■] ,25 [■]]
University of California San Diego Shortness of Breath Questionnaire	Dyspnea when performing 21 different activities. Three additional questions inquire about activity limitations due to shortness of breath, fear of harm from overexertion, and fear of shortness of breath.	24 items	Each item scored from 0 (not at all) to 5 (unable to do because of breathlessness), scaled from 0-120	PC – ILD [24 [■]]
<u>Mental Health</u> Hospital Anxiety and Depression Scale	Anxiety and Depression	14 items (7 for anxiety, 7 for depression)	4-point Likert scale from 0 to 3; higher scores indicate greater levels of anxiety or depression	PC – COPD [36 [■]], ILD [24 [■]]

Table 1 (Continued)

Instrument	Domains	Items	Scoring	Population and references
Other	Sleepiness in various situations	8 items	Scale of 0–3 for each situation, with total scores ranging from 0 to 24; higher scores indicate greater sleepiness	PC - ILD [24 [■]]
Epworth Sleepiness Scale				
Pittsburgh Sleep Quality Index	Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction	19 items	Each question is scored from 0 to 3, with higher scores indicating more severe sleep disturbances. A global score above 5 suggests poor sleep quality.	PC - ILD [24 [■]]
Palliative Performance Scale	Ambulation, activity level, self-care, intake, consciousness level	5 areas scored in 10% increments	Range from fully independent (100%) to fully dependent or death (0%)	PC - COPD [11 [■]]
The Edmonton Symptom Assessment Scale	Pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well being, shortness of breath	10 items	0-to-10 scale; higher scores indicate more severe symptoms	PC - LTx candidates [20 [■]], COPD [11 [■]]
Supportive Care Needs Survey	Psychological, health system, physical & daily living, patient care & support, and sexuality.	34 items	Each item is scored using a five-point Likert scale ranging from 1 (no need, not applicable) to 5 (some need, high need for help)	PC - CF [64]

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FILD, fibrotic interstitial lung disease; HRQL, health-related quality of life; ILD, Interstitial lung disease; LTx, lung transplant; PC, palliative care.

values. However, about 20% may experience a significant deterioration in mental health HRQL measures in the first-year posttransplant with older age being a risk factor for decline [1[■],21]. Furthermore, some LTx recipients experience a complex and prolonged hospital course, which can lead to impairments in HRQL or present with symptoms such as dyspnea [22[■]]. Palliative care support can help cope with some of these challenges including physical or mental health concerns, medication side effects, and return to daily function posttransplant [7[■]]. Further, given the high readmission rates in the first year posttransplant [23], PC support during these admissions or during transition periods can be beneficial.

PALLIATIVE CARE ASSESSMENT TOOLS AND PATIENT-REPORTED OUTCOME MEASURES

Several patient-reported outcome measures have been utilized in the PC setting to evaluate HRQL, respiratory symptoms, mental health, and other domains including pain, sleep, and daily function (Table 1). These questionnaires, though originally

developed for other contexts, have been effectively applied in patients with advanced lung disease managed by PC, including LTx candidates. These patient reported outcome measures have included generic (i.e. Short-Form 12) [17[■]] and disease specific HRQL questionnaires (i.e. St. George's Respiratory Questionnaire) [11[■],24[■]], along with dyspnea and cough questionnaires (i.e. COPD assessment test) [11[■],25[■]]. Other instruments utilized in PC have covered a broader spectrum of assessments including sleep quality, spiritual care, mental health and other facets of daily living, as described in Table 1.

PALLIATIVE CARE MANAGEMENT STRATEGIES

Pretransplant

In LTx programs, PC is well positioned to support optimal symptom management and function, communication (including goals of care and advance care planning conversations), and support patient's family and caregivers [26]. Palliative care places a significant emphasis on the effective management

of distressing symptoms. Several reviews have been published in support of managing symptoms while balancing both disease modifying and PC interventions in patients with advanced lung disease such as COPD [27], ILD [28], and pulmonary arterial hypertension [29]. Emerging evidence specifically focusing on the impact of PC on patients in LTx programs [20[■]] is consistent with studies conducted in the broader context of PC for advanced lung disease. In a recent systematic review evaluating 8 studies (7 randomized control trials), Santos and Reis-Pina (2023) revealed that PC interventions improved breathlessness in patients with chronic respiratory disease [19[■]]. Studies of other mixed nonmalignant populations (including COPD) have also demonstrated improvement in symptoms after PC intervention [14,15].

Among the approaches to managing dyspnea, opioids stand out for their efficacy. Although the literature on their use specifically in the LTx population is limited, these medications are commonly used to alleviate dyspnea with clear benefits in the advanced lung disease population [16,18,30]. Opioids alleviate dyspnea primarily by binding to μ -opioid receptors, which modulate the central neural processing of respiratory sensation and reduces the brainstems responsiveness to hypoxia and hypercapnia [31]. A recent systematic review of patients with chronic respiratory diseases revealed a consistent symptom reduction in patients with moderate-severe levels of dyspnea (Medical Research Council dyspnea score > 3) after opioid use [32]. Another PC study in patients with advanced lung disease revealed that dyspnea scores remained unchanged despite disease progression [11[■]]. Although opioids are recognized for their efficacy in alleviating dyspnea, concerns regarding their safety remain an important point of contention [33].

Emerging evidence suggests that with careful management, opioids can be safely utilized to reduce patient dyspnea without increasing post-LTx risks. Hesitation to prescribe opioids in the pre-LTx population is grounded in the fear of increased mortality, opioid dependency, and respiratory depression post-LTx [33]. Although recent studies show that opioid use pretransplant predicted greater use posttransplant, there was no increased risk of mortality, re-transplantation rates and opioid dependency [34,35].

In LTx populations, PC support and management of dyspnea and cough, may allow patients to function better, have greater exercise capacity and remain independent longer. The ability of PC to support patient function has been poorly studied and is only indirectly measured in mixed scales of HRQL assessments. This is also believed to be

complicated by the lateness of referrals, and progressive deterioration faced by patients with advanced lung disease [16,36[■],37[■],38]. Thus, the literature on PC effects in the advanced lung disease and transplant populations has been mixed [17[■],18,19[■]]. Further, evidence demonstrates that symptoms in LTx candidates can be heterogeneous and do not always reflect objective measures of illness severity [20[■]], often a trigger for referral to PC, especially in those who are younger, more racially diverse, and have higher psychosocial risk factors [39[■]].

Posttransplant

In earlier studies, PC involvement post-LTx has been limited [40], which is consistent with other solid-organ transplant populations [41]. In a single-centered retrospective study of almost 600 lung transplant recipients, integration of PC was improved with an incidence of 27% and 43% at 1 and 5 years, respectively [42]. Over 60% of PC encounters occurred in the first year posttransplant, including 34% during the index transplant hospitalization. Furthermore, over 90% of all encounters occurred in the inpatient setting [42]. As the majority of support was provided in the first year posttransplant, it suggests that many LTx recipients experience PC needs early after transplantation. Further, a study from our center in solid organ transplant recipients illustrated that involvement of the transition pain service posttransplant reduced opioid use and psychological impact of pain, and helped with management of chronic pain [43[■]].

Several studies have described the benefits of PC in mixed intensive care unit (ICU) populations [44,45[■]]. Recent systematic reviews have demonstrated that the strategies to enhance PC involvement in the ICU have beneficial effects on improved communication, patient HRQL and symptom management, along with caregiver outcomes, as well as decreased ICU and hospital length of stay (with no effect on mortality) [44,45[■],46]. Although dyspnea can continue to present itself post-LTx [22[■]], no studies to our knowledge have assessed how effectively opioids manage dyspnea in the post-LTx period, which presents a promising avenue and should be further explored.

Patients may experience symptoms related to pain, cognitive impairment, caregiver burden, depression and posttraumatic stress disorder, as well as side effects of new immunosuppressant medications [21,47]. Furthermore, the post-LTx poses a high risk for hospital readmissions due to infection, gastrointestinal symptoms, and complications arising from chronic allograft dysfunction [48]. Patients waiting

for re-transplant have even further complexity, with research indicating that they struggle with additional concerns surrounding communication, social support and relationships between other patients, caregivers, healthcare professionals, and the healthcare system [49]. Thus, the higher rates of hospital readmissions, symptoms, and chronic allograft dysfunction in the post-LTx provide opportunities for PC involvement in improving symptoms and HRQL.

COMMUNICATION, CARE COORDINATION, AND SUPPORT

Open and effective communication among healthcare providers, patients, and their families is a core aspect of PC, facilitating shared decision-making and care coordination throughout the LTx journey. Palliative care encourages proactive discussions about future care preferences and goals, involving patients, families, and healthcare providers [50]. Several recent studies have demonstrated improvement of advance care planning and goals of care with PC intervention in chronic lung disease [19²²,51]. These conversations have been shown to improve satisfaction with care, communication metrics, patient and caregiver health status (i.e. anxiety) and healthcare utilization [52]. Palliative care emphasizes open communication, helping patients and their families understand the transplant process, potential outcomes, and available options, thus, education provided by PC teams can help patients make informed decisions aligned with their values and preferences, in addition to addressing anxiety, depression and emotional challenges associated with their transplant journey.

Supporting caregivers and family members is an important role of PC. Pawlow *et al.* [53] evaluated the supportive care needs of primary caregivers of LTx candidates and found many reported needs in the following areas: expectations for future, who to call with healthcare concerns, financial, legal, and work issues, as well as caregiver feelings and worries. Another recent study of 76 patient/caregiver dyads participating in a nurse-led early PC intervention demonstrated significant improvement in caregiver's knowledge, disease preparedness, and confidence in caring for the patient [51]. These and other recent studies describing the lived experiences of caregivers highlight the necessity for early assessment and management of the needs of caregivers in LTx [54,55].

PALLIATIVE CARE MANAGEMENT MODELS

Research has yet to determine how best to integrate PC or model services to meet the needs of patients and caregivers in LTx programs, although several

suggestions have been made [26]. To ensure patients receive the support they need, programs may screen for PC needs at LTx candidacy evaluation and/or throughout their transplant journey, a system regularly adopted by cancer programs [56]. Although trigger tools have faced criticism for their perceived inability to identify PC needs accurately [57], specifically, matching the right patient with the appropriate timing, there is potential to develop triggers for PC referral. For instance, these triggers could be activated when a patient experiences deterioration, either subjectively or as indicated by patient-reported outcome measures or physiological assessments such as the 6MWT, or when they undergo admission or are declined for transplant [26,39²³].

Once the specific needs are identified, patients and caregivers could be provided care by members of the transplant team, local respirologists or their family physician (i.e. primary PC) or referred to the transplant organization's local PC team. Palliative care teams may also be integrated (i.e. consulted) at the time of candidacy evaluation, allowing PC teams to follow patients along on their journey pre and post-transplant, including those that are not accepted or delisted. Palliative care teams may follow up with patients based on patient and caregiver needs, and if appropriate, support communication, help coordinate care (i.e. care at home or psychosocial supports) and optimize symptoms, allowing for the time needed to develop trust and build relationships with patients and their caregivers.

FUTURE DIRECTIONS

The utilization of PC in LTx is evolving and has gained increased recognition in the last decade for its impact on symptom management, HRQL, and physical function in several areas (Table 2). Physical function and exercise capacity are major predictors of patient health outcomes, especially for those with advanced lung disease in a transplant program. Although the impact of PC in supporting patient function, independence and exercise capacity has been poorly studied, there are several integrative models of PC and rehabilitation demonstrating improvements in dyspnea, 6MWT, HRQL and healthcare utilization [58,59²⁴]. Understanding the role of PC in supporting patients trying to maintain or improve their functional capacity is an exciting area for discovery, not only for transplant medicine but all patients with chronic lung disease. It will also help us understand where and when integration should occur for these patients, as typically PC is involved late in the disease trajectory, when being able to improve functional status is more challenging. Further, there is a need for refinement and

Table 2. Future clinical and research directions in palliative care and lung transplantation

Domains	Questions
Assessments	• How should PC and needs assessments be integrated into transplant programs at the time of transplant candidacy evaluations, listing and posttransplant? • What patient reported outcome measures should be utilized as part of PC assessment in the lung transplant population? • What is the role of online applications and activity trackers in promoting daily function?
Standard interventions/approaches	• What are the best strategies to support patients with PC needs and their caregivers? • What is the role of opioid use in the post-transplant period in symptom management? • How does management of dyspnea and cough with opioids pretransplant affect their use posttransplant? • What are the optimal models of PC intervention delivery?
Outcomes	• How does access to PC and support of communication, advance care planning and goals of care conversations during patient's transplant journey improve subsequent access to PC and decrease healthcare utilization? • How does PC support combined with pulmonary rehabilitation improve LTx candidate's daily function and exercise ability? • How does PC support patient's independence with basic and instrumental activities of daily living?
Other considerations	• Can PC support be delivered with the same effectiveness using video communication, or is a hybrid approach best? • What is the best way to deliver PC support in specific lung transplant settings (i.e. bridge to transplantation, peri-operative, and chronic allograft dysfunction)?

PC, palliative care.

validation of PC tools that have often been used in advanced lung disease populations extrapolated from oncological settings. Physical activity applications and activity trackers may be a promising intervention to promote physical function in the setting of rehabilitation and PC support. There is also an increased need to develop interventions to support caregivers during the transplant journey who often experience significant emotional stress and impaired quality of life. The evaluation of these PC interventions on how they can affect pre and posttransplant outcomes remains an important area of future investigation.

CONCLUSION

Palliative care has gained increased recognition in its support of LTx candidates with respect to symptoms, HRQL, and function. PC management in the form of opioid prescription, emotional support, and end-of life care discussions can be provided across several settings (outpatient, inpatient) and throughout the transplant journey. Future directions include focus on optimizing physical function and well being while awaiting LTx, as well as expanding the role of PC support in the early and late posttransplant periods for both patients and their caregivers. Given the increasing age and patient complexity of LTx recipients, the importance of PC support in LTx will continue to evolve.

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Conflicts of interest

There are no conflicts of interest.

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