REGULAR ARTICLE

Palliative Care and Pulmonary Arterial Hypertension

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Background: Pulmonary arterial hypertension (PAH) is a chronic and progressive disease associated with impaired health-related quality of life and survival. Palliative care (PC) is patient- and family-centered care provided by an interdisciplinary team with an overarching goal of alleviating suffering and improving quality of life for patients with advanced illness. PC in other chronic diseases is associated with improved quality of life, symptom management, illness understanding, and reduced caregiver burden, but there is limited data regarding PC in PAH. Despite limited evidence, there is strong rationale for involving PC specialists in the longitudinal management of PAH.

Implications for Clinicians: There are currently no guidelines to help clinicians determine the most appropriate timing for referral of PAH patients to PC specialty teams. Consequently, referrals are limited and often delayed. Adoption of a standardized approach to PC referrals based on clinical or patient triggers could facilitate earlier involvement of PC as an adjunct to ongoing PAH disease-directed care.

Conclusions: Incorporation of PC in the longitudinal management of PAH may be beneficial to address the multidimensional aspects of living with a chronic and life-limiting illness.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic and progressive pulmonary vascular disease associated with significant morbidity and mortality. PAH is characterized by pulmonary vasoconstriction and vascular remodeling which can ultimately lead to right heart failure and death. PAH is also associated with significant symptoms as well as impaired health-related quality of life (HRQOL)[1] across varied physical, social, and emotional domains.[1,2] PAH therapeutics delay disease progression and improve symptoms, hemodynamics, exercise capacity, and survival but unfortunately are also commonly associated with adverse effects which may further impair HRQOL.[3] Despite the importance of HRQOL in the overall patient experience of living with PAH, few therapies are available to specifically address and improve HRQOL in PAH. Palliative care (PC) provides patient- and family-centered care with an overarching goal of alleviating suffering and improving QOL for patients with advanced illness. Despite its potential benefits, PC is underutilized in PAH, and there is little data to guide clinicians regarding how to incorporate PC into their clinical practice. This review provides an overview of PC and its utility in other cardiopulmonary diseases, summarizes available evidence regarding PC in PAH, and suggests potential roles for PC in the longitudinal management of patients with PAH.

PAH IS ASSOCIATED WITH SIGNIFICANT MORBIDITY AND MORTALITY

HRQOL is a multidimensional patient-reported outcome (PRO) that refers to the general wellbeing of an individual. PAH negatively impacts HRQOL across the spectrum of physical, social, and emotional domains.[1,2] PAH is associated with symptoms, such as dyspnea, fatigue, impaired exercise capacity, lower extremity edema, lightheadedness, syncope, and depression.[4,5] Although there have been significant recent advances in treatment of PAH, PAH-targeted therapies are commonly associated with side effects which carry an additional symptom burden, and can include headache, heartburn, nausea, flushing, dizziness, edema, and pain, among others. Despite treatment, most patients continue to experience symptoms that impact their HRQOL as well as other aspects of their lives, such as employment and social interactions.[6] PAH can also be associated with emotional and psychological distress, manifested as feelings of frustration, anger, and sadness.

HRQOL is a significant predictor of outcomes in PAH.[2] Patients with impaired HRQOL at diagnosis have increased hospitalizations and worse survival, even after adjusting for disease severity.[1,2] Despite its importance as a prognostic marker and its importance to an individual's overall wellbeing and daily life, HRQOL is not routinely assessed in clinical practice and is rarely con-

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sidered a primary endpoint for clinical trials or other interventions. Although current PAH therapeutics can improve variables, such as functional class, pulmonary hemodynamics, and 6-minute walk distance, they often do not address the multidimensional aspects of PAH such as the cognitive, emotional, social, and financial impacts.

In addition to its impact on HRQOL, PAH is a progressive disease associated with impaired long-term survival.[7] Despite the adverse prognosis associated with PAH, studies have found that completion of advance health care directives and utilization of PC services are low. According to one single-center study, less than half of PAH patients had completed advance health care directives at the time of death.[8] Despite the poor prognosis associated with interventions such as cardiopulmonary resuscitation (CPR) and mechanical ventilation in PAH, 31% and 40% of patients, respectively, received CPR and mechanical ventilation at the end of life (EOL)[8,9] and 80% of patients died in a health care setting.[8] More than half of patients died in the intensive care unit with only 8.6% of patients receiving PC before death[8]. Overall in-hospital mortality for patients with PAH and right heart failure is high, with estimates ranging from 14% to as high as 30% to 48% for patients admitted to the intensive care unit.[9,10] Despite the poor prognosis associated with hospitalizations, PC was consulted in only 2.2% of PAH hospitalizations according to a national study.[11] Overall, these studies suggest that there is an unmet need in PAH to improve prognostic awareness and communication with both patients and caregivers regarding goals of care to ensure the PAH care team is providing goal-consistent care throughout the continuum of disease.

PC: AN OVERVIEW

Patients with serious illness encounter numerous issues that can detrimentally affect their perceived QOL. PC is an interdisciplinary model that provides patient- and family-centered care, with an overarching goal to alleviate suffering and to improve QOL for patients with advanced illness. It is a common misconception that PC is synonymous with EOL care and hospice; the two are on the same spectrum but distinct entities. For patients to receive the full benefits of PC, early integration, in conjunction with disease-directed therapy, is likely the best plan of care (Figure 1). Incorporating palliative principles early into a patient's disease course can result in improved QOL and symptom management, better illness understanding, completion of advance directives, enhancement in coping skills, and reduction in caregiver burden.[12–14] Contrary to many patient and medical provider fears, PC is not associated with reduced survival.[15,16] Therefore, the World Health Organization recommends inclusion of PC early in the course of illness.[17]

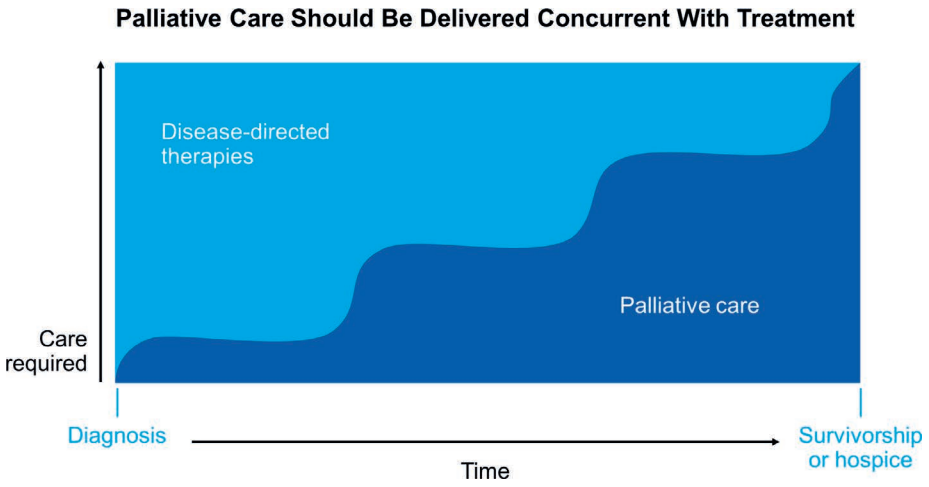

Figure 1: A model of palliative care delivered concurrently with disease-directed therapies.[41]

PC IN OTHER CARDIOPULMONARY CONDITIONS

PC has traditionally been rooted in the oncologic setting, but authors of studies have shown that PC can have a dramatic impact on patients with advanced nononcologic disease, including cardiopulmonary disease.[15,16,18–24] Like PAH, patients with advanced congestive heart failure (CHF) often experience progressive and debilitating physical, psychosocial, and spiritual concerns. In addition to the predicted symptoms of dyspnea and fatigue, many patients with CHF also suffer with pain and depression.[25,26] Spiritual distress has also been identified as a concern in patients with CHF.[27] Compelling evidence of benefit for integration of PC for patients with advanced heart failure has been demonstrated in numerous trials, showing improved QOL and patient satisfaction, improved physical and mental health and spiritual wellbeing, and completion of advance directives.[16,18–20] Most major cardiology societies, the Joint Commission, and the Centers for Medicare and Medicaid Services have developed guidelines for incorporation of PC in patients with advanced cardiac disease.[24]

Likewise, patients with advanced pulmonary disease, such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease, have reported poor QOL, high symptom burden, involving both physical and mental health, and high rates of caregiver distress.[21,22] Breathlessness is an exceedingly common manifestation of advanced pulmonary disease despite optimal medical therapy for the underlying illness. Breathlessness can be substantially improved in the setting of an interdisciplinary care model incorporating PC into usual care.[15,21] Mood disorders and existential distress are often unrecognized and undertreated in patients with advanced pulmonary disease.[23] Furthermore, it is well established that untreated psychosocial and spiritual distress may influence a patient's treatment preferences.[23] Given the palliative approach to care, which includes close attention to emotional, social, and spiritual health domains, an opportunity exists to significantly impact outcome measures, both in terms of symptom

management and perceived qualify of life, and patients' treatment preferences.

Given the severe symptoms with advanced cardiopulmonary disease, advance care planning is very important, yet authors of one study demonstrated that less than one-third of patients with oxygen-dependent COPD had completed an advance directive.[28] Patients with advanced cardiopulmonary disease demonstrate a high rate of health care utilization in the last year of life, often in dissonance with their goals. The average median annual cost for a patient with advanced CHF is $24383, with the majority stemming from hospitalizations.[29] Patients with advanced COPD incur additional costs with mean estimates of $34911 in the last 6 months of life, again, largely related to inpatient care with substantial intensive care utilization.[30] Involvement of PC has been shown to reduce health care expenditures in the last year of life by helping patients and families navigate difficult decision making, provision of care that is in line with patient-specific goals and preferences, and timely referral to hospice.[16] Historically, most patients with advanced cardiopulmonary disease died in the hospital; however, palliative involvement is associated with increased likelihood of dying at home, which aligns with most patients' preferences.[31]

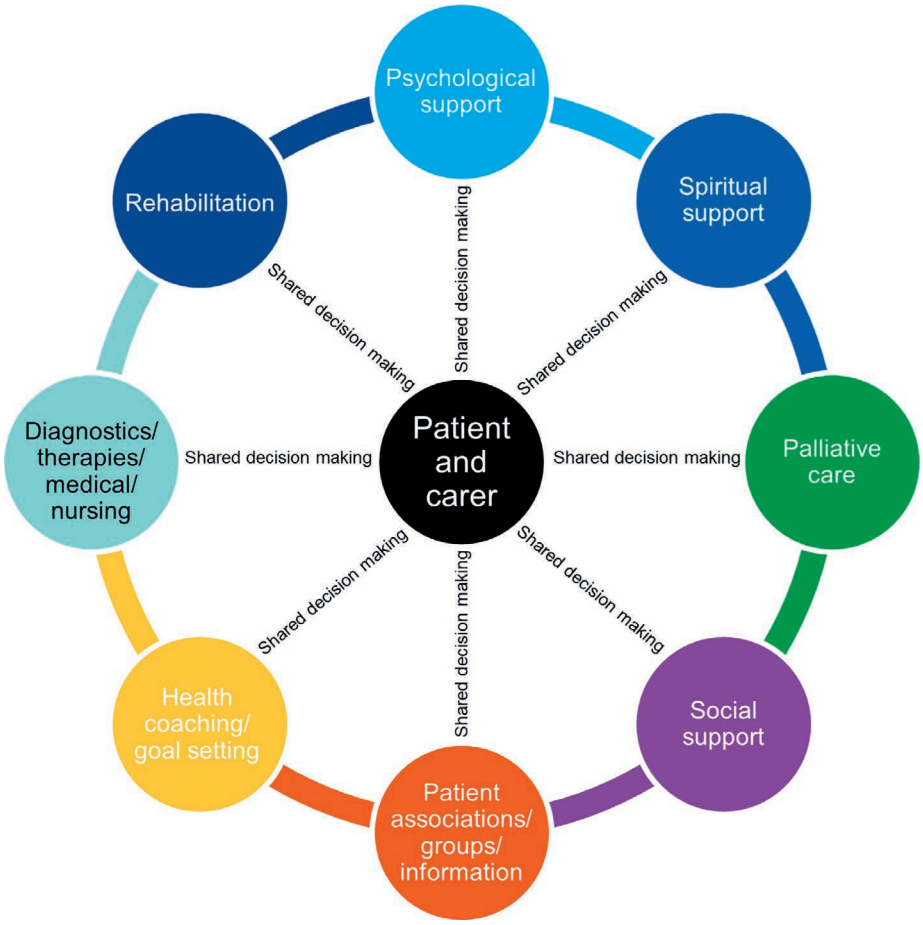

Figure 2: Components of a multidimensional approach to care of patients with pulmonary arterial hypertension, from McGoon et al.[3]

PC IN PAH

Despite the established benefit of PC in other cardiopulmonary diseases, there have been few studies addressing the role of PC in PAH. PC referrals are low for patients with PAH, both in the inpatient and outpatient setting, despite many of these patients having intensive support and symptom management needs.[11,32] Survey-based studies of PAH physicians and patients have identified several barriers to regular, early PC involvement, including patient and physician perceptions regarding the role of PC.[32,33] In a study on physician-perceived barriers to PC referral for patients with PAH, worry about the appearance of "giving up hope" was rated highly as a barrier, in addition to feeling the consult unnecessary in dealing with QOL or EOL needs for patients.[32] The misconception that patients could not receive PC along with active disease-modifying therapies for PAH was another clinician-perceived obstacle to referral. PC has also been incorrectly associated with only EOL and hospice.[32,33] Anxiety and declination from patients and caregivers surrounding PC referral also contribute to limited and late referrals.[32,33] Health care disparities and access to PC services may also represent barriers to PC referral, as suggested by an analysis of the National Inpatient Sample, which found that there were geographic, socioeconomic, and racial differences associated with PC utilization in PAH as well as lower rate of referrals for patients without private insurance.[11]

Despite limited evidence, there is an important rationale for earlier referral to PC for patients with PAH. PC referral early in the disease course can be beneficial for preparedness planning for both patients and caregivers, in addition to supporting shared decision making throughout the continuum of care. The prognostic uncertainty often associated with PAH, along with cost-related medication barriers and high rates of in-hospital death, make early and skilled discussions imperative to support patient autonomy and values.[4] Early PC referral in PAH can provide systematic advance care planning with discussions of surrogate decision makers, with a focus on what is a meaningful QOL to the patient. In addition, planning for acceptable transitional care plans and engagement in "what-ifs" discussions can be meaningful with early PC involvement.[4] The support of the PC interdisciplinary team in PAH is also very important in providing psychosocial support for both patients and caregivers, helping to acknowledge the challenges and emotions that come with a chronic life-limiting and debilitating illness.

The care of patients with PAH requires a multidimensional approach with a focus on alleviation of symptoms while supporting emotional, social, and

psychological wellbeing (Figure 2).[5] Many palliative treatment options exist, including pharmacologic, nonpharmacologic, and procedural. The use of low-dose opioids and benzodiazepines can be helpful for dyspnea and concomitant anxiety.[4] Nonpharmacologic treatments, such as supervised exercise regimens, meditation and guided imagery, and supplemental oxygen when appropriate, can be used to offset symptom burden as well.[34] Assessments for depression, anxiety, and insomnia, with appropriate screening and referrals for psychotherapy or psychiatric consultation, are also important, given the high prevalence of mood disorders among patients with PAH.[35] When patients with PAH have escalation of symptoms, have recurrent hospitalizations, and are closer to a more limited prognosis at EOL, having already been established with PC can help with patient familiarity of the team, making engagement in complex communication, in partnership with other primary teams, more beneficial and connected. Given the complexity of PAH management and the negative impact of PAH on HRQOL, PC has much to offer patients with PAH through the 8 domains of PC, which include supporting patients and families through structures and processes of care, management of physical and symptom needs, psychological, social, spiritual, and cultural aspects of care, care of the patient nearing EOL, and navigation of ethical and legal aspects of care.[36]

ROLES FOR PC IN PAH AND HOW TO INCORPORATE PC INTO CLINICAL PRACTICE

According to recent PAH treatment guidelines, there is no evidence to provide direct recommendations regarding utilization of PC services in PAH.[37] Thus, clinicians are left with little guidance to help determine the most appropriate timing for referral to PC specialists. In the absence of evidence or specific recommendations, referrals are delayed and typically occur at the EOL, when it is often too late to make meaningful improvement in an individual's HRQOL. To overcome barriers and facilitate earlier referrals, it can be helpful to have a standardized approach, either based on clinical or patient triggers. Clinical triggers could include escalation of therapy (initiation of parenteral prostacyclin therapy or triple therapy, for example) or events such as hospitalizations, lung transplantation referral, or clinical deterioration. Risk stratification can improve prognostic awareness and can also serve as a guide regarding timing of referrals. There are several tools for risk stratification in PAH, so one approach would be to refer patients who fall into a "high-risk" category.[38] These approaches based on clinical triggers would help to automate referrals, so they are part of routine care and longitudinal management. In conjunction with PC referrals, particularly those based on prognosis or clinical deterioration, it is imperative that PAH clinicians have ongoing discussions with patients to facilitate prognostic awareness and to provide education regarding the role of PC as an adjunctive therapy in the ongoing management of PAH.

Additional research studies are needed to help determine the most appropriate patients and timing for referral to PC specialists. At Mayo Clinic Rochester, we are currently engaged in a patient-triggered randomized controlled trial of PC plus usual care versus usual care alone.[39] In this single-center study, we are enrolling patients with impaired HRQOL (regardless of disease status or prognosis) as assessed by the SYMPACT score, a PAH disease-specific and validated PRO tool, and randomizing them in a 1:1 fashion to PC plus usual care or usual care alone.[40] The primary outcome of this study is HRQOL. PRO-triggered PC referral represents an opportunity to address an individual's symptoms and concerns to facilitate living as well as possible through symptom management and coping support regardless of his or her disease prognosis or clinical status. The approach of PRO-triggered referrals also mitigates previously described patient and clinician barriers to utilization of PC services, such as concern that referral implies "giving up" or a poor prognosis.[32,33] The study is ongoing, and the results could help guide clinicians regarding an alternative approach to facilitate PC referrals but will need to be studied in a multicenter clinical trial.

FUTURE DIRECTIONS

Improved evidence is needed to help determine the impact of PC on HRQOL and other important patient-centered outcomes in PAH and to help guide clinicians regarding patient selection and appropriate timing of PC referrals. Without evidence and without education of providers and patients regarding the role of PC, early and regular utilization of PC services in the longitudinal management of PAH will continue to be limited. As PH clinicians, however, we owe it to our patients to use all the available tools we have, including PC, to alleviate their symptom burden, mitigate side effects of therapy, and ensure we are maintaining goal-consistent care that aligns with their values and wishes.

CONCLUSIONS

In summary, PAH is associated with impaired HRQOL and survival. Although current PAH-targeted therapies improve symptoms and pulmonary hemodynamics and delay disease progression, they are not curative, are commonly associated with adverse effects, and do not address all aspects of impaired HRQOL in PAH. PC, an interdisciplinary model of patient- and family-centered care with the goal of alleviating suffering and improving HRQOL, is underutilized in PAH but may be beneficial to address the unmet needs of PAH patients and the multidimensional aspects of living with a chronic and life-limiting illness.

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