Pulmonary Hypertension and Palliative Care: What, When, Where, and Why?

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Summary: Pulmonary hypertension (PH) can be associated with a high level of symptom burden from the disease as well as its treatment. Involvement of palliative care (PC) services may help facilitate discussion regarding goals of care, prognostic planning, and treatment options focused on improving quality of life (QOL).

Background: PC is active total care of a patient whose disease is not fully responsive to curative therapies, with symptom control as the top priority. After a life-limiting diagnosis is made, health care teams and patients determine prognosis, whether cure is attainable or reasonable, what treatment options are available, and how treatment or nontreatment will impact QOL and survival. QOL is often the focus of palliative interventions, with the goal to minimize symptoms and empower patients with accurate information to help affirm life and meet objectives of care.

Implications for clinicians: PC can begin at the onset of symptoms in a disease that cannot be cured. Early PC may help facilitate discussion regarding goals of care when patient expectations are discordant with prognosis. While PC is a responsibility of all clinicians, subspecialist assistance can be helpful when a clinical decline occurs, in the setting of uncertainty, when patients are removed from the transplant list, or when long-term QOL issues are present.

Conclusion: Communication with patients who have PH can be delicate and requires an understanding of the disease’s process, trajectory, and prognosis. PC teams possess communication skills that may benefit patients and providers with QOL optimization, delivery of difficult news, advanced care planning, and shared decision-making.

Pulmonary hypertension (PH) involves progressive remodeling of the pulmonary vasculature, resulting in elevated pulmonary artery pressure, right ventricular failure, and death. PH is classified into 5 groups depending on etiology and hemodynamic parameters, which impact prognosis and treatment options. PH’s negative impact on quality of life (QOL) is well-documented with common symptoms including fatigue, overall decline in physical and emotional well-being, pain, dyspnea at rest or exertion, chest discomfort, lower-extremity edema, abdominal bloating, and early satiety. With the advent of PH-directed medications, median survival has improved from 2.8 years to more than 7 years.

Symptoms can occur in the setting of progressive PH, as well as from PH-directed treatment. In a study of over 300 patients with PH, the majority of patients (69%) noted significant rest or exertional dyspnea or fatigue as a major symptom, while also reporting fatigue (39%), pain (35%), and depression (32%). A patient’s QOL also can affect primary caregivers including spouses, children, and friends. Despite these challenges, only 8% of patients in a multicenter survey considered palliative care (PC) involvement as an option, and only 1.4% of patients have actually seen PC clinicians as regular providers within their multidisciplinary care team.

Palliative care is the active total care of the patient whose disease is not fully responsive to curative therapies, with symptom control as the top priority. PC focuses on anticipation, prevention, and treatment of symptoms or suffering, with improvement in QOL as a center point of care. Efforts with PC should empower patients by affirming life, but also in recognizing that sometimes death is inevitable. Despite being mentioned as a concern by patients with PH and their providers, no specific therapies are excluded from a PC plan of care.

Over the past 2 decades, the palliative paradigm has shifted toward establishment of a comprehensive management program by multidisciplinary teams that are involved before the end of life. PC is more comprehensive than hospice care, and is recommended to begin when pervasive symptoms and QOL issues exist in the setting of an incurable, life-limiting illness.

Hospice care is a specific subset of PC with the distinction of providing supportive care to patients who have a terminal illness with limited life expectancy of less than 6 months if the disease follows its anticipated course (Figure 1). Hospice care is a Medicare or private insurance benefit in which care is also provided by an interdisciplinary team, most often in patients’ homes. Care is directed at maximizing comfort, dignity,
and QOL as patients approach the end of life. Patients receiving hospice care are typically no longer receiving disease-modifying treatments, notably, because hospice reimbursement is capitated on a per diem basis. The reimbursement must cover the entirety of patients’ care related to the hospice diagnosis, including but not limited to durable medical equipment, medications, and nursing care. This model presently reimburses an average of $160 per day (noting some geographic variability). When viewed in this manner, it becomes clearer why certain disease-directed medications such as parenteral prostaglandins and oral vasodilators such as endothelin receptor antagonists (ERAs) or phosphodiesterase type 5 (PDE-5) inhibitors may be cost prohibitive for some hospices (Table 1).

WHY PC AND WHAT CAN IT ADD TO THE PLAN OF CARE?
Critical initial steps are to address patient expectations and establish goals of care that are important to the patient and caregiver(s). After a serious or life-limiting diagnosis is made, health care teams and patients often need to determine prognosis, understand whether or not cure is attainable or reasonable, what treatment options are available and what the risks/benefits of these treatments are, and how treatment or nontreatment will impact QOL and survival. PC providers often focus less on being “negative” about the prognosis, rather, they strive to ensure that patients receive realistic and hopeful information to make the best possible choices. PC models continue to evolve with the most up-to-date schema, depicting PC initiation early in the disease process with increasing inclusion as the disease progresses, rather than late integration once conventional medical therapy has failed to arrest disease progression or suboptimally treat symptoms and disease (Figure 2). PC’s primary focus is on symptom control while empowering the patient and his/her caregiver to live as well as he/she can for as long as possible. Early incorporation of PC may help facilitate discussion regarding goals of care when patient expectations are discordant with prognosis. Namely, PC consultation has

<table>
<thead>
<tr>
<th>Care</th>
<th>Occurs When in Illness Trajectory</th>
<th>Primary Focuses of Care</th>
<th>Reimbursement Model</th>
<th>Delivered by</th>
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<tbody>
<tr>
<td>Palliative Care</td>
<td>Longitudinal or episodic Can begin with the onset of serious, life-limiting illness</td>
<td>Symptom management Quality of life Delineating goals of care Supporting families and caregivers</td>
<td>Reimbursement is analogous to other subspecialty consultation (i.e., infectious disease, cardiology)</td>
<td>Clinician who is delivering primarily, or by a subspecialist who may have support of an interdisciplinary team</td>
</tr>
<tr>
<td>Hospice Care</td>
<td>Approaching end of life Generally begins when life expectancy is less than 6 months, if the disease runs its expected course</td>
<td>Team-based support services To support patients, families, and caregivers Aggressive symptom management Where comfort and quality of life are major primary goals Bereavement and volunteer support</td>
<td>Can be Medicare or from private insurers often modeling after Medicare model Limited per diem stipend (~$200/day) for all care related to hospice diagnosis Use of costly medications may be restricted</td>
<td>Hospice agency involved, which may be overseeing care, or may be collaborating with a primary physician or specialist care team</td>
</tr>
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<td>Comfort Care Only</td>
<td>Very end of life Generally begins in final hours or days, in hospital or home Starts when all treatments that are not focused on comfort are discontinued</td>
<td>Focus is purely on comfort of the patient Medications that are not contributing to comfort are discontinued Opioids, anxiolytics, and sedatives are used in an appropriate fashion to maximize comfort Not ALL medications should be stopped if they can help the patient to achieve their goals of care</td>
<td>Variable Depends on whether or not a patient is hospitalized, in a facility, or at home Depends on whether or not hospice care has been elected</td>
<td>Variable Depends on whether or not a patient is hospitalized, in a facility, or at home Depends on whether or not hospice care has been elected Depends on specific care needs</td>
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been shown to facilitate the honing of advance directives into preparedness plans, addressing end-of-life scenarios more common in a particular disease process.\[^{11}\]

Historically, most patients with PH express wishes to die in the comfort of their home surrounded by their loved ones. Yet, two-thirds of such patients die in a hospital setting. In one study of patients with PH, more than 80% of in-hospital deaths occurred in the intensive care unit (ICU).\[^{12}\] Importantly, disease-directed PH medications or associated hospital policies (such as requiring a patient to be in the ICU or a monitored bed) may influence these outcomes. Limited data exist regarding end-of-life experiences of patients with PH; however, in one study, caregiver knowledge about PC and hospice services was noted to be less than that of life-support options.\[^{12}\] It is critical for patients and families to understand all alternatives available to them in the setting of advanced illness, to allow for empowered and informed choices honoring patients’ goals, preferences, and values approaching the end of life.

**QOL AND SYMPTOM BURDEN IN PH**

Palliative care involvement may be appropriate to begin at the time of diagnosis, even if prognosis is not established. In the setting of pulmonary arterial hypertension (PAH) or PH due to other etiologies, PC management can assist with symptom burden and QOL at any point, help when a clinical decline occurs or when patients are removed from the transplant list, or can support long-term comanagement. The heavy and often complex symptom burden in patients with PH/PAH can represent a management challenge, and can be a major source of negative impact on QOL for patients and their primary caregivers. In a recent survey, physicians with experience treating patients with PAH noted they most frequently encountered patients with exertional dyspnea, fatigue, edema, depression, and anxiety, and described high self-reported comfort levels in addressing PH-specific medications to improve these symptoms. However, the same physicians reported less confidence in addressing pain management, depression, and other QOL issues, suggesting a role for PC.\[^{8}\]

While not always related to a need for PC, many patients with PH mention feeling isolated and experiencing feelings of insecurity, and note their disease impacts their physical health and activity as well as their mental health, social functioning, and emotional well-being.\[^{13}\] Health-related QOL surveys have shown that patients with PAH describe symptom burden on par with the severely reduced QOL reported in patients with chronic obstructive pulmonary disease and renal failure, and treatment-resistant cancer.\[^{14}\] A common challenge is that for many of these patients, traditional hemodynamic parameters (aside from right atrial pressure) often fail to correlate with impaired QOL in the setting of PAH.\[^{15}\]

Patients with PH frequently mention symptoms including fatigue, exertional dyspnea, and sleep difficulty,\[^{2}\] and concomitant psychiatric disorders are also commonly described and affect up to 35% of patients with PH.\[^{16}\] Tools to assess patient-reported outcomes may be helpful in determining the QOL-related issues. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) was developed to measure patient-reported outcomes in 3 domains: symptoms, functioning, and QOL, and it has been used in PH populations as well as other inventories such as the SF-36 (short form).\[^{17}\] Patients’ CAMPHOR scores have been shown to correlate well with SF-36 scores, as well as 6-minute walk test (6MWT) distance.\[^{18}\]

Many of the treatment options for PAH require extensive planning and adherence to daily routines, which can be challenging, but these drugs also result in variable side effects requiring further adjustments to daily plans. For example, PDE-5 inhibitors may result in gastroesophageal reflux, jaw pain, skin flushing, and headaches.\[^{19}\] ERAs may result in nasopharyngitis/nasal congestion, headache, anemia, liver failure, and lower extremity edema.\[^{20,21}\] Prostacyclin analogues often result in skin flushing/hot flashes, nausea, headache, peripheral neuropathy, and diarrhea as well as complications from central intravenous catheters for parenteral therapy.\[^{22}\] Soluble guanylate cyclase stimulators may cause headache, skin flushing, hot flashes, systemic hypotension, and syncope.

Historically, PC involvement occurs near the end of life in the setting of severe symptomatic right heart failure refractory to optimal medical management, often after initiation of dual or triple therapy. Despite frequent visits and improved disease/symptom awareness with earlier diagnosis and many treatment options, symptom burden remains high and incorporation of PC may assist in improvement of QOL. The level of support can be tailored to the clinical situation. However, PC involvement historically occurs in the minority because of perceptions that the patient was doing well or was “not sick enough” for PC, or the topic was not broached by their primary provider.\[^{1}\] Of 76 experienced physicians who treat

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PAH patients, most affirmed major PAH symptoms and expressed high comfort levels with treating symptoms and discussing end-of-life care plans with patients and family. Yet, only 43% of physicians reported a comfort level in assessing QOL and less so indicated confidence managing QOL issues.8 The majority of surveyed physicians requested PC consultation within the last 12 months, most commonly for end-of-life care/active dying (59%), hospice referral (46%), comanagement of dyspnea, or impaired QOL (40%) (Table 2). Barriers to PC consultation include patient non-approval (51%) and the perception of “giving up” by the patient (43%), and 36% of providers felt comfortable addressing symptom management, QOL, and end-of-life care without need to include PC (Table 3).8

When PH physicians were surveyed about therapeutic options for a case vignette describing an ill PAH patient with functional class IV symptoms/end-stage PH on combination therapy and intolerant to prostacyclin analog with 6 to 12 months of prognosis, most respondents recommended initiation of oxygen and diuretic escalation (Figure 3).8 Approximately half of respondents recommended a clinical trial (51%), while 49% considered higher-risk invasive intervention of atrial septostomy. Despite a poor prognosis and evidence of treatment failure, only 40% of polled physicians considered PC consultation and 12% weighed hospice as an appropriate option.8 The results highlight the historical perceived role of PC in the PH medical community and emphasize a growth opportunity.

Palliative care consultation can play an important role in the care of patients with refractory symptoms in PH. Dyspnea in particular can be an especially burdensome and frightening symptom, and breathlessness may persist and progress despite maximal disease-directed interventions. The primary treatment of dyspnea is to address the underlying cause; however, it is important to conceptualize all of the potential factors that may play a role in dyspnea when managing a patient with subjective breathlessness. “Total dyspnea” refers to the multitude of physiologic, psychological, social, and existential influences on a patient’s sense of dyspnea.23,24 Opioids have been shown to be both effective and safe in the treatment of subjective dyspnea25,26; however, providers often cite a lack of experience in their use and concerns about legal and physiologic consequences as barriers to their use.27 PC teams have expertise in advanced symptom management and may be beneficial for patients with a high symptom burden, particularly in the setting of refractory dyspnea.

### Table 2. Common Reasons Reported by Physician Respondents for Palliative Medicine Referral in Patients With PH.8

<table>
<thead>
<tr>
<th>Reason for Referral</th>
<th>N (%)</th>
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<tr>
<td>End of life/active dying</td>
<td>45 (59)</td>
</tr>
<tr>
<td>Hospice referral</td>
<td>35 (36)</td>
</tr>
<tr>
<td>Impaired quality of life</td>
<td>30 (39)</td>
</tr>
<tr>
<td>Goals of care discussion</td>
<td>24 (32)</td>
</tr>
<tr>
<td>Pain management</td>
<td>19 (25)</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>11 (14)</td>
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WHY: COMMUNICATING AND PROGNOSTICATING IN PH WITH UNCERTAINTY

Communication with patients who have PAH requires preparation and a knowledge base of the underlying disease process, disease trajectory, and prognosis. These communications may arise from the primary PAH treatment team or may come from different parts of the multidisciplinary team depending on comfort level and expertise. Collaboration with PC may be initiated with an intensive up-front assessment at the time of diagnosis, with long-term follow-up on an as-needed basis when symptoms or side effects occur, or may be initiated only when symptoms/side effects begin to outweigh the derived benefit from PH-directed therapies. How do we measure successful or beneficial PC interventions? Quality metrics in palliative medicine may be best measured by QOL rather than length of survival as a surrogate marker. The ultimate goal of PC is a patient-centered focus with a plan that aligns with the patient’s value system and provides a supportive structure to uphold those values and improve QOL. Despite historical obstacles, implementation of PC may improve QOL and provide a respite from symptoms and medication side effects while neither hastening nor postponing death.

Prognostic prediction tools may assist the clinician in determining appropriate and timely evaluation and intervention.
for patients with PAH. These interventions may include but are not limited to invasive and noninvasive testing, PH-directed medication up- or down-titration, and implementation of a PC plan. Benza et al provided a framework for predicting outcome in patients with PAH through the REVEAL risk score calculator, which utilizes hemodynamic information, clinical information, and epidemiologic data readily available in most patients. The score allows risk stratification of PAH patients and outlines certain high-risk features such as connective tissue disease associated–PAH, portopulmonary hypertension, hypotension, tachycardia, elevated mean right atrial pressure, pericardial effusion, and 6MWT distance among other variables. Prognostication that identifies a patient at high risk of morbidity or mortality may provide a valuable opportunity to implement PC at a point that can positively impact QOL rather than delaying involvement until end of life. Research trials in PAH recently have had a shift toward hard endpoints such as time to “clinical worsening,” defined as functional class deterioration, initiation of a parenteral prostacyclin agonist, hospitalization, transplant, atrial septostomy, or death rather than relying predominantly on a change in 6MWT distance. The REVEAL risk score accurately predicts 1-, 2-, and 5-year survival to assist clinicians in detecting those at high risk for not only clinical events such as hospitalization but also overall poor prognosis. For example, 1-year survival in 3001 PAH patients with “clinical worsening” was 78% vs 94% in patients who did not meet criteria for clinical worsening (Figure 1). The pattern was similar in newly diagnosed patients as well as in patients with a previous diagnosis.

Disease trajectory appeared to accelerate most in the 4 to 6 months after a hospitalization. 6MWT distance has long been used by clinicians as a simple measure of functional capacity in patients with PAH. The distance is part of the REVEAL risk calculator with overall cutoff values of >440 m or <165 m, imposing a positive or negative prognostic indication respectively. Farber and colleagues recently illustrated the prognostic ability of 6MWT distance deterioration on serial measurement to reflect worsening prognosis and demonstrated that stable or improved walk distance had no change on survival.

Recently, REVEAL investigators demonstrated utility of the REVEAL risk score calculator at serial assessment, highlighting that risk score changes have prognostic implications. Only 38% of patients (n=959) had no change in risk score, while 32% had an improvement and 30% had a worsening in score. The 1-year survival for patients with “decreased score” (improvement in variables) compared to “no change in score” and “increased score” (worsening in variables) was 94%, 90%, and 85% respectively. Increased risk score by even 1 point (worsened score) carried with it a hazard ratio of 1.67, while score improvement equated a hazard ratio of 0.57 when adjusting for risk at enrollment into the REVEAL registry. Despite advances in medical therapy, improvement in long-term survival remains low at 61% to 65%. Change in REVEAL risk score or worsening in 6MWT distance on serial evaluation reflects a change in disease trajectory and may provide an important opportunity to not only modify medical therapy but also explore initiation of PC to assist in symptom attenuation and QOL improvement.

Communication about disease process, trajectory, and prognosis may be challenging and riddled with significant uncertainty as providers are often dealt the difficult task of extrapolating population-level estimates to an individual patient with innumerable potential confounders. With a goal of truthful, honest discussions about prognosis, providers may face concurrent fears about taking away patients’ hope and concerns about lack of training or appropriate time for these discussions. Three central tasks have been described when approaching uncertainty with patients and families: to normalize uncertainty, address the associated emotions, and help manage the effects of the uncertainty. Shared decision-making has been highlighted by the American Heart Association and seeks to have providers and patients work together to make important treatment decisions in the context of a patient’s preferences and values in an iterative manner. PC teams possess advanced communication skills that may benefit the patient and providers in the processes of delivering difficult news, performing advance care planning, and making shared decisions.

References


