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REVIEW

Palliative care and end of life management in patients with idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic disease with an unknown etiology that causes deterioration of the structure of the lung parenchyma, resulting in a severe and progressive decline in respiratory function and early mortality. IPF is essentially an incurable disease, with a mean overall survival of 5 years in approximately 20% of patients without treatment. The combination of a poor prognosis, uncertainty about the disease's progression, and the severity of symptoms has a significant impact on the quality of life of patients and their families. New antifibrotic drugs have been shown to slow disease progression, but their impact on health-related quality of life (HRQoL) has to be proven yet. To date, studies have shown that palliative care can improve symptom management, HRQoL, and end-of-life care (EoL) in patients with IPF, reducing critical events, hospitalization, and health costs. As a result, it is essential for proper health planning and patient management to establish palliative care early and in conjunction with other therapies, beginning with the initial diagnosis of the disease.

Key words: End of life; palliative care; health-related quality of life; idiopathic pulmonary fibrosis.

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The value of the palliative care in idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic disease of unknown etiology, characterized by a deterioration of the structure of the lung parenchyma with consequent progressive decline in respiratory function and early mortality, to be comparable in its evolution and in the impact on the quality of life to neoplastic diseases. IPF is characterised by major reductions in quality of life and survival and has similarities to certain malignancies [1]. The health-related quality of life (HRQoL) of the IPF patients is impaired with regard to their general quality of life and the domains of physical health and level of independence. In particular, IPF patients have problems with pain and discomfort, energy and fatigue, sleep and rest, activities of daily living, dependence on medication or treatments, working capacity, ability to acquire new information and skills, participating in and possibilities for recreation/leisure [2]. Despite this, palliative care (PC) in IPF is little used and an organizational difficulty in accessing it is still evident. Due to the unpredictable nature of IPF, early intervention with the initiation of PCs, which include both drug and non-drug therapies, can reduce the burden of symptoms and improve the quality of life of patients and their caregivers [1].

PCs are needed for a wide range of chronic diseases such as cardiovascular disease (38.5%), cancer (34%), chronic respiratory disease (10.3%), AIDS (5.7%), and diabetes (4.6 %) and are based on the patient's needs rather than on the patient's prognosis; this is appropriate at any age and at any stage of severe disease and can be provided in conjunction with curative treatment [3]. According to the World Health Organization (WHO), in fact, PC is defined as "... an approach that improves the quality of life of patients and their families by addressing the problem associated with life-threatening diseases, through the prevention and relief of suffering, through the early identification, flawless assessment and treatment of pain and other physical, psychosocial and spiritual problems" [3]. The erroneous perception that PCs are synonymous with end-of-life (EoL) care deprives patients of their early approach, creating a culture of abandonment without optimizing its effectiveness. PCs can provide better outcomes for patients and their caregivers leading to improved quality of life, often at a lower cost, even if attempts to change traditional health services have had limited success and PCs generally remain only a service that responds to a social need [4].

The ATS/ERS guidelines on IPF management and therapy recommend PCs for the patients, as an adjunct to disease-focused care and should be addressed already during outpatient visits in all patients, in particular those with severe clinical impairment and/or with other comorbidities, both as advance directives of care and as end-of-life issues [5]. It is of note that IPF patients enrolled in PC programs live longer and enjoy a better quality of life, as well as having greater control over symptoms, such as dyspnoea, asthenia, weight loss, psychomotor agitation that accompanies the stages of advanced disease [6].

In a recent study by Younus *et al*. [7], data from 298 patients and their approach to palliative treatment were compared in different clinics; 63% of the patient cohort received PCs. In patients followed in interstitial lung disease (ILD) clinics with multidisciplinary disease management, the primary approach to care resulted in more patients receiving PCs, higher rates of management of non-drug dyspnoea, and treatments with opioids and oxygen therapy, which began 15 and 5 months before death, respectively [7]. Reliance on PC specialist referral for PC initiation outside of the ILD clinic resulted in delayed care [7]. In spite of this, patient referral for palliative care is delayed and most of them die in hospital. Indeed, in a recent retrospective study at the University of Pittsburgh's Simmons Center for ILD, end-of-life decisions were not taken in time and 57% of deaths occurred in hospital, whereas only 13,7% of the deceased had been sent to PCs [8].

Conversations about death and dying can be difficult, and doctors, patients, or family members may find it easier to avoid them altogether and continue treatment, leading to inappropriate end-of-life treatment [4]. In a study by Kalluri *et al*. [9], obstacles to advance care planning (ACP) have been identified, such as unpredictable disease evolution, insufficient and difficult communication, and poor prioritization. Therefore, knowing the end-of-life options can allow patients to make reasoned choices and reduce the risk of deaths in the ICU, as well as guide doctors in implementing early and meaningful conversations, as proposed by the authors in planning the ACP in the IPF (Figure 1) [9]. In this process, practical guidance and training are needed to improve practitioner competence and trust in the ACP, as well as clarity within organizations about role, policy and responsibilities.

The decision-making process in the planning of the PC and the EoL

In recent years, the main goals of PC in IPF have been focused on improving the quality of life by addressing related symptoms, social and psychological needs and seeking to have timely diagnosis and early access to holistic and palliative care treatment. Thus, by applying better supportive care (BSC), defined by all as therapeutic interventions aimed at controlling symptoms in patients with progressive diseases, PCs offer patients the opportunity to improve their quality of life, reduce the burden symptoms with a reduction in unplanned hospital admissions [10].

A potential model of PC for IPF patients was described by the study of Veigh *et al*. [11], which proposes three levels of PC for patients with ILD, COPD and bronchiectasis, supporting the ongoing holistic assessment of patient needs (Figure 2). The first level supports a holistic approach to care, that is introduced with the diagnosis of the disease and should include both general and specialized pulmonary PCs. The beginning of the complexity of symptoms leads to the second level, suggesting that health professionals must also evaluate the need to introduce specialized PC services. When patients develop complex symptoms that general practitioners and pulmonologists feel they are no longer able to manage effectively, they move to level three of the model, which proposes to go directly to specialized PC services. This study reinforced the importance of proactive PC that identifies the needs of the individual patient, and it is not influenced by their prognosis [11].

Starting from the three levels of complexity, it is possible to identify levels of intensity and appropriate settings for the provision of PCs, which are classified into three macro-areas: palliative approach, shared care and specialist PCs. All three levels of delivery can be integrated within the Local Palliative Care Network. For the palliative approach, the most appropriate setting is represented, in relation to the various phases of the disease and its severity, respectively by the patient's home, by the hospital (outpatient or in hospital), by extra-hospital facilities, by residences nursing homes and health residences for the disabled.

For patients of the second or intermediate level of complexity of needs, the team of specialist PCs acts by sharing the treatments and therapeutic objectives with the patient and agreeing them with a plurality of health professionals who participate in the care, each with their own specific skills and most appropriate areas of inter-

vention at home, or in the hospital to support the ward team, in the hospital or specialist outpatient clinic of PCs.

For a high level of complexity of the needs of the patient and of the caregiver/family unit, the responsibility for care lies with the PC specialist team. The GP and the branch specialist can continue to play a role mainly aimed at fostering the continuity of the treatment path and supporting the relational aspects. The most consistent care setting is the hospital or even the home through being taken care of by teams of specialized, multidisciplinary and dedicated PCs (home UPC) [12-14].

End of life decision making in medical practice is not a straightforward process; in fact, it involves not only legal but also ethical obligations. In this regard, it is worth to underline the cultural path that has developed in Italy since 2003 and culminated in 2017 with the approval of a specific law, which is based on the principles of protection of life, health, dignity, and self-determination of sick person [15]. This law, in fact, protects the right to life, health, dignity and self-determination of the person and establishes that no health treatments can be started or continued without the free and informed consent of the person concerned, except in the cases expressly provided for from law. Everyone has the right to know their health conditions and to be fully informed and updated to them about the diagnosis, prognosis, benefits and risks of the indicated diagnostic tests and health treatments, as well as about possible alternatives and the consequences of any refusal of medical treatment and diagnostic assessment or the renunciation of the same. All this has to be recorded in the patient's medical record and electronic health record [15]. The law also explicitly refers to consent an Advance Planning/Shared Care (APC) as a tool capable of enhancing the Advance Treatment Planning (ATP) witnessed by the role of the Trustee [15].

However, religious and cultural values, often superimposed on social or psychological needs, must be recognized and considered [16]. Notably, the study of Evangelista et al. that examined thirty-nine publications on the relevance of the spiritual dimension in the care of patients with palliative care, pointed out that religious and spiritual beliefs and performing spiritual practices, like meditation and praying, for example, can reduce anxiety and distress caused by terminal diseases, because these facilitate easing patients' mind [17]. It is also important to discuss both the possibility of "not-resuscitating" (DNR or AND - allow natural death) and "not-intubating" (DNI), with patients and their families, to avoid unnecessary therapies or unwanted interventions, upon entering the hospital in the terminal phase [18]. Rajala and colleagues have shown that the orders not to resuscitate (DNR) and the decisions of EoL come late and that the therapies probably continue until the last days of life, not considering the futility of these interventions. It sometimes may hard to make the decision not to ventilate a patient referred for acute respiratory failure. Decision not to ventilate usually depends on assessment of futility of care depending on poor short-term prognosis, patient's wishes and the high probability of poor quality of life in the future. Before making such decision doctors usually try to look for evidence on previous outcomes in similar cases [18]. It is underlined that medical interventions, such as CPR and ICU care, which are often considered futile by current medical standards, are not futile at all, but have significant ritual-

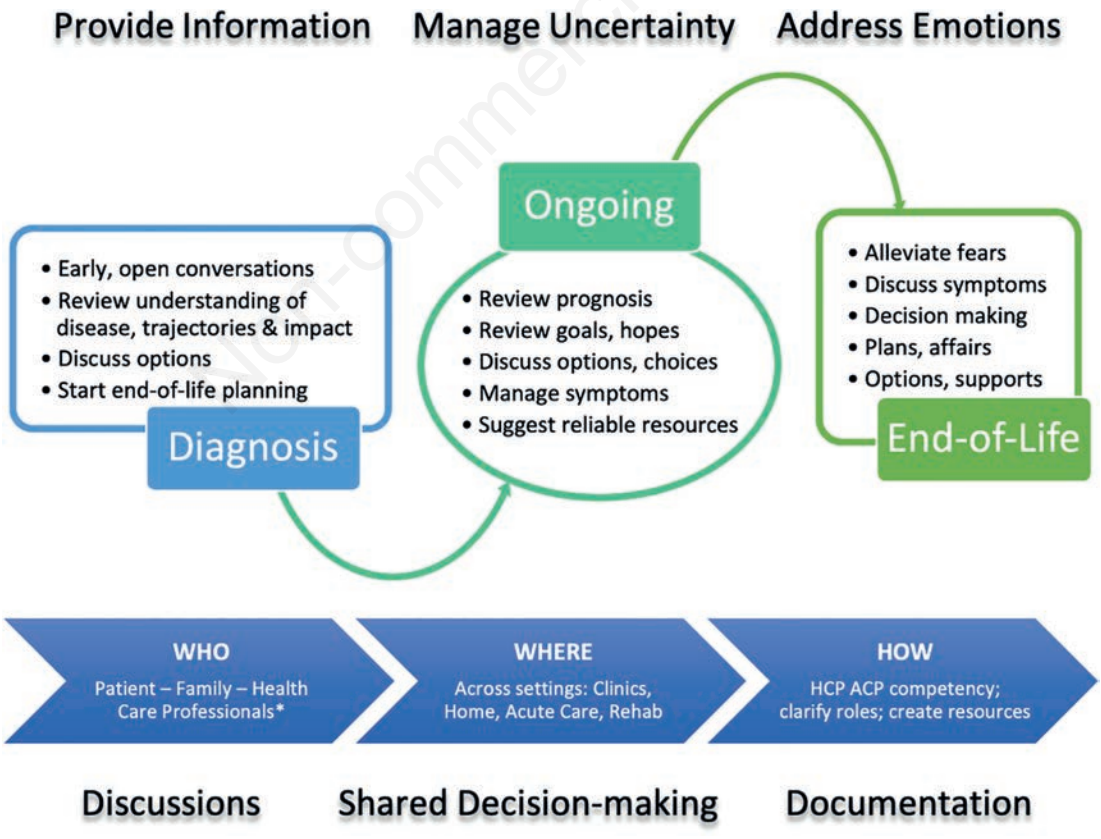

Figure 1. Framework of the Advance Care Planning (ACP) decision program under IPF. HCP, healthcare professionals involved; ACP, advance care planning. *Specialists and general practitioners, nurses, health professionals. Retrieved from: Kalluri M, *et al.* Am J Hosp Palliat Care 2022;39:641-51; with permission. License: https://creativecommons.org/licenses/by-nc/4.0/

istic value and serve important social functions in the process of dying. This work offers a new perspective on the ethical debate concerning medical futility and provides a means to explore how the social value of treatments may be as important in evaluating futility as biomedical criteria [19,20]. Most patients with IPF die in hospital with life-prolonging procedures and frequent use of opioids, this is an indicator of intent to relieve symptoms, but decisions of EoL still occurs very late. Advance care plans are the first discussion for EoL management and could improve PC for patients with IPF [18,21].

The Italian Society of Anesthesia Analgesia Resuscitation and Intensive Care (SIAARTI), in the last update [22], addressed the treatment of intensive care in terminal patients, since still today many clinicians implement them as a therapeutic option, especially when a defensive logic is prevailing. However, in recent years there has been a more attentive approach to the real needs of the sick person, in relation to the opportunity to undertake or continue an intensive care plan. Therefore, a "proportionate" treatment, that is legitimate and ethically licit has been identified only if, in addition to being clinically appropriate, it is consciously accepted by the sick person and is able to consistently be included in the person's life plan [22]. Anyway, all of this has not found adequate application during the recent COVID-19 pandemic, which has further fuelled the fear of death and reinforced the idea of health services as the sole guardians of death. The doctors and, above all, the relatives of the deceased person were absolutely not prepared for the idea of death, always present and/or possible, and the patients died of medical death, often alone in hospitals and intensive care

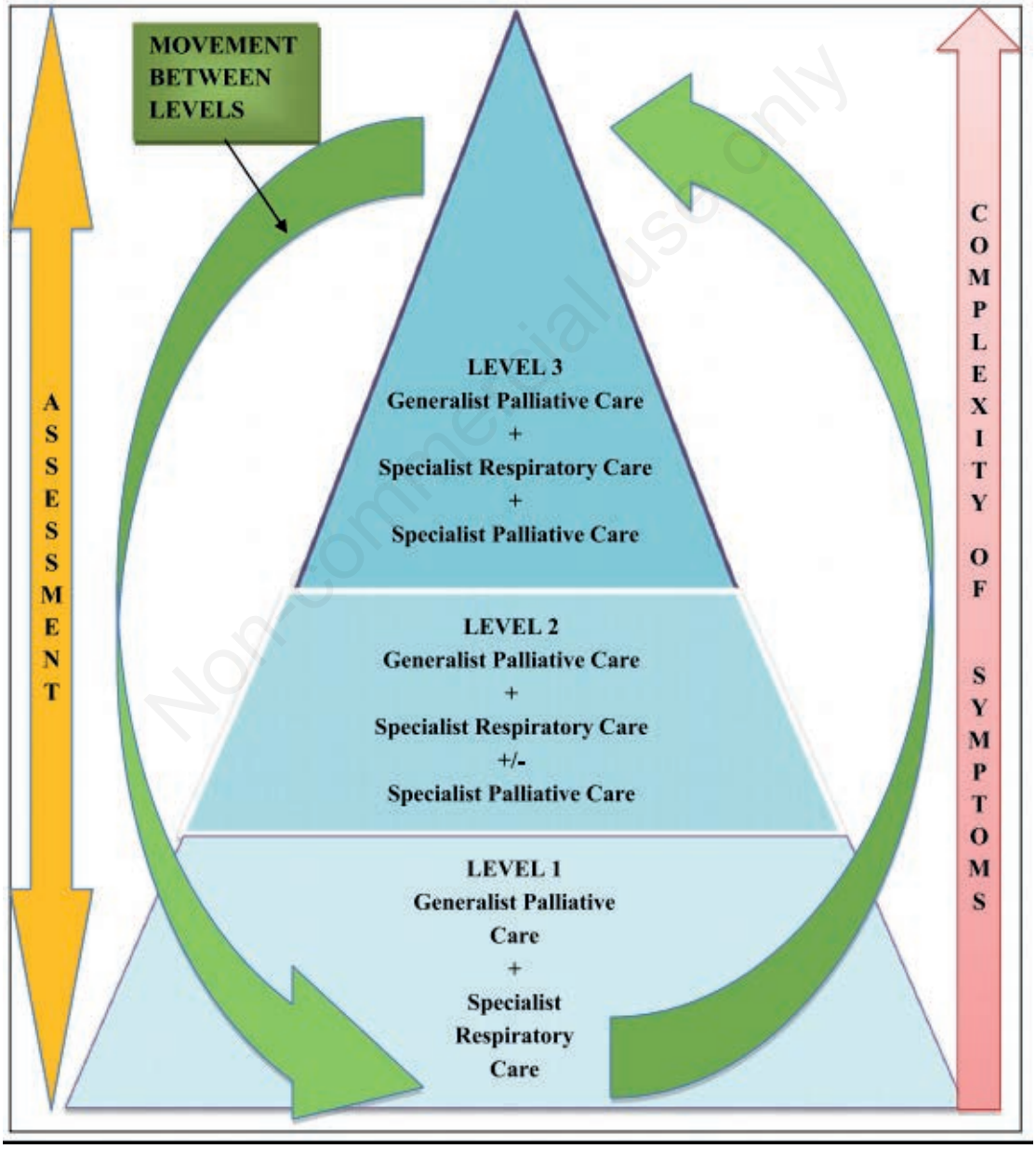

Figure 2. **Palliative care model for patients with non-malignant respiratory disease. Modified from: Veigh CM, *et al.* BMC Palliat Care 2018;17:6; with permission. License: http://creativecommons.org/licenses/by/4.0/**

units, unable to communicate with the family if not remotely [4]. It is important underline the COVID -19 pandemic forced health staff and decision makers to cope with a desperate shortage of resources (obliging to ration resources almost in a logic of combat medicine), setting up a scenario which could sooner or later materialize in public health services and, in such a context, should be important the role of telemedicine [23].

As the pandemic is hopefully coming to an end, there is no concrete evidence of a change in welfare, but only contrary signs that show how governments prioritize attempts to reduce only the number of deaths and not the extent of suffering, placing great emphasis on providing intensive and sub-intensive care and more lung ventilators, but not laws and programs on PCs. Mourning has been neglected, on the other hand anxiety about death and dying seem to have increased [4].

This pandemic period should help political leaders and health authorities to move as quickly as they can to ensure that there are enough resources, including personnel, hospital beds, and intensive care facilities, for what is going to happen in the next years [24]. Moreover, it would be necessary to solve organizational problems to prepare the health system to respond to a similar emergency in a joint, coherent, and homogeneous way across the country, as planned in the WHO document. In this perspective, Pulmonary Units and specialists can play a fundamental role in coping with the disease not only in hospitals, as intermediate care units, but also at a territorial level in an integrated network with GPs [25]. All of this may have had negative implications even in areas not strictly related to the pandemic, such as in the case of patients with IPF.

The timing of palliative care and EoL treatments

Care for people at the EoL, rather than being guided by rigorous protocols, should be based on clinical evidence and tailored to the patient's preferences and needs, in order to create individualized care plans in an early timing [16]. The guidelines of the General Medical Council on the EoL provide recommendations on communication and shared decision-making and constitute a useful resource for all health professionals [26]. In this regard, it is essential to recognize the EoL condition of patients with IPF by evaluating changes in signs/symptoms, such as to be able to identify them within the multidisciplinary team. Treating and taking care of patients is defined by a "simultaneous care" program that must start from the early stages of the disease (Figure 3) [27] as the progression of the disease will lead to an intensification of palliation inversely proportional to the reduction in the efficacy of pharmacological treatments, traditional supportive, and rehabilitation [27-29]. In a study by van Manen *et al*., a new model is proposed for the continuous treatment of IPF structured for comprehensive care, including palliative and EoL care. With this model, summarized in an "ABCDE" scheme (Figure 4), patient support was achieved by providing relevant information and adequate support and by providing care that improves patient comfort, focusing on the treatment of symptoms and comorbidities [30].

In recent years, the main goals of PC in IPF have been focused on improving the quality of life by addressing related symptoms, social and psychological needs, and seeking to have timely diagnosis and early access to holistic care and palliative treatment. Patients with IPF present many symptoms during the natural history of the disease and there is a need to use better supportive care (BSC), defined as the set of interventions and the multi-professional approach, aimed at improving and optimizing HRQoL (Table 1) [31]. Almost all patients with IPF experience progressive dyspnoea, with a greater or lesser impact on their quality of life. Dyspnoea and the resulting anxiety, in addition to decreased exercise tolerance, lead to functional disability and social limitations. In the management of dyspnoea, it is important to exclude comorbidities such as: pulmonary hypertension, heart disease, muscle weakness, sleep disturbances, and psychosocial factors [32]. Frequent use of opioids is used in PC phases, reflecting a great need to control dyspnoea in end-stage patients. Despite this, no

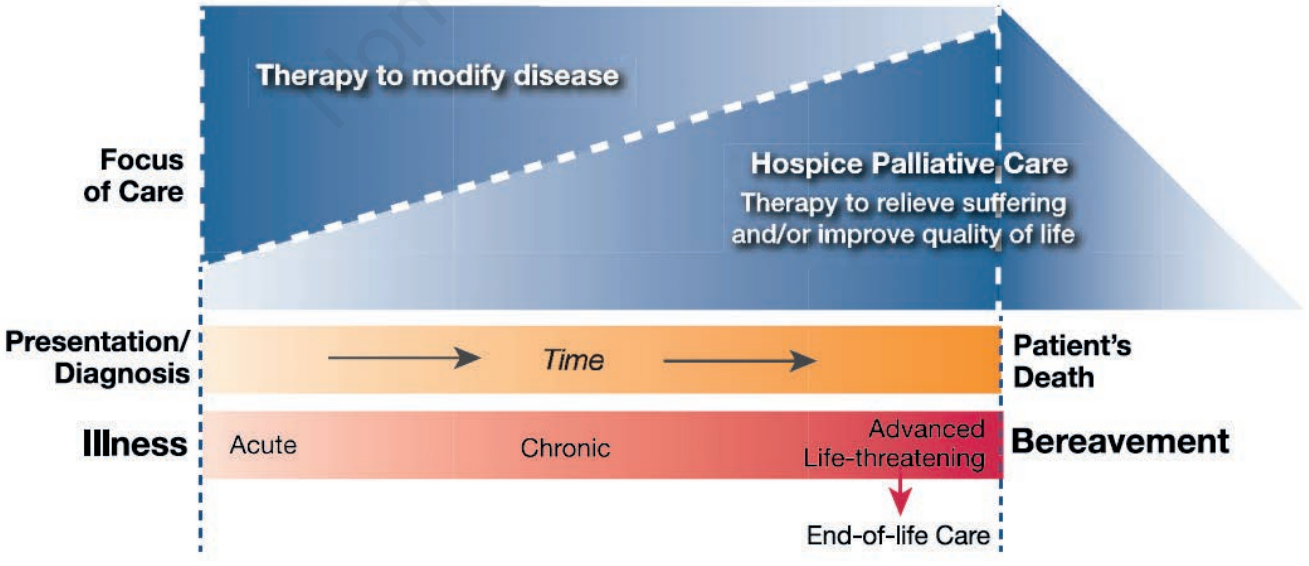

Figure 3. The role of hospice palliative care during illness. Retrieved from: A Model to Guide Hospice Palliative Care, Canadian Hospice Palliative Care Association, 2013; with permission.

controlled studies support the use of opioids in dyspnoea in patients with IPF, as they are often seen as EoL care, although it is widely used in refractory dyspnoea in general [32,33]. In this regard, in a study of 27 patients with IPF treated with opioids for worsening dyspnoea, none showed any significant increase in $PaCO_2$ or reduction in PaO_2 and all patients experienced significant relief of dyspnoea and decreased respiratory rate. The authors concluded that opioids reduce work of breathing, hence decrease respiratory rate, but do not affect alveolar ventilation [34]. This is also supported by the results of other small retrospective studies and, therefore, opioids should be evaluated as an early palliative treatment in these patients [35,36]. The poor prognosis of the disease and its progressive course can underlie feelings of sadness, fear, anxiety and panic. In a Swedish study, anxiety was more common (66%) in patients with IPF than in cancer patients (17%), so out of them 25% received antidepressants and 44% received anxiolytics [37]. Depressive symptoms are important predictors of quality of life and their treatment has not been studied in IPF but can certainly be alleviated with a supportive psychological care strategy [38]. Another reported symptom of IPF is cough which has been associated with disease progression. The exact mechanism underlying cough in patients with IPF is unknown but is most likely "multifactorial" and due to mechanical, biochemical and sensorineural changes, as well as to the associated comorbidities. Low-dose steroids are routinely prescribed for cough in IPF, although there is little data to support their effect [39]. Recent evidence suggests that the antifibrotic drug pirfenidone may have a positive effect on cough, not as effective as the more recent nintedanib, whose effect on cough is still unknown. Although there are no convincing data on cough suppressants in IPF, some patients report relief from these agents [40]. Another non-negligible symptom in patients with IPF is reduced exercise tolerance, which with the progression of the disease leads to less physical activity of the patients, negatively influencing social participation. Pulmonary rehabilitation (PR) can be an excellent therapeutic approach, offering significant short- and long-term improvements in exercise capacity, HRQoL and degree of dyspnoea. Therefore, rehabilitation should be recommended as a standard treatment for patients with IPF with early referral, allowing patients to benefit most from it predominantly when they are still in good physical condition [41]. In the general framework of palliative treatment, another important point is the management of respiratory failure which represents a natural evolution of IPF. In its approach, mechanical ventilation is rarely effective and must be used judiciously in these patients [42]. Non-invasive mechanical ventilation (NIV) has been used to relieve dyspnoea as a palliative treatment and in acute chronic obstructive pulmonary disease [43]. The benefit of using NIV in symptomatic therapy of patients with IPF has not been demonstrated and, therefore, NIV is not routinely recommended. A study on a large cohort of patients with IPF has shown that mechanical ventilation is associated with a mortality rate of 50%, but that its palliative use may be appropriate in relieving dyspnoea in selected patients. However, mechanical ventilation can be a useful bridge for lung transplantation, provided that the transplant can be performed quickly [44]. Contrary to NIV, oxygen therapy is recommended for IPF patients with hypoxemia, so it is not surprising that most patients with IPF have received oxygen therapy. An effective alternative to NIV and/or oxygen therapy alone is high flow nasal cannula therapy (HFNC), which provides a high flow of heated and humidified oxygen. Oxygen therapy with HFNC is a relatively new method for the treatment of hypoxemic respiratory failure and dyspnoea. In a randomized controlled trial of normocapnic patients with severe hypoxemic respiratory failure, HFNC was comparable to NIV in reducing the need for invasive ventilation, but was superior in relief of dyspnoea and reduction in respiratory rate [45]. HFNC is a ventilation technique that requires less training from hospital medical and nursing staff than NIV, so it can be applied to a greater number of patients even in ordinary wards outside the intensive setting [46]. HFNC can be used for severe respiratory failure hypoxia of any cause, including interstitial lung disease, cancer, and pneumonia, but data are still scarce on its use in patients approaching end of life.

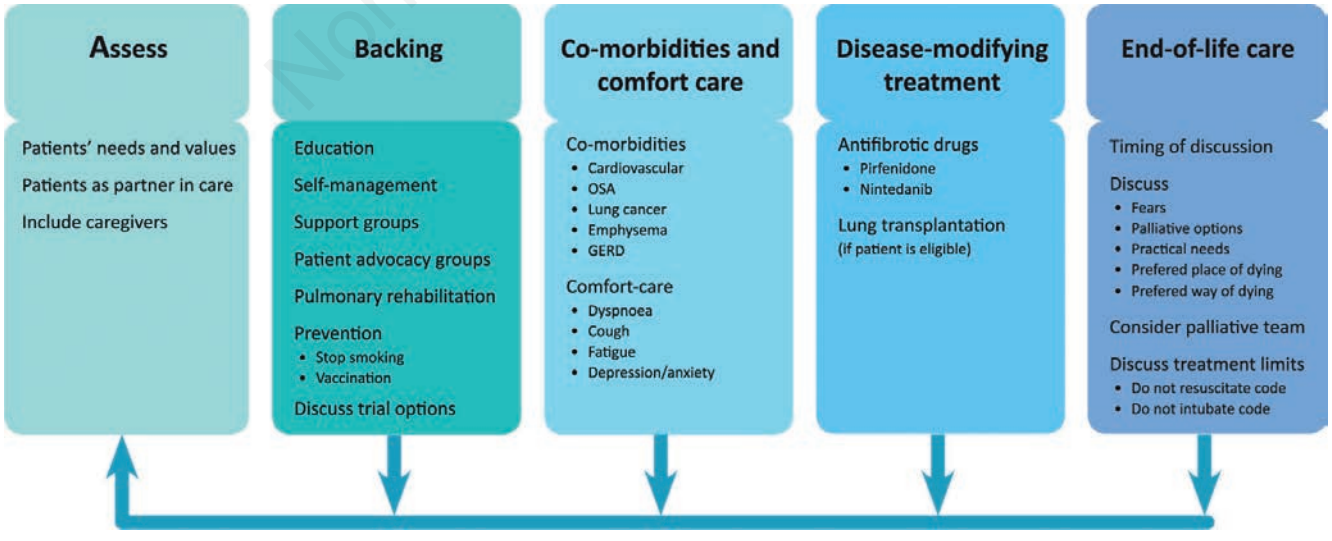

Figure 4. The ABCDE model shows a possible structured approach for the comprehensive care of IPF, including palliative care throughout the course of the disease. Retrieved from: van Manen MJ, et al. Ther Adv Respir Dis 2017;11:157-69; with permission.

In the absence of treatments, which can slow and/or modify the evolution of fibrosis, with significant effects on respiratory failure, future research should aim at patient-centered results as well as HRQoL, both as experimental endpoints and as important measures of efficacy of therapeutic interventions [47]. In chronic diseases, including IPF, it becomes essential to establish Diagnostic-Therapeutic Assistance Path (DTAP) based on guidelines already prepared and shared. In this regard, a DTAP for IPF has recently been drawn up in the Campania Region (Italy), where PC and EoL therapy delivered by a multidisciplinary team of doctors, nurses and social workers in any care setting (home or hospital), represent a real strength [48].

Conclusions

Palliative care provides excellent outcomes for patients and their caregivers and leads to improved quality of life, often at a lower cost, but attempts to raise awareness in the NHS have had limited success and PCs generally remain only a few real social needs with a poor response from basic, hospital and/or territorial care services. It should be desirable for healthcare professionals to recognize that advance care planning is not about bringing the patient closer to the end of life, but a holistic communication process that addresses symptoms, psychosocial and emotional needs, alleviates fears, promotes hope and arouses involvement.

In this process, the following items are necessary: guidelines, greater training and skills of health professionals, greater confidence in advance planning of care, greater clarity within health and social organizations regarding the role, policy and responsibilities around to palliative care. Death, dying and bereavement have become increasingly unbalanced and relationships and interpersonal relationships are being replaced by health professionals and operational protocols. EoL care has become highly medicalized and families and communities have been pushed to the side-lines, losing familiarity and confidence in supporting death, dying and bereavement. Furthermore, the Lancet Commission on Global Access to PC and Pain Relief has shown that the relationship with death in low- and middle-income countries is unequal, as the rich ones receive excessive care while the poor ones, the majority, receive little or no attention or relief from suffering and have no access to opioids [49].

IPF is characterized by significant reductions in the quality of life and survival and, in its evolution, can be compared to a neoplastic pathology. However, PC is still conspicuously inaccessible to many patients with IPF compared to oncological diseases [1]. In the terminal stages of the disease, patients with IPF suffer from debilitating cough with severe dyspnoea, as well as significant physical and functional impairment, associated with significant comorbidities such as pulmonary hypertension, cardiovascular disease and lung cancer, which worsen their quality of life and survival.

Finally, integrating palliative care more and more into the clinical approach in patients with IPF means trying to evaluate multidisciplinary care pathways, encouraging treatments with oxygen, opiates, alternative therapies like HFNC, and rehabilitation for symptom control, already from the initial stages of the disease. Therefore, although the impact of PCs on HRQol in IPF has not been fully demonstrated yet, there is no doubt that early supplementation of palliative care can undoubtedly improve symptom management, HRQol and EoL care, reducing critical events and hospitalization, as well as healthcare costs.

Table 1. Better supportive care (BSC) for managing the most frequent signs and symptoms in patients with idiopathic pulmonary fibrosis (IPF). Reproduced from: Ferrara G, *et al.* Eur Respir Rev 2018;27:170076; with permission. License: https://creativecommons.org/licenses/by-nc/4.0/

Symptom/factors limiting QoL	Tool for assessment	Interventions
General well-being	EQ-5D	Management of symptoms influencing QoL
	SF-36/RAND	Mindfulness/meditation
	SGRQ-IPF#	Physical rehabilitation¶
	K-BILD#	Nutritional support
	ATAQ-IPF#	
Dyspnoea	mMRC	Physical rehabilitation¶
	SGRQ-IPF#	Supplemental oxygen
	K-BILD#	Treatment of PH with sildenafil¶
	ATAQ-IPF-cA#	Pharmacological interventions (morphine/benzodiazepines)¶
	UCSD SOB#	
Cough	LCQ#	Poor effect of usual anti-tussive drugs
	VAS#	Systemic steroids
	CQLQ#	Thalidomide¶
		Gabapentin
		Opiates
		PSALTI
Anxiety/depression	EQ-5D	Counselling/cognitive behavioural therapy
	SF-36/RAND	Antidepressants
	K-BILD#	Physical rehabilitation
	SGRQ-IPF#	Nutritional support (loss of appetite)
	ATAQ-IPF-cA#	
Weight loss	NA	Nutritional support
Comorbidities	NA	Treatment of PH with sildenafil¶
		Anti-reflux measures in patients with GORD

Abbreviations

AND, allow natural death;
APC, advance planning/shared care;
ATP, advance treatment planning;
BSC, better supportive care;
DNI, not-intubating;
DNR, not-resuscitating;
DTAP, Diagnostic-therapeutic assistance pathways;
EoL, end-of-life care;
HFNC, high flow nasal cannula therapy;
HRQoL, health-related quality of life;
ILD, interstitial lung disease;
IPF, idiopathic pulmonary fibrosis;
NIV, non-invasive mechanical ventilation;
PC, palliative care;
WHO, World Health Organization.

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