Review Article

End stage pulmonary disease

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Abstract: Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality. Lung cancer is the number one cause of cancer mortality by far. End-stage lung disease and lung cancer will often result in distressing symptoms such as dyspnea and pain. The impact of advanced nonmalignant lung disease such as COPD on quality of life and functioning is similar to that of lung cancer. Palliative care should be offered to those patients early and concurrently with restorative care. Early palliative care in lung cancer improves quality of life and can even prolong life. A timely discussion about end-of-life care including mechanical ventilation should be encouraged in advanced cases. The fear of causing emotional distress is usually unfounded and the patients will appreciate the honest discussion. Palliative care in lung disease as in general should follow a multidisciplinary approach with a special emphasis on dyspnea and pain control. Pulmonary rehabilitation remains a useful tool in palliative care. Terminal discontinuation of mechanical ventilation is ethically justified if the patient or his surrogate decision maker wants that. Immediate extubation and gradual decrease of ventilatory support are both acceptable and each has advantages and disadvantages. Aggressive use of opiates and sedatives in a dying person is acceptable even if the risk of hastening death is high.

Keywords: Lung disease; lung cancer; palliative care; dyspnea

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Introduction

End-stage lung disease resulting in severe dyspnea and debilitation is a common indication for palliative care referral. Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and ranks third behind only heart disease and cancer in the US (1). COPD and other chronic lower respiratory conditions are responsible for close to 150,000 deaths a year in the US alone. Lung cancer claims even a higher number of deaths and is by far the number one cause of cancer-related mortality. End-stage lung disease imposes an enormous emotional and financial burden on patients and patient families. Progressive respiratory conditions frequently lead to respiratory failure and persistent distressing symptoms such as severe dyspnea.

Dyspnea is a highly unpleasant subjective perception of difficulty breathing. Pain and dyspnea are the most taxing symptoms in the terminally ill. Their management has been and remains an important aspect of palliative care. The treatment of dyspnea is challenging and it is often undertreated. A detailed discussion on dyspnea and cough including treatment options can be found in a different article of the journal *Public Health and Emergency* (*PHE*).

Palliative care initially focused on the end-of-life care (2). Subsequently, the scope of palliative management expanded to improving quality of life for patients and families regardless of the stage of disease. Even though it is commonly viewed as the next logical step after restorative therapy has failed and it remains the main component of end-of-life management, palliative care can be delivered concurrently with curative intent efforts (3).

Chronic obstructive pulmonary disease (COPD)

COPD is a lung disease most commonly caused by tobacco smoke exposure. COPD is characterized by an obstructive

pattern (flow limitation) evident on spirometry. The airflow obstruction is progressive and irreversible. Chronic bronchitis is a clinical syndrome of chronic cough and sputum production closely related to COPD. Emphysema is another aspect of the same smoking-related pathology characterized by histological or radiological evidence of alveolar destruction. In clinical practice, COPD, chronic bronchitis and emphysema are often used interchangeably as they reflect different aspects of the same underlying, most commonly tobacco-related, lung pathology. The palliative management of other obstructive lung conditions—bronchiectasis, bronchiolitis obliterans and severe fixed bronchial asthma—is similar to that of COPD.

The prevalence of smoking has steadily declined in most of the Western world since the 60–70s but tobacco use remains quite prevalent worldwide. With an aging population and the progress made in cardiovascular prevention and early cancer detection, the importance of COPD to health care, especially end-of-life care, is growing. COPD is a progressive disease and further loss of function is often observed after smoking cessation. The affected individuals are frequently unaware of their condition for many years. It is not uncommon for the symptoms to develop decades after quitting smoking due to the natural loss of lung function with aging. Continuous tobacco exposure, however, results in accelerated lung function deterioration. The relationship between the severity of COPD measured by airflow impairment on spirometry and symptoms is not quite predictable and varies from person to person. Once the pulmonary reserve is exhausted symptoms will develop. The course of COPD is characterized by disease exacerbations with relatively quiescent periods in between. An exacerbation can lead to unexpected death. Subsequent recovery may not be complete, resulting in a step-wise deterioration of lung function. For this reason, the prognosis is quite variable and expected survival may be difficult to accurately predict even in severe cases. The BODE index is a popular way to estimate long-term survival in COPD (4). It takes into account: the body mass index, airflow obstruction, dyspnea severity and exercise capacity. The BODE index ranges from 0–10. The highest quartile (BODE 7–10) carries mortality of 80% at 52 months. However, even in this most severe group, the 1-year survival exceeds 90%. Therefore the BODE index is inadequate to identify candidates for end-of-life care. Frequent exacerbations, general functional decline and worsening symptoms will alert a vigilant health care professional of the high likelihood of the patient entering the terminal stage of their disease. The impact of symptoms of end-stage COPD on quality of life and functional status is comparable to that of cancer (5). Although palliative and hospice care have been traditionally viewed as part of cancer management, more attention is paid today to non-malignant yet equally debilitating conditions. When faced with an advanced condition, providers should discuss palliative care strategies along with disease specific restorative therapy and prevention. The patient's attitude toward intubation and mechanical ventilation should be explored. Living wills and advanced directives may need to be encouraged if not already in place. Clinicians often avoid these unpleasant topics, which may deprive the patient of an early palliative intervention and proper preparation with regards to their personal affairs (6). Fears that this discussion will cause undue distress are generally unfounded. The patients by and large want to be well informed and most will appreciate a frank discussion about end-of-life care. Their attitudes to mechanical ventilation and resuscitation cannot be predicted based on age and disease severity (7). Patients' information needs, however, are variable and an individual approach should be undertaken in each case (8).

In severe, end-stage cases, chronic respiratory failure sets in with persistent and debilitating symptoms. Dyspnea is invariably present and often dominates the patient's life. It requires aggressive management, especially in the terminally ill. Since flow limitation and difficulty ventilating are a hallmark of COPD, bronchodilators constitute an important component of therapy. β_2-sympathomimetic agonists (albuterol, salmeterol) and anticholinergic agents (ipratropium, tiotropium) are used for this purpose. Bronchodilators relax the smooth muscles in the airways and improve airflow. Inhaled corticosteroids have been widely used in COPD for maintenance therapy. Their role in bronchial asthma is well established but the effectiveness of inhaled steroids in COPD is more controversial. Enteral and parenteral steroids may be needed in severe cases of persistent symptomatic bronchospasm or during exacerbations of otherwise less severe disease. Oxygen is almost always needed in end-stage COPD and often in less severe cases due to hypoxemia. Oxygen improves survival in COPD and may alleviate dyspnea in hypoxemic patients (9).

Theophylline may be of some value for symptomatic relief in COPD. It is believed to have bronchodilator and anti-inflammatory properties (10). Unfortunately, the narrow therapeutic window and potential for adverse effects limit its use.

Smoking cessation is of utmost importance for all COPD

patients but the terminally ill. Eliminating tobacco exposure results in mild but rapid improvement in lung function. The rate of further decline in nonsmokers is half of that in those who continue to smoke (11). Smoking cessation in the setting of end-of-life care is more controversial. The benefits for the terminally ill are likely minimal. Safety considerations may be of higher importance as oxygen use is universal in this patient population. The fire hazard is real and the patient and his caretakers need to be educated and advised against the use of open fire when oxygen is in use (12). Fortunately, smoking is not very common among individuals dying of lung disease and suffering from severe dyspnea.

Respiratory rehabilitation is increasingly recognized as an effective method to maintain functional status and manage symptoms in COPD (13). As the focus shifts to palliative care in progressive respiratory failure, high intensity endurance training to maintain functional ability may become less feasible. However, several low-intensity protocols, including interval training and single-leg ergometry, have demonstrated ability to improve dyspnea and functional capacity (14). The disease trajectory in COPD is defined by slow progression punctuated by exacerbations. This is in contrast to the precipitous decline observed in lung cancer and other rapidly progressive conditions (15). Thus, pulmonary rehabilitation remains an important tool in the management of COPD even after the focus shifts to palliative care. Other aspects of pulmonary rehabilitation including education (breathing strategies, energy conservation and work simplification, end-of-life education), psychosocial and behavioral intervention (coping strategies, stress management) become more relevant (16). A Cochrane review concluded that rehabilitation "relieves dyspnea and fatigue, improves emotional function and enhances patients' sense of control over their condition. These improvements are moderately large and clinically significant." (17). COPD patients with severe dyspnea benefit as much from pulmonary rehabilitation as patients with less severe disease (18). These individuals should not be excluded from rehabilitation programs.

Noninvasive ventilation may be helpful for symptomatic relief of breathlessness in COPD. It decreases the need for intubation, shortens the hospital stay and improves in-hospital mortality rate in patients with COPD exacerbation requiring intensive care admission (19). Intubating and placing the patient on mechanical ventilation is often a psychological line that both the patient and the clinicians are sometimes reluctant to cross. Noninvasive ventilation is an acceptable temporary solution to treat symptoms and bridge the patient over an acute complication such as COPD exacerbation or pneumonia. This mode of ventilation, however, generally requires an alert and, to some extent, cooperative patient and can be, in and of itself, a source of discomfort. It should never be offered as a permanent solution and its use should be discouraged if no improvement in the patient's condition is expected. Noninvasive ventilation can be used in respiratory failure of any etiology, not just COPD. It is particularly beneficial in pulmonary edema as positive pressure ventilation decreases venous return to the heart and thus improves pulmonary congestion (20).

Depression and anxiety often complicate both malignant and non-malignant end-stage lung disease and are especially frequent in patients suffering from constant dyspnea (21). Management of mood disorders and anxiety is an integral part of the palliative management of these patients. Pharmacological treatment and/or psychotherapy can be of help. If needed, consultation should be sought from a psychiatrist.

Lung cancer

Currently, bronchogenic carcinoma is the most common cancer causing death. Due to their unique role in the circulation, the lungs are also a common location for metastatic hematogenous spread of other malignancies. The disease trajectory of lung cancer and most other types of cancer is characterized by initially preserved functional capacity followed by rapid decline and death (15). This makes identifying individuals in the final stage of their disease easier compared to COPD. The 90-day mortality of patients with inoperable non-small cell lung cancer who present with respiratory failure approaches 100% (22).

The final year of life of lung cancer patients is quite similar to that of patients with chronic lung disease. The prevalence of dyspnea in chronic lung disease is higher—94% *vs.* 78% in lung cancer. Anorexia is more common in lung cancer—76% *vs.* 67%. The rate of cough, nausea, low mood and insomnia is similar (23). The high rate of severe symptoms has a large impact on the quality of life of those patients. Palliative care is an extremely valuable tool to address discomfort and distress in this patient population (*Table 1*).

A detailed discussion of dyspnea, pain and cough can be found elsewhere in this journal. As the same general treatment principles apply to the management of those ever-troublesome symptoms in lung cancer, herein these issues will not be addressed in much detail.

Table 1 Palliative measures in lung cancer

Symptom/complication	Treatment	Remarks
Bone metastases	Pain medications, external beam radiation, steroids, bisphosphonates, calcitonin, systemic radionuclides, internal fixation, endoprosthesis, arthroplasty, chemotherapy	Squamous cell carcinoma has the lowest response rate to radiation. Steroids may be beneficial if high osteolytic activity is present. Bisphosphonates are effective, low-toxicity adjunctive agents
Spinal cord compression	External beam radiation, surgical stabilization, high dose steroids, chemotherapy	Early intervention in ambulatory patients is effective in preserving mobility
Brain metastasis	Surgical resection of solitary lesions, external beam radiation, stereotactic radiosurgery, chemotherapy, steroids	Palliative treatment of brain metastasis may help slow disease progression and prolong survival
Superior vena cava syndrome	Caval stents, external beam radiation, chemotherapy	If technically feasible, caval stents provide best results
Anorexia	Megestrol, medroxyprogesterone, olanzapine, cannabinoids, cyproheptadine	Treatment not always necessary
Malignant pleural effusion	Thoracentesis, pleurodesis, pleural catheters, chemotherapy	Outpatient placement of tunneled catheters is an effective long-term solution
Airway obstruction/ hemoptysis	Laser, electrocautery, argon plasma coagulation, cryotherapy, balloon dilatation, metallic and silicone stents, high-dose radiation brachytherapy, photodynamic therapy, bronchial artery embolization, lobectomy	Mortality of lung cancer-related massive hemoptysis is 60%

Muskuloskeletal and nervous system complications

The localized and proliferative nature of lung cancer sets it apart from other, mostly diffuse, lung conditions. Not common in other lung disorders, pain from local or metastatic tissue invasion often complicates the course of lung cancer. As any cancer pain, it can be severe and debilitating. Opiates are frequently needed. External beam radiation can be applied with palliative intent to treat symptoms of locally spreading malignant tumor (airway obstruction, pain) or metastatic lesions (bone, brain). On average, about ¾ of bone metastatic lesions respond well to radiation therapy with the exception of squamous cell cancer, whose response rate is less than 50% (24). Higher fractionated doses have the most predictable and lasting response but a single large fraction can be helpful in providing quick pain relief, especially in patients with short survival expectancy and small extremity lesions (25). The application of the latter is limited by the higher rate of local adverse effects. Adding steroids to radiation therapy may benefit some patients, especially those with high levels of urine hydroxyproline excretion indicating high osteolytic activity (26). Bisphosphonates are well tolerated and can be effective for pain management. More importantly, they can be used as an adjunctive treatment added to radiation therapy. The combination is more effective than either modality alone with minimal or no additional toxicity (27,28). The response rate of this regimen exceeds 90%. Although not widely used for this purpose, calcitonin has been found by some to be effective in alleviating pain related to bone metastases (29). Other data suggest that the role of calcitonin as an adjunctive agent in the treatment of intractable pain is extremely limited (30). Administration of bone-targeted enteral or parenteral radionuclides (most commonly Strontium^{89}, Samarium^{153} or Phosphorus^{32}) has shown a variable response rate but can be a useful addition when medical therapy is not sufficient and external radiation is not feasible (31-33). Prophylactic internal fixation of impending pathological fractures can be considered in ambulatory patients (34). The following criteria have been proposed for preventive fixation: persisting or increasing local pain despite the completion of radiation therapy, permeative involvement, a solitary well-defined lytic lesion greater than 2.5 cm, a solitary well-defined lytic lesion circumferentially involving more than 50% of the cortex and metastatic involvement of the proximal femur associated with a fracture of the lesser trochanter (35). Endoprosthesis

or total arthroplasty may be needed for intracapsular or very proximal lesions (36). Transcutaneous injection of ethanol can be attempted in terminally ill patients with intractable pain not responding to other treatment modalities (37).

Spinal cord compression is a disabling complication of metastatic bronchogenic carcinoma. Ambulatory patients have a very good chance to preserve their mobility if promptly treated (38). Radiation is considered first-line therapy. Surgical intervention with laminectomy, debulking and/or stabilization should be considered in the case of spinal instability, progressive neurologic deterioration from bony collapse and compression, intractable pain or failure of conservative means of treatment (39). High doses of dexamethasone (96 mg/day) have been shown to favorably affect outcome in metastatic cord compression related to solid tumors (40). Lower doses are probably not effective (41).

About one third of patients with non-small cell lung cancer develop brain metastasis—an ominous sign indicating poor short-term prognosis. An aggressive approach with surgical resection, stereotactic radiosurgery, radiation and/or chemotherapy can provide some control over the disease progression and meaningful survival benefit (42,43). Steroids are effective but their benefit is temporary (44). Steroids are recommended for concurrent use with radiation therapy. Their application should be limited to 1 month due to the high rate of adverse effects beyond the first 3–4 weeks (45).

Superior vena cava (SVC) syndrome

SVC syndrome is a complication of chest malignancies caused by occlusion of SVC by external compression. The affected patients develop swelling of the face and upper extremities often associated with dyspnea. SVC syndrome requires urgent management. Traditionally external radiation has been the modality of choice for lung cancer and other malignancies expected to respond to radiation. More recently, caval stents have been added to the palliative clinician's armamentarium (46).

A Cochrane review suggested that stents might be the most effective treatment in SVC syndrome (47). Chemotherapy, usually in addition to radiation, can be helpful in small cell lung cancer (SCLC), lymphoma and other chemosensitive tumors.

Anorexia

Anorexia is common in end-stage lung disease—both malignant and non-malignant. The degree to which poor appetite and weight loss impact the patient's quality of life is variable. Some patients are not particularly distressed by these symptoms. For others, anorexia and weight loss are a constant reminder of having an incurable disease (48). Symptomatic treatment with megestrol (49), olanzapine (50), medroxyprogesterone, cyproheptadine or cannabinoids can be offered to those patients. Cannabinoids are also effective antiemetic agents (51). Nausea is common and can be extremely troubling to patients receiving chemotherapy. It should be aggressively treated. Appetite stimulants and nutritional support unfortunately do not improve lean body mass significantly as cachexia is caused by upregulated catabolic pathways and not just by poor oral intake (52).

Malignant pleural effusions

Malignant pleural effusions are common in lung cancer and can complicate other malignancies. Lung carcinoma is the number one cause of malignant effusions (53). Management of symptomatic pleural collections is an important aspect of the palliative care of these patients. Thoracentesis is helpful in the acute treatment of large symptomatic effusions. Recurrence is common and often rapid. Indwelling tunneled and nontunneled pleural catheters as well as pleurodesis can be considered in those cases. Tunneled indwelling catheters are an effective way to manage malignant effusions and feature a low complication rate (*Figure 1*). The procedure can be done in an outpatient setting. Symptomatic improvement is seen in more than 95% of the cases (54). Spontaneous pleurodesis is common. For these reasons, tunneled catheters are becoming the treatment of choice for recurrent malignant effusions and are clearly superior to other options in patients with trapped lung (55).

Airway obstruction and hemoptysis

Airway compromise resulting in obstruction or hemoptysis may require aggressive palliative measures. The choice of intervention depends on the urgency of the situation, lesion anatomy and desired outcome. In the case of intraluminal obstruction, debulking procedures can be performed using laser, electrocautery, argon plasma coagulation or cryotherapy. Balloon dilatation can be applied to short negotiable airway stenosis, frequently supplemented by stent deployment or performed prior to brachytherapy (56). Airway stents help maintain patency after debulking or dilatation. Uncovered metallic stents are relatively easy to place and do not require rigid bronchoscopy. They may

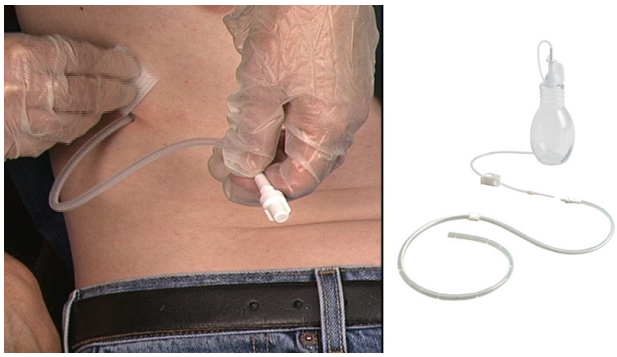

Figure 1 PleurX® tunneled catheter. (Courtesy of CareFusion Corporation).

be a good choice for external compression or emergent procedures but their long-term efficacy is limited due to tumor ingrowth and overgrowth when used for intraluminal lesions (57). Silicon stents may be more appropriate for more lasting results but those do require rigid bronchoscopy and are more prone to migration (58).

High-dose radiation (HDR) brachytherapy is used to deliver internal radiation directly to tumors located in the large airways in order to promptly resolve obstruction or control bleeding (59). It can be used as stand-alone treatment or as an adjunctive modality following external radiation, stent placement or debulking procedures. Brachytherapy does not eradicate the tumor lesions and rarely prolongs survival but it can be an extremely effective palliative measure, especially combined with external radiation. The palliation rate for hemoptysis exceeds 95% and HDR improves dyspnea and chest pain in 80–90% of the cases (60).

Photodynamic therapy uses light to inflict tissue injury to targeted malignant lesions after the application of light sensitizers, usually polyhematoporphyrins. It is a useful palliative measure to treat inoperable airway lesions with a high rate of successful resolution of endobronchial obstruction (61). The bronchoscopic illumination is performed 1–3 days after the administration of the photosensitizer. For this reason, photodynamic therapy is not suitable for emergent treatment. Lesions with a surface area exceeding 3 cm^2 are generally considered poor candidates for photodynamic therapy (62).

Hemoptysis can be palliated with bronchial artery embolization. If endobronchial intervention or embolization are not feasible or are unsuccessful, palliative lobectomy or pneumonectomy are occasionally done in patients who are otherwise considered unsuitable candidates for curative surgery (63). Mortality of massive hemoptysis (blood loss ≥200 mL/24 h) in lung cancer is 60% despite any intervention-much higher than in other etiologies (64).

Chemotherapy

The palliative application of chemotherapy is common in lung cancer. Platinum-based regimens have traditionally been the treatment of choice for non-small cell lung cancer. Pemetrexed, a taxane (docetaxel), gemcitabine or a vinca alkaloid (vinorelbine) is generally added to the regimen. Vascular endothelial or epidermal growth factor (EGF) inhibitors may have a role in selected cases. Poor performance status patients are usually not considered good candidates for full chemotherapy. The rate of adverse reactions is high and survival is poor in those patients (65). They can be palliated with a single EGF receptor inhibitor if a sensitive mutation has been identified in the tumor. This regimen can improve the patient's functional status. Gefitinib, a commonly used EGF receptor inhibitor, used as monotherapy has shown a response rate of 70%, a disease control rate as high as 90% and median survival of 18 months in patients with poor functional status, who are not suitable candidates for full chemotherapy (66).

SCLC is an aggressive malignancy that progresses rapidly and metastasizes early. Chemotherapy is the treatment of choice as SCLC is rarely curable by surgery (67). Radiation therapy is added to the regimen for disease limited to the same hemithorax (limited stage SCLC). SCLC is very chemo- and radiosensitive with a high initial response rate. The most commonly used chemotherapy regimen is a combination of a platinum-based agent and etoposide. Quick relapse is however the rule and only 10–15% of patients with limited stage disease achieve survival beyond five years (68). Therefore, at the onset of the treatment regimen, chemo- and radio-therapy are considered both curative-intent and palliative. This is an example that the separation of restorative and palliative therapy is often artificial and symptom control can be pursued along with curative efforts.

It has long been recognized that early palliative care in metastatic non-small cell lung cancer results in significant improvements in quality of life and mood. Patients receiving timely palliative therapy live longer and require less aggressive care at the end of life (69). Early multidisciplinary symptom management is highly recommended.

Other lung diseases

The general principles outlined previously about the

management of advanced COPD and lung cancer are applicable in other forms of end-stage lung disease and respiratory failure. The disease specific treatment is tailored to the particular disease. Bronchodilators are often used even if the underlying respiratory condition is restrictive and does not affect primarily the airways (e.g., idiopathic pulmonary fibrosis, other interstitial lung diseases). There is little evidence or sound theoretical consideration to justify the use of bronchodilators in the absence of obstruction but it is hard to condemn this practice when faced with a severely symptomatic patient and limited treatment options.

In like manner, oxygen use is acceptable in dyspneic non-hypoxemic patients if it provides subjective relief.

Although most research has been done in COPD, there is clear evidence that pulmonary rehabilitation is no less beneficial in other respiratory conditions (70). Individuals with advanced interstitial lung disease, especially idiopathic pulmonary fibrosis, have generally a shorter disease trajectory compared to COPD. Nevertheless, pulmonary rehabilitation clearly improves dyspnea, fatigue, functional capacity and overall quality of life in this population (71). Unfortunately, the benefits are rarely sustained six months later if the program is discontinued (72).

Withdrawal of mechanical ventilation

In the intensive care setting, the transition from curative care to end-of-life palliative care is often made in mechanically ventilated patients. This step is frequently a difficult one and may involve withdrawal of mechanical ventilation, which can cause a great deal of distress not only to the patient but also to the family and the involved health care professionals. Terminal extubation has been viewed by some as a drastic measure with consequential ethical and legal implications. It has been argued that withdrawing essential life support is not different than "killing" the patient or euthanasia. When the parents of Karen Ann Quinlan, a 21-year-old girl in a persistent vegetative state following a cardiac arrest, asked for her daughter to be removed from the ventilator in 1975, they met with a lot of resistance. The hospital refused to discontinue mechanical ventilation, which led to a legal battle and intense debates. Since then, the courts in the US have clearly rejected the view that withdrawal of life support was "killing" the patient and reaffirmed the patients' and their surrogate decision makers' right to refuse any and all treatment (73). Today, there is a broad consensus that it is appropriate to withdraw life-sustaining care including mechanical ventilation in certain situations and especially upon a specific request by the patient (74). The principle of patient autonomy allows patients and their surrogates to forego or actively discontinue any undesired treatment. It is less clear what the right approach is when the patient lacks decision capacity and there is no surrogate decision maker. Accepted practices vary by locale and jurisdiction. Considering the serious consequences of the decision to withdraw life-sustaining support, it is recommended to solicit a broader discussion involving other health care professionals, e.g., an ethics committee (75). Similar approach is recommended when there is a disagreement among health care providers and/or family members regarding treatment goals and plan of care. As a competent patient has always the ultimate decision power, it is advisable to lighten or temporarily discontinue sedation if possible, so the patient can participate in the decision-making.

The question of whether it is acceptable to withdraw life-support has been covered extensively in the literature (74). There is much less consensus on what the best way to do that is and especially how to discontinue ventilatory support. Patient comfort and the family's expectations should guide the clinician. Both extubation and gradual weaning of oxygen or ventilatory support are acceptable. Proponents of the latter argue that complete mechanical ventilation withdrawal may result in severe distress and dyspnea. Keeping the endotracheal tube in place may be beneficial for patients who have excessive airway secretions. The argument against slow weaning is that it prolongs the dying process, thus possibly increasing patient's suffering and the family's grief experience (75). There are no good data comparing various methods of life support withdrawal. The clinicians should work with the patient and the family to determine the optimal approach based on their own comfort level and the patient's individual needs. Organ and tissue donation may need to be discussed prior to withdrawal. Both the family and the clinical staff should be prepared for the possibility of delayed death even if the patient appears to be heavily dependent on the respirator. Unexpected prolonged survival after terminal extubation may lead to emotional exhaustion and frustration in the family. Doubts about the appropriateness of the decision to withdraw life-sustaining care may arise. In order to prevent this, it is advisable to counsel the patient's family about the unpredictability of the death process. As mechanical ventilation withdrawal has the greatest potential to cause distress, all other essential treatment should be generally withdrawn first. For example, discontinuing pressor

treatment in a patient in shock may lead to a relatively peaceful death without the need to embark on more drastic measures such as extubation. Pacemakers can be turned off. Implantable cardioverter-defibrillators deserve special mention. Those should always be turned off in anticipation of death. Electrical shocks from those devices can be extremely distressing and painful. Defibrillating a dying patient in the setting of terminal care is not justified. Conventionally, the defibrillator and antitachycardia pacing ("overpacing") function can be deactivated noninvasively by placing a magnet over the device (76). When in doubt, a consultation with a specialist or the manufacturer should be sought. Paralytic agents should be discontinued as they have no palliative value and may actually worsen distress. Withdrawal of life support should be done when neuromuscular function is restored unless that will cause an unacceptable delay and suffering to the patient. Great care should be taken in those cases to ensure comfort as signs of even severe distress may not be apparent. Eliminating fluid and enteral intake is advised in order to avoid aspiration, pulmonary edema and excessive secretions resulting in "death rattle". Anticholinergic agents such as atropine and scopolamine can be administered to diminish respiratory and oral secretions and have been found to be quite effective in the management of "death rattle" (77). The patients need to be premedicated with opiates and often sedatives. Aggressive dyspnea management is needed after discontinuation or weaning of life support. Opiates are always required to ensure comfort if the patient was ventilator dependent. Benzodiazepines and neuroleptics should be liberally used for treatment of anxiety and terminal delirium. Hastening death by aggressive use of opiates and sedatives used to ensure comfort in the dying patient is acceptable under the principle of the "double effect" (78). This principle states that an action may be morally justified even if it has foreseeable but unintended undesired consequences. Therefore, administering high doses of an opiate to provide pain control and comfort is not considered euthanasia even if the risk of causing death is high. In view of the ultimate goal to provide comfort, sedation should not be limited out of fear of hemodynamic compromise. The family members should be given a choice to be present for the process of life support withdrawal. Spending the final moments of life with the family may be comforting to the dying patient. Being present is often important spiritually and emotionally to the family too. Witnessing the last breath of their loved one may serve as closure and facilitate the bereavement process.

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None.

Footnote

Conflicts of Interest: This article has been originally published in the book *The Art and Science of Palliative Medicine*.

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