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Palliative Care and Chronic Obstructive Lung Disease

Manoj Karwa MD*, Alpana Chandra MD,
and Adnan Mirza MD

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem in the United States and throughout the world with a global prevalence estimated at 9.3 per 1000 males and 7.3 per 1000 females (all ages). (Vital and Health Statistics, 1996; Murray and Lopez, 1997). COPD was ranked as the sixth most common cause of death worldwide in 1990, and the Global Burden of Disease Study predicted that it would become the third most common cause by 2020 (Lopez and Murray, 1998). In 2003, an estimated 10.7 million adults in the U.S. were reported as having physician diagnosed COPD. However data from the NHANES III (National Health and Nutrition Evaluation Survey) estimated that approximately 24 million adults in the U.S. have evidence of impaired lung function, indicating an underdiagnosis of COPD especially in its milder forms which are most amenable to treatment. It is estimated that there may be 16 million people in the U.S. currently diagnosed with COPD (Hilleman *et al*., 2000; NCHS, 2002). Mortality and morbidity is significant in patients who have severe COPD, are elderly and have acute exacerbations of COPD requiring hospitalization or ICU admission. According to estimates by the National Heart Lung and Blood Instiute, in 2004 the total annual expenditure for COPD in the U.S. was $37.2 billion, including $20.9 billion for hospital costs and treatment of the disease and $1,613 billion in indirect costs such as work loss. (National Institutes of Health. National Heart, Lung and Blood Institute, 2002). Despite the relatively high prevalence, morbidity, and mortality, end-of-life care such as hospice placement occurs in only a small percentage of patients with COPD.

MANOJ KARWA • Assistant Professor of Medicine, Division of Critical Care Medicine, Gold Zone first floor, Montefiore Medical Center, 111th East 210th Street, Bronx, New York 10467. ALPANA CHANDRA • ADNAN MIRZA • Fellow in Critical Care Medicine, Division of Critical Care Medicine, Gold Zone first floor, Montefiore Medical Center, 111th East 210th Street, Bronx, New York 10467 and * Corresponding author: Assistant Professor of Medicine, Division of Critical Care Medicine, Gold Zone first floor, Montefiore Medical Center, 111th East 210th Street, Bronx, New York 10467.

1. Definition, Pathophysiology and Classification of COPD

COPD is a slowly progressive disease in which the airways are obstructed and there is accelerated loss of lung function over time. The American Thoracic Society incorporates chronic bronchitis, emphysema and airway hyper-reactivity in its definition. The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a collaborative project of the National Institute of Heart, Lung and Blood Diseases and the World Health Organization, highlights the progressive nature of COPD. GOLD defines COPD as a disease state characterized by airflow limitation that is not fully reversible and associated with an abnormal inflammatory response of the lungs to inhalation of toxic substances (Barnes, 2000; Pauwels *et al*., 2004; American Thoracic Society and European Respiratory Society, 2004). Over 80% of COPD cases are due to tobacco use or exposure. Patients with COPD are plagued by symptoms of cough, increased sputum production, and exertional dyspnea disproportionate to their age and activity level. With continued exposure patients develop increased exercise intolerance, dyspnea at rest, and an overall decrease in their quality of life.

In COPD, inflammation of lung parenchyma and small airways, causes increased mucous production, airway hyper-reactivity, and emphysematous changes within the lungs. These factors cause irreversible expiratory flow limitation and hyperinflation of the lungs, lessening the efficiency of the diaphragm in inspiration and expiration of the lungs. These features contribute to ineffective ventilation and gas exchange. Over time secondary pulmonary hypertension and cor pulmonale (right sided heart failure) develop (Sullivan *et al*., 2000).

Hyperinflation, often called air trapping, refers to an increase in the volume of air in the lungs resulting from the inability to fully exhale, or expiratory flow limitation. The sudden and abrupt accumulation of air contributes to the sensation of respiratory discomfort and breathlessness. Dynamic hyperinflation is hyperinflation that is associated with any physical activity—walking, climbing stairs or any other tasks that increase breathing demands. Currently both the ATS and GOLD agree that cough, sputum production, dyspnea, or exposure to risk factors be considered in making the diagnosis of COPD. In addition, there should be evidence of irreversible airflow limitation by the FEV1/FVC ratio $\leq 70\%$ after use of a bronchodilator medication. (FEV1 = forced expiratory volume in one second, FVC = forced vital capacity). The ATS/ERS (European Respiratory Society) severity score leave as to some extent does help predict health status, utilization of healthcare resources, development of exacerbation, and mortality. These scoring systems should be used as tools and not substitute for clinical judgment in evaluating the severity of disease (Table 7.1).

TABLE 7.1. Comparison of the ATS/ERS and gold scoring systems (3, 77, 85, 91)

Severity or stage	ATS / ERS	Gold
At risk or stage 0	FEV1/FVC >70 %, FEV1 ≥80% Patients who: Smoke or have exposure to pollutants Have cough, sputum, dypnea Have family history of respiratory disease	Normal spirometery Chronic symptoms of cough, or sputum production
Mild or stage I	FEV1/FVC ≤ 70%, FEV1 ≥ 80%	• FEV1/FVC < 70% • FEV1 ≥ 80% predicted • with or without chronic symptoms (cough, sputum production)
Moderate or stage II	FEV1/FVC ≤ 0.7, FEV1 50–80	• FEV1/FVC < 70% • 50% ≤ FEV1 < 80% predicted • with or without chronic symptoms (cough, sputum production)
Severe or stage III	FEV1/FVC ≤0.7, FEV1 30–50	• FEV1/FVC < 70% • 30% ≤ FEV1 < 50% predicted • with or without chronic symptoms (cough, sputum production)
Very severe or stage IV	FEV1/FVC ≤ 0.7, FEV1 < 30	• FEV1/FVC < 70% • FEV1 < 30% predicted or FEV1 < 50% predicted plus chronic respiratory failure

2. Natural History of the Disease

2.1. Decline in Lung Function

In adults over 30 years, FEV1 normally declines by about 30 ml per year, but this doubles in patients with COPD and active heavy smokers (Anthonisen *et al*., 2002; Anthonisen *et al*., 2005; Guidelines Group of the Standards of Care Committee of the BTS, 1997; James and Hallenbeck, 2003). The onset of symptoms such as, exertional dyspnea is variable, but often does not occur until the FEV_1 has decreased to a range of 40% to 59% of the predicted normal value (American Thoracic Society and European Respiratory Society, 2004; Guidelines Group of the Standards of Care Committee of the BTS, 1997; Pauwels *et al*., 2004; Sutherland and Cherniack, 2004). This may explain the underdiagnosis in the earliest stages of COPD. The stage of the

disease portends the prognosis, and follow-up data from two longitudinal studies indicate that moderate and severe stages of the disease are associated with higher mortality rate and risk of death. (Anthonisen, 1986; Mannino *et al*., 2003). (Figure 7.1 and 7.2) When the FEV1 goes below 1L, the mortality rate is in the range of 50% at five years. (Fletcher and Peto, 1977).

2.2. Acute Exacerbations of Disease

The progressive decline in lung function in COPD is often interrupted by a debilitating increase in symptoms, requiring hospitalization, commonly known as an acute exacerbation of COPD (AECOPD). AECOPD generally occurs at GOLD stage II disease or higher, is usually caused by viral or bacterial infections, and heralded by an increase in symptoms (Fagon and Chastre, 1996). A decline in FEV1 may or may not correlate with the frequency of exacerbations (Decramer *et al*., 1997; Kessler *et al*., 1999; Osman *et al*., 1997). However, studies do suggest that early mortality is correlated with AECOPD requiring hospitalization.

Patients with acute exacerbations admitted to an ICU face a hospital mortality rate as high as 24%. For patients 65 or older, the mortality rate is 30% at the time of hospital discharge, increasing to 59% at one year. There were findings in a prospective study by Seneff and associates of ICU admissions

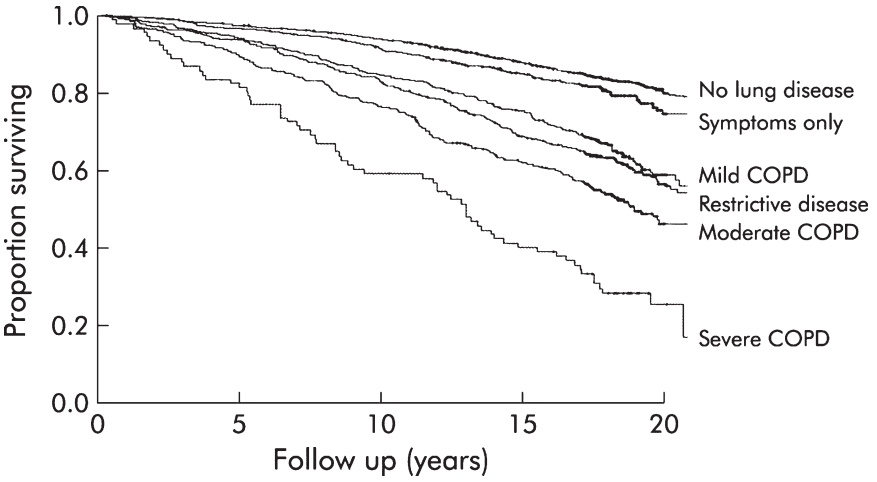

FIGURE 7.1. Kaplan-Meier curve for death among 5542 participants stratified by degree of lung function impairment From the National Health and Nutrition Examination Survey 1971–5 and follow up to 1992. With permission from Mannino, D.M., *et al*., *Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study*. Thorax, 2003. 58(5): p. 388-93. (68)

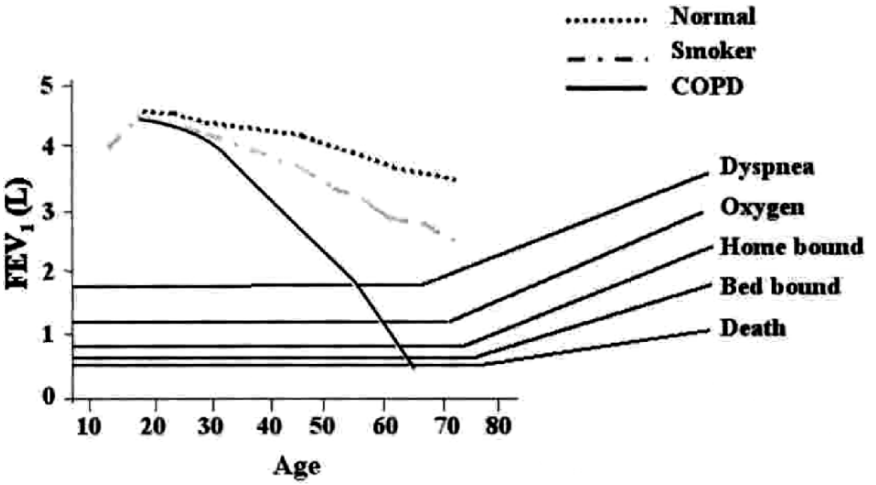

FIGURE 7.2. Natural History of COPD compared to smokers without COPD, and 'normals'. Dyspnea, need for oxygen, sedentary life style and mortality are correlated with the FEV1. Adapted with permission from Fletcher, C. and R. Peto, The natural history of chronic airflow obstruction. Br Med J, 1977. 1(6077): p. 1645-8. (34)

for acute exacerbation of COPD. Of interest, development of non-respiratory organ system dysfunction was shown to be the major predictor of hospital mortality and 180-day outcomes. (Seneff *et al.*, 1995)

Almagro, in a prospective study of 135 consecutive patients admitted for AECOPD, showed that mortality at six months, one year and two years was 13.4%, 22%, and 35.6% respectively. Moreover, hospitalization for AECOPD was an independent predictor of mortality for subsequent hospitalizations. The risk increased with the number of previous hospitalizations. (Almagro, 2002) In a retrospective study of a cohort of 166 patients, admitted for AECOPD and requiring mechanical ventilation, 28% died in the hospital. The need for invasive mechanical ventilation for more than 72 hours was an independent predictor of poor outcome. The study was conducted by Nevins and Epstein at New England Medical Center, Tufts University School of Medicine. (Nevins and Epstein, 2001)

2.3. Quality of Life

According to the National Health Information Survey (NHIS) 1980-1996, between 1994 and 1996, 57.5% of patients with self reported COPD (no spirometric testing was employed), 38.6% had activity limitation, and 8% reported COPD associated activity limitation (Mannino *et al.*, 2002). In the NHANES III, between 1991-1994, of the patients with spirometric evidence of moderate COPD (FEV1/FVC ≤ 70%, and FEV1 < 80%), 18% had difficulty

walking a quarter of a mile, 13.9% had difficulty lifting or carrying 10 pounds, and 7% needed help in handling routine chores.

As only supplemental oxygen therapy improves survival, and smoking cessation is the only intervention that retards decline in lung function in COPD, it is obvious that most other treatments are aimed at improving quality of life. Although physiologic variables, to a great extent, correlate with severity of disease and mortality, many patients with only minimal disease have a disproportionate number of symptoms and functional limitation. This is partly due to the multifaceted nature of COPD, with patients not only having airflow limitation but under nutrition, other existing co-morbid illnesses, dynamic hyperinflation, and pulmonary hypertension. Thus patient's perceptions and ability to adapt, largely define the quality of life. Ultimately patients are more concerned with symptom relief and improvement in their functional status.

Commonly used respiratory disease specific quality-of-life questionnaires include the Chronic Respiratory Disease Questionnaire (CRQ), Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ), Pulmonary Function Status Scale (PFSS), St. George's Respiratory Questionnaire (SGRQ), and the Seattle Obstructive Lung Disease Questionnaire (SOLQ). The description of these instruments is beyond the scope of this chapter and the reader is referred to several excellent reviews (Guyatt *et al*., 1993; Mahler *et al*., 1992; Testa and Simonson, 1996).

Several studies have shown that patients with COPD have both poorer general and disease-specific Health Related Quality of Life (HRQOL) scores (Ferrer *et al*., 1997; Hajiro *et al*., 1998; Mahler *et al*., 1992; Mahler and Mackowiak, 1995). Breathlessness and pain were described as "very distressing" in the last year of life in 76% and 56% of patients with COPD respectively, cough in 46% and anorexia in 15% (Edmonds *et al*., 2001). Poorer HRQOL scores have been correlated with increased number of hospitalizations and mortality (Fan *et al*., 2002). Anxiety, nutritional status, and marital status have all been implicated as predictors of mortality, and more so as disease severity increases (Santo Tomas and Varkey, 2004). Domingo-Salvany *et al*. followed a cohort of 321 male COPD patients over five years and found that the SGRQ, as well as the SF-36 health survey score, independently correlated with both all-cause and respiratory mortality. Patients with ATS stage III COPD had a 60% survival, stage II a 73% survival, and stage I an 89% survival at four years (Salvany, 2002). (Figure 7.3) The investigators also demonstrated that a four point increase in the SGRQ score was associated with an increase in risk of global mortality of 5.1%.

2.4. Causes of Death

Major causes of death in COPD include acute or chronic respiratory failure, pulmonary infection, heart failure, pulmonary embolism, cardiac arrhythmia, and lung cancer. A prospective cohort study of 135 patients admitted for AECOPD found that the causes of death were respiratory failure (50%),

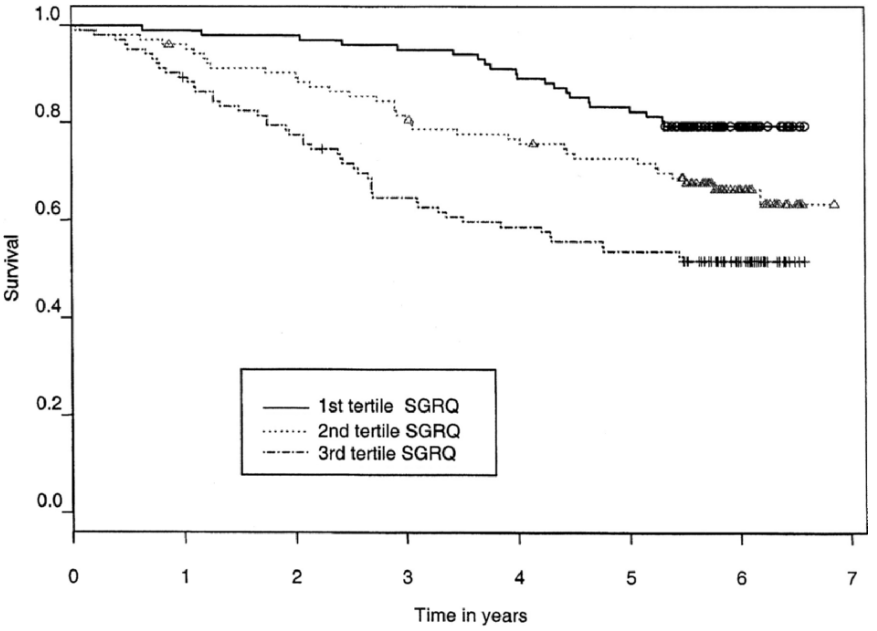

FIGURE 7.3. SGRQ tertiles and survival probabilities in COPD patients. Reprinted with permission from Salvany AD *et al*., Health-related Quality of Life and Mortality in Male Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2002: 166; 680–685. (82)

cardiovascular disease (19%), cancer (6%), and unknown / other (25%). Chronic heart failure was the most frequent associated comorbidity (OR 2.3). (Hansell *et al*., 2003; Meyer *et al*., 2002; Zielinski *et al*., 1997).

In 2003, 122,283 patients died of COPD and 52% of deaths were in women. This was the fourth consecutive year in which the number of COPD deaths in women exceeded those in men. Although COPD causes almost as many deaths as lung cancer, knowledge of the impact of COPD in the late stages of illness is limited. In one study Elkington and associates assessed the healthcare needs of COPD patients in the last year of life by means of a retrospective survey of the informants of 399 COPD deaths in four London health programs (Elkington *et al*., 2005). Symptoms, day-to-day functioning, contact with health and social services were assessed. Based on the reports, 98% of patients were breathless all the time or some of the time in the last year of life; other symptoms present all the time or sometimes included fatigue or weakness (96%), low mood (77%), and pain (70%). Patients lacked surveillance and received insufficient services from primary and secondary providers in the year before they died. The investigators also noted the absence of palliative care programs and the need to address issues such as uncontrolled symptoms and end-of-life planning (Elkington *et al*., 2005).

2.5. *Patterns of Functional Decline and Death*

The pattern of declining function is not correlated well with FEV1, although the probability of death is. Early reports on the natural history of COPD as it relates to FEV1 showed a strong correlation. (Fletcher and Peto, 1977) (Figure 7.2) This is, however, an oversimplification and represents an average of all the patients studied. Not all patients follow the classical trajectory outlined. In fact decline in FEV1 is more likely to be quite varied from patient to patient. (Figure 7.4) The pattern of death is best described as the entry-

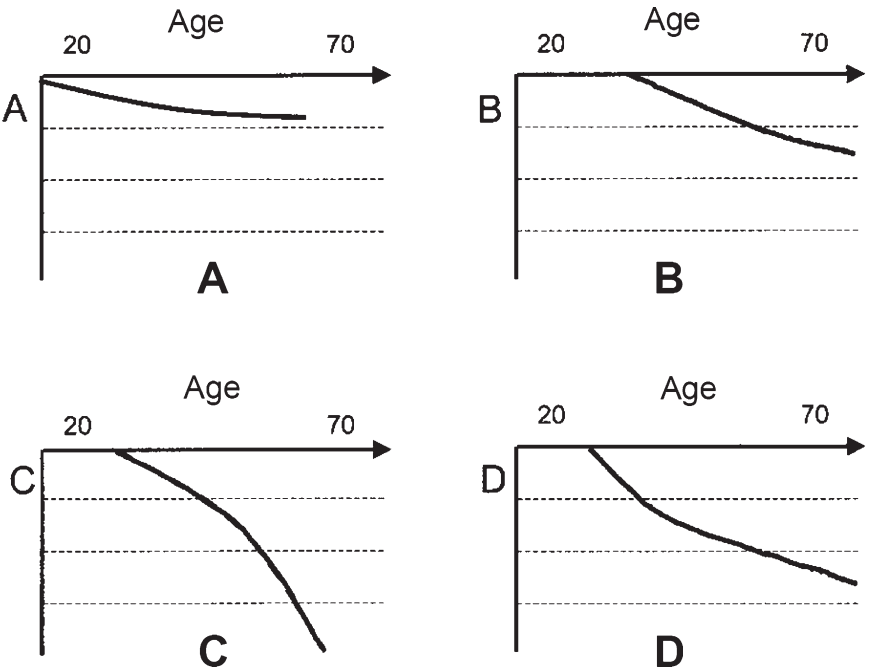

FIGURE 7.4. Different patterns of functional decline in COPD: shows four examples of the various courses that individual COPD patients may follow. Panel A illustrates an individual who has cough and sputum production, but never develops abnormal lung function (as defined in this Report). Panel B illustrates an individual who develops abnormal lung function but who may never come to diagnosis. Panel C illustrates a person who develops abnormal lung function around age 50, then progressively deteriorates over about 15 years and dies of respiratory failure at age 65. Panel D illustrates an individual who develops abnormal lung function in mid-adult life and continues to deteriorate gradually but never develops respiratory failure and does not die as a result of COPD. With permission from Pauwels RA, Buist AS, Calverley PM, *et al*, the GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2004 Update. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Available at www.goldcopd.com accessed December 2004. (77)

reentry pattern. Here patients have sudden acute declines followed by substantial improvements, while still having an overall downward trend in function,in contrast to the trajectories for cancer and frailty. (Lukert, 1994) (Figure 7.5).

Lunney *et al*. analyzed the functional decline of 4190 decedents who died within 12 months of an initial interview for the period between 1981-1987 (Lunney *et al*., 2003). Decedents with organ failure (COPD and heart failure) were compared to decedents with cancer, frailty, and victims of sudden death. Decedents of the organ failure group had a more erratic decline when compared to the cancer group, and sudden death group. (Figure 7.5) Cancer decedents had a much steeper decline in level of function during the last three months of life when compared to the other three groups. The organ failure group had more functional limitation in the first half of the year than those in the cancer group. Organ failure decedents were more likely to be elderly compared to the cancer and sudden death group, and the elderly in all groups were four times more likely to require assistance

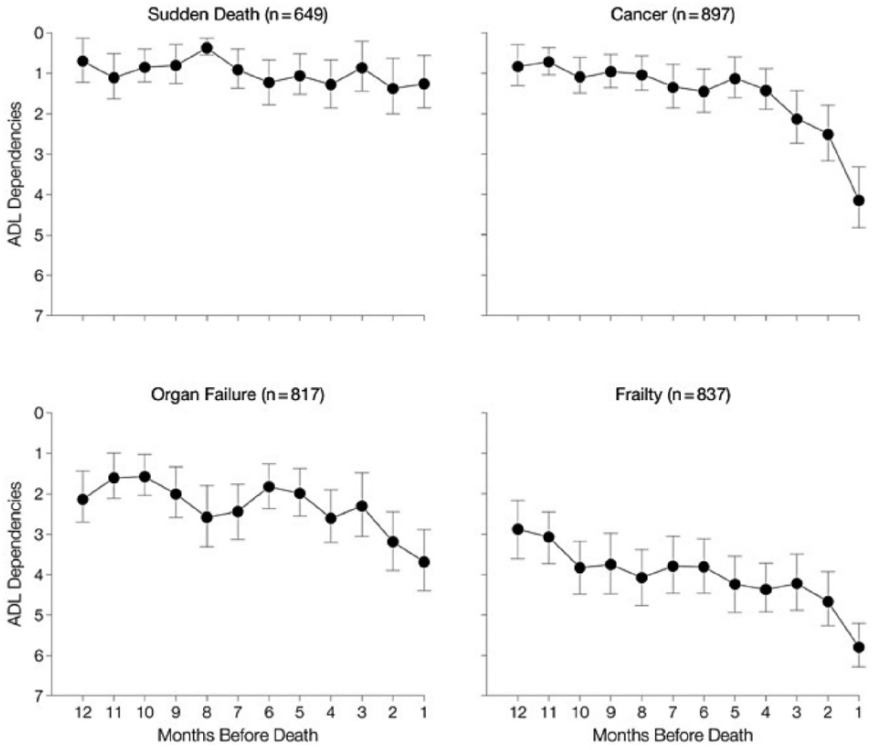

FIGURE 7.5. Various patterns of functional decline towards death. Reprinted with permission from Lunney JR *et al*., Patterns of functional decline at the end of life, JAMA, 2003; 289(18), 2387-2392. (58)

(Lunney *et al.*, 2003). These observations are significant in that the pattern of functional decline is less predictable in patients with COPD. This in turn influences one's expectancy of death, need for hospice care, and advance directive planning.

These observations have been reinforced in a study done by Teno *et al.* (Teno *et al.*, 2001). Using a mortality followback survey of the decedents next of kin and death certificates from the National Centers for health statistics 1993, they analyzed the pattern of functional decline (days of difficulty with activities of daily living, and mobility), as well as the the use of hospice services, and site of death in 3,614 decedents during the last year of life. They compared decedents of cancer, heart failure, COPD, cerebral vascular accidents, and diabetes mellitus. Decedents of cancer were more likely to have received hospice services and to die at home than the other groups. Decedents of COPD were the most likely to die in a hospital. Cancer decedents had a higher level of function than those in other groups at one year prior to death, but at five months prior to death the cancer group experienced a much steeper decline in function. (Figure 7.6) More precipitous functional decline correlated with hospice involvement and dying at home (Figure 7.7).

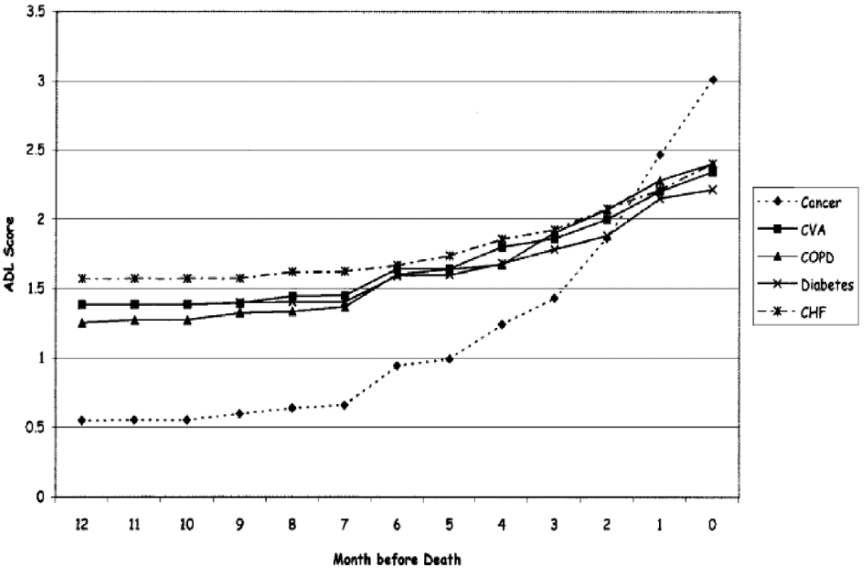

FIGURE 7.6. Activities of Daily living scores one year prior to dying in cancer and non cancer patients. Reprinted with permission Teno JM *et al.*, Dying Trajectory in the Last Year of Life: Does Cancer Trajectory Fit Other Diseases? Journal of Palliative Medicine; 2001, 4(4):457-464. (96)

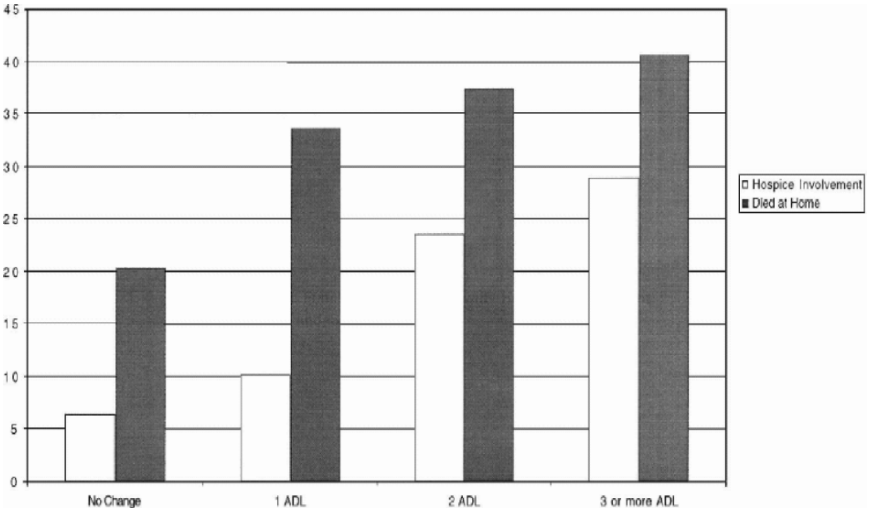

FIGURE 7.7. Correlation between Activities of daily living, hospice involvement and site of death Reprinted with permission from Teno JM *et al*., Dying Trajectory in the Last Year of Life: Does Cancer Trajectory Fit Other Diseases? Journal Of Palliative Medicine; 2001, 4(4):457-464. (96)

3. Burden of COPD

Disability and death from COPD is increasing. (Costello *et al*., 1997; James *et al*., 2005; Manning, 2000; Yach *et al*., 2004) COPD has already risen to become the fourth most common cause of death and is the only common cause of death in the U.S. whose prevalence has increased over the past 20 years. (Hurd, 2000; Mannino *et al*., 2000)

In 2000 there were a total of 7,997,000 outpatient visits, 1,549,000 emergency room visits, and a total of 726,000 hospitalizations for patients with COPD. (Mannino *et al*., 2000) According to the National Health Interview Survey, of patients having COPD, 64.6% were employed, 18.4% reported any limitation of activity, and 7 to 8% had COPD related limitation of activity and difficulty handling routine needs of daily living (Vital and health statistics, 1996). COPD is responsible for work loss of approximately $9.9 billion per year in the U.S.

COPD is a major cause of chronic disability and predicted to become the fifth most common cause of disability in the world by 2020. COPD is a major cause of health care expenditure that now exceeds the costs associated with asthma by more than a factor of three (Sin *et al*., 2002; Strassels *et al*., 2001; Sullivan *et al*., 2000). In a survey of 3,265 patients and 905 physicians, Halpern *et al*., calculated that the indirect cost of COPD was $,1527 (from work loss) and the total cost was $5,646. When analyzing direct costs, the annual cost of health care utilization per patient was $4,120, and the highest cost of any individual resource being that of inpatient hospitalizations ($2891). (Halpern

et al., 2003) An interpretation of the study is that COPD is more costly to the health care system and society than to patients with COPD alone.

Total treatment cost is highly correlated with disease severity. A pharmacoeconomic analysis was conducted by Hilleman and associates at the Creighton University School of Pharmacy, Omaha. Healthcare resource utilization and costs were identified through chart review and stratified using the ATS criteria. They calculated that patients treated for stage III COPD had the highest average cost ($10,812 per patient per year), and patients with stage I COPD had the lowest cost ($1,683 per patient per year) (Hilleman *et al*., 2000). Stage III patients had an average of 3.2 hospitalizations per year compared to 0.3 of patients with stage I disease. Furthermore over five years the mortality for patients with stage III disease was 33% compared to 0% and 17% of patients with Stage I and II disease respectively. (Table 7.2) Of the $ 20.9 billion spent in direct medical costs for COPD only 3.3% was spent on home health care services and 13.4 % on nursing home care. (National Institutes of Health. National Heart, Lung and Blood Institute, 2004)

4. Palliative Care

4.1. Insights from the SUPPORT Trial and Prognostication

As we have seen there is an increase in mortality with the severity of the COPD as measured by spirometry, age, smoking status, body mass index, number of AECOPD, need for mechanical ventilation, HRQOL measurement

Table 7.2. Breakdown of costs of care for COPD patients by severity of disease

	Severity of COPD		
Cost categories	Stage I†	Stage II†	Stage III†
Initial drug acquisition cost	$ 299 (18)	$ 529 (11)	$ 634 (6)
Add-on drug acquisition cost	$ 213 (13)	$ 191 (4)	$ 132 (1)
Total drug acquisition cost	$ 512 (31)	$ 720 (14)	$ 766 (7)
Oxygen therapy	0 (0)	$ 699 (14)	$ 2,012 (19)
Laboratory/diagnostic test cost	$ 345 (20)	$ 493 (10)	$ 610 (6)
Clinic visit cost	$ 82 (5)	$ 148 (3)	$ 171 (2)
Emergency department visit cost	$ 62 (4)	$ 319 (6)	$ 483 (4)
Hospitalization cost	$ 680 (40)	$2,658 (53)	$ 6,770 (63)
Total cost	$1,681 (100)	$5,037 (100)	$ 10,812 (100)

Costs are presented as per patient per year (percentage of total cost). †p, 0.01 for each cost variable and total cost across the three severities of COPD. Reprinted with permission from Hilleman DE *et al*., Pharmacoeconomic evaluation of COPD. Chest 2000; I 18:1278-l285. (46)

TABLE 7.3. Prognostic factors in chronic obstructive pulmonary disease

FEV1	54% 5-year survival. Mean FEV1 1.04 ± 0.41. **(27, 68, 77)**
Age	Mortality higher in the elderly. Mean age 61 ± 8 yrs. Mean FEV1 36.1 ± 11.4%. **(5, 68, 71)**
PaO2	Increased mortality when PaO2 < 55 untreated. **(74)**
BMI	24% 5-year survival for BMI < 20 kg/m2. Mean FEV1 31% ± 12. All required LTOT. **(17)**
Dyspnea	SGRQ and SOLDQ correlated with mortality independent of FEV1 **(82)**
Apache II	Apache II score on admission to general medicine ward correlated with death at 3 years. 50% mortality at 3 years for Apache II > 20 **(27, 79)**
Hospital admission to ICU for AECOPD with respiratory failure	Unselected COPD patients administrative database. In-hospital mortality 2.5% **(76)** 22% mortality at 1 year after hospitalization **(2)**
Hospital admission to ICU for AECOPD with respiratory failure	15% in-hospital ICU mortality rate. 46% required invasive mechanical ventilation. Nonsurvivors mean Apache II 25.6 ± 8.7. **(73)**
BODE index	Better predictor of mortality than FEV1 **(16)**

scores, and other physiological variables. (Table 7.3) Despite this seemingly abundant and convincing data, identifying patients with COPD who are at risk of dying with in six months is far from precise.

The landmark investigation, Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT), offers great insight into the outcomes of hospitalized COPD patients, in terms of six month survival, patient preferences about advance directives, practices surrounding advance directives, patient physician communication, and use of hospital resources prior to death. For example, Connors and associates studied a prospective cohort of 1,016 adult patients enrolled in SUPPORT; all were hospitalized with an acute exacerbation of COPD. The likelihood of a poor outcome was markedly increased after acute exacerbation particularly in association with a PaCO2 of 50mmHg or more, indicating an excess of carbon dioxide in the blood which can lead to hypercarbic respiratory failure (Connors *et al*., 1996; Knaus *et al*., 1995).

In a separate analysis of SUPPORT phase I and II, of patients with COPD who died within one year of enrollment, Lynn *et al*., found that 15% to 25% of the patients spent the last six months of life in the hospital. It was only in the last few days that the model was able to predict a lower survival; despite this there was still a 30% likelihood of surviving past six months (Connors *et al*., 1996; Lynn *et al*., 2000).

In a study using data from SUPPORT phase I and II, Fox *et al*., tested the utility of applying five general and two disease-specific clinical criteria (based on the then National Hospice Organizations criteria for hospice eligibility)

for identifying a survival prognosis of six months or less after surviving hospitalization for a serious illness. The five general criteria used were readmission to a hospital within two months, home care after discharge, dependency in three activities of daily living, weight loss of more than five pounds within two months, and an albumin level of less than 25 g/L. The two COPD-specific clinical criteria used were presence of cor pulmonale and a reduced blood oxygen level (PaO2 of 55 mm Hg or less) while receiving oxygen therapy. Three sets of combined criteria (broad, intermediate and narrow inclusion) were used, aimed at providing low, medium, or high thresholds for hospice eligibility. Broad inclusion required only one of the seven clinical criteria, intermediate required three, and narrow required five. Of a total of 900 patients with COPD, 74% survived for longer than six months. Of the 900 patients approximately 30%, expressed a preference for palliative care. When survival was analyzed using the combination criteria 68% of patients in the broad inclusion set survived more than six months, 67% in the intermediate set, and 50% in the narrow set. Only 3.3% were actually discharged to hospice and the large majority of these patients died within six months. Thus the greatest prognostic factor for survival less than six months was discharge to hospice (which was not part of the criteria tested). The authors concluded that using criteria to predict six month mortality and hospice eligibility were not so much inaccurate as they were unrealistic for this patient population (Connors *et al*., 1996; Fox *et al*., 1999).

The last year of life for patients with COPD is markedly different in comparison to patients who die of cancer. As described by Teno *et al*. and Lunney *et al*., COPD patients experience a pattern of dying marked by periods when they are seriously ill and recover. (Figures 7.5-7.7). Although the overall prognosis of these patients is considered poor, even in comparison to some terminal cancer patients, they tend to live for variable periods of time in a state of ill health. Their death is less predictable, and often may come suddenly and unpredictably. This has important implications in regards to prognostication for hospice services. It also has psycho-social effects on the patient in that they may not have time to realize and accept death as natural part of their life cycle. In addition families of the patient may not have sufficient time to bereave and acclimate to their loss.

4.2. Advance Directives in COPD

Since predicting survival of less than one year or six months is inaccurate, discussion about advance directives can be challenging for the physician. Patient autonomy about such decisions is both in line with the principles of palliative care as well as with the patient's preferences. In one study by Heffner *et al*., 88.6% of patients in a pulmonary rehabilitation program wanted to know about advance directives (AD), yet only 19% had discussions with their physicians and only 14.3% thought that their physicians knew their wishes (Heffner *et al*., 1996). In the SUPPORT trial only 38% of COPD

patients showed preference for do not resuscitate (DNR) orders, but 78% expressed wishes for comfort care measures, saying that they 'would rather die' than be attached to a ventilator 'all the time' (Lynn *et al.*, 2000). Approximately 46% of all DNR orders for the patients in SUPPORT (including patients with COPD) were made within two days of death. This highlights the lack of any gradual transition from active care to palliative hospice care and reflects the erratic dying trajectory of these patients. The failure of the SUPPORT interventions to improve physician patient communications, timing of DNR orders, physician knowledge of patients wishes, and to decrease the days spent in the ICU on ventilators is not surprising in the case of COPD for this very reason. Thus one may adopt the philosophy that palliative care should not necessarily preclude life-sustaining therapy in the case of COPD. However, in keeping with this line of care one should note that approximately 25% to 30% of patients have significant pain, 70% to 85% have dyspnea, and about 20% have confusion, all of which increased closer to time of death (Edmonds *et al.*, 2001; Lynn et al., 2000).

Discussions about AD should address patient preferences for cardiopulmonary resuscitation (CPR) and mechanical ventilation, discussions with family members if allowable, provisions for surrogate decision making, alternatives to aggressive therapies, education about the nature of COPD and inaccuracies about prognostication, and assurance of adequate symptom control. The caregiver should keep in mind the patient's perception of discussions about AD. Physicians tend to mark the discussion as an operational tool directing which therapies are to be used and which not, and fear the removal of hope. However the patient may regard this as an event signaling their preparation for death and fortifying their psychosocial, emotional, and spiritual needs.

4.3. Delivery of Palliative Care in COPD

Palliative care for end-stage COPD includes assessment and management of the patient's suffering and concerns on several different fronts. These include alleviating physical suffering, providing both emotional and spiritual support, as well as keeping a constant line of communication for both the patients and their families. Thus the emphasis shifts from focusing on abnormal laboratory values and more on the quality of life. The delivery of this multifaceted type of care through the use of comprehensive teams employing physicians, social workers, chaplains, and psychologists, has met with some success in improving the patient's dyspnea, anxiety, spiritual well being and sleep quality. (Rabow *et al.*, 2004)

Probably the most disabling symptom for the patient with end stage COPD is the sensation of dyspnea which is often not explicable only on the basis of physiological factors (American Thoracic society, 1999; Sorenson, 2000). Dyspnea assessment is subjective but can be graded according to the Borg 12 point scale ranging from 0 for 'nothing at all' to 12 'maximal dyspnea'

(Borg, 1990; Sorenson, 2000). Sixty percent of the SUPPORT patients had severe dyspnea in the last two months of life and 90% during the last three days (Lynn *et al*., 2000). The main stay of therapy for dyspnea has been the use of opioids. Opioids help in decreasing all phases of ventilation, which correlates directly with the level of dyspnea, as well as directly decreasing the sensation. They have also shown to be of benefit in reducing exertional dyspnea (Light *et al*., 1989). In a meta-analysis of randomized double blind placebo controlled trials of opioids for dyspnea, Jennings *et al*. found a positive and greater effect of relief of dyspnea with the use of both oral and parenetral opioids compared to nebulized opioids. Additionally there was no difference noted between the use of single versus multiple dosing regimens (Jennings *et al*., 2002). But there is the danger of decreasing ventilation to life threatening levels.

Coinciding with the sensation of dyspnea is the feeling of anxiety and depression (Light *et al*., 1989). The SUPPORT trial as well as other studies examining HRQOL in patients with COPD attest to this. In SUPPORT patients had low levels of both anxiety and depression, which became more prevalent in the population closer to death. Low-dose benzodiazipines help in the management of anxiety but have no direct effect on the sensation of dyspnea. At least one study has shown that use of sedation for palliation of symptoms is not necessarily associated with a lessening of prognosis (Cherny and Portenoy, 1994). Both anxiolytics and antidepressants do have a therapeutic rationale in dyspnea treatment but convincing evidence for the efficacy is scant (Argyropoulou *et al*., 1993; Mannino *et al*., 2000; Mitchell-Heggs *et al*., 1980; Smoller *et al*., 1998). Oxygen is another therapy widely used in the palliation of dyspnea, however many of the trials have focused on improvement of physiological variables as opposed to alleviation of breathlessness. Existing trials show a varied outcome in the reduction of breathlessness however (Booth *et al*., 2004). Furthermore oxygen therapy is one of the few therapies that has been shown to improve survival in patients with COPD who have oxygen deficiency (hypoxia). (Nocturnal Oxygen Therapy Trial Group, 1980)

The use of forced air via a simple fan has proven to be of some benefit in alleviating dyspnea (Mannino, 2002; Spence *et al*., 1993). Chest wall vibration, delivered in phase with the respiratory cycle, vagotomy, acupuncture and acupressure have been tried but there are too few published studies to support their routine use (Benditt, 2000; Berglund *et al*., 1971; Jobst *et al*., 1986; Maa *et al*., 1997; Sibuya *et al*., 1994). There is an increasing trend in the enrollment of patients with severe COPD into pulmonary rehabilitation programs although they have not shown to decrease mortality or baseline physiology, rehabilitation does increase exercise tolerance, help alleviating baseline and exertional dyspnea, and improve HRQOL scores. In addition the programs serve as a unique setting for the initiation of discussion of advanced directives. (Heffner, 2000)

Noninvasive ventilation has usually been used as a curative intervention for certain varieties of respiratory failure but might also be useful as a palliative

measure for the relief of dyspnea. (Cazzolli and Oppenheimer, 1996) While most medications used to treat dyspnea have the potential to reduce the life span by reducing the respiratory drive and causing hypercarbic respiratory failure, noninvasive ventilation may produce just the opposite effect by supporting respiration and prolonging life as well as relieving symptoms of dyspnea. This might also be used to support patients with advanced COPD during acute exacerbations who reject mechanical ventilation. However a prerequisite for its use is that the patient be alert enough to comprehend its use and be able to cooperate as well as tolerate the therapy. With non invasive positive pressure ventilation (NPPV) verbal communication can be maintained, whereas this is severely impaired with endotracheal intubation and can generate fear, anxiety and feelings of isolation in the dying (Hansen-Flaschen, 2000). NPPV has been shown to improve the quality of life, impact on neuropsychological function, and improve sleep quality (Elliott *et al.*, 1992; Perrin *et al.*, 1997; Strumpf *et al.*, 1991). Hence NPPV is a novel option for palliation easily rendered by a well-trained and competent respiratory staff. The use of NPPV is an emerging palliative therapy for patients with severe COPD although convincing evidence for its routine use is not present.

Excess secretions, while not the most common pulmonary symptom in dying patients, are nevertheless troublesome. If significant in volume they can cause airway obstruction, trigger a persistent cough, increase dyspnea and interfere with sleep. Atropine sulfate, hyoscyamine sulfate (Levsin), and hyoscine hydrobromide (scopolamine) have all been used to some degree of effectiveness and atropine drops administered to the back of the throat in terminally ill patients provide fairly rapid relief from excess secretions. Broad-spectrum antibiotics, bronchodilators and mucolytics have been the primary therapeutic intervention for exacerbation of COPD and might also be useful otherwise. Airway clearance devices are used to clear the airways of mucus for the purpose of improving breathing and reducing the chances for respiratory infections to develop. For example, exhaling through a positive expiratory (PEP) device creates oscillation in airway pressures. The flutter helps to mobilize secretions. PEP devices promote mucus clearance in part by preventing airway closure and increasing collateral ventilation. Relatively new, intra-pulmonary percussive ventilation (IPV) has been found to be as effective as chest physiotherapy and aerosol therapy in enhancing sputum production. Approximately 20% of the patients in the SUPPORT trial had severe pain with the incidence increasing as death approached (Classens, 2000). Thus attention to symptom management is of the utmost priority. Pain may be the consequence of rib or vertebral compression fractures which may occur as a result of osteoporosis (bone loss) that is associated with prolonged corticosteroid therapy. Treatment may be compromised by the limited pulmonary reserve. When tolerated, long-acting opioids can be used alone or in combination with non-steroidal anti-inflammatory drug (Hansen-Flaschen, 2000; Light *et al.*, 1989). Mechanical supports are often recommended are

often recommended for patients with compression fractures, but may be poorly tolerated in patients with COPD as they can constrain diaphragmatic excursion. (Lukert, 1994)

In caring for the terminally ill patient with little or no pulmonary reserve, it is more helpful to consider the therapeutic options in alleviating suffering than focus on the treatment of the disease. Lastly a thought should be given to withdrawal of life support if this is in line with the patients known wishes.

4.4. Hospice Care

Increasingly patients involved in the care of the dying advocate expanding access to hospice care for patients with COPD, heart failure and other chronic disease. However, to be eligible, these patients typically must have a projected survival of six months or less. According to the National Hospice and Palliative Care Organization's 2003 estimate, lung diseases as a whole accounted for 6.7% of hospice admissions and 6.8% of hospice deaths (The National Hospice and Palliative Care Organization, 2002; The National Hospice and Palliative Care Organization, 2005). The 2000 National Home and Hospice Care Survey estimated that 4.3% (4,500) of then current hospice patients had a primary diagnosis of COPD, and 5.5% (13,100) a secondary diagnosis. When hospice discharges are analyzed, COPD as a primary diagnosis accounts for 4.4% (27,600) of all hospice discharges, and 4.7% (38,000) when as a secondary diagnosis. The discharges for COPD diagnosis have been rising since 1996 (General Accounting Office, 2000; Haupt, 2003). Even though COPD is the fourth leading cause of death in the US it accounts for less than 5% of hospice cases.

Patients receiving hospice care have a greater variability in survival time compared to cancer patients. At least one study does show that there is a longer survival for COPD patients in hospice care compared to non-hospice care (Christakis and Escarce, 1996; Fox *et al*., 1999; Pyenson *et al*., 2004). The cost for hospice care compared to non hospice care is generally less, but when compared to cancer patients receiving hospice care is considerably higher given the different death trajectory (Gage and Dao, 2000; Pyenson *et al*., 2004). For example, Pyenson and associates conducted a cost comparison between patients who do or do not elect to receive Medicaid-paid hospice benefits. The study included data for 8,700 Medicare beneficiaries. For the majority of cohorts, mean and median Medicare costs were lower for patients enrolled in hospice care. The lower costs were associated with a longer time until death (Christakis and Lamont, 2000; Connors *et al*., 1996; Fox *et al*., 1999). Current Medicare hospice benefit guidelines for pulmonary diseases (including COPD) enrollment include the following

- Presence of chronic lung disease as documented by any of the below
  - Disabling dyspnea at rest, poorly responsive or unresponsive to bronchodilators, resulting in decreased functional capacity, *e.g*., bed to chair

existence, fatigue, and cough; documentation of FEV1, after bronchodilator _ 30% of predicted is objective evidence for disabling dyspnea, but is not necessary to obtain.

- Progression of end-stage pulmonary disease, as evidenced by increasing visits to the emergency department or hospitalizations for pulmonary infections and/or respiratory failure or increasing physician home visits prior to initial certification. Documentation of serial decrease of FEV1_ 40 mL/yr is objective evidence for disease progression, but is not necessary to obtain.

- Hypoxemia at rest on room air, as evidenced by Po2 _ 55 mm Hg or oxygen saturation _ 88% on supplemental oxygen determined either by arterial blood gas levels or oxygen saturation monitors (these values may be obtained from recent hospital records) or hypercapnia, as evidenced by Pco2 _ 50 mm Hg. This value may be obtained from recent (within 3 mo) hospital records.
- Right heart failure secondary to pulmonary disease (cor pulmonale), *e.g.*, not secondary to left heart disease or valvulopathy.
- Unintentional progressive weight loss of _ 10% of body weight over the preceding 6 mo.
- Resting tachycardia _ 100 beats/min.
- Documentation certifying terminal status must contain enough information to confirm terminal status upon review. Documentation meeting the above criteria would meet this requirement. If the patient does not meet the above criteria, yet is deemed appropriate for hospice care, sufficient documentation of the patient's condition that justifies terminal status, in the absence of meeting the above criteria, would be necessary. Documentation might include comorbidities, rapid decline in physical or functional status in spite of appropriate treatment, or symptom severity that with reasonable reliability is consistent with a life span prognosis of _ 6 mo.

In attempting to determine eligibility for hospice enrollment one should take into account several other factors aside from the Medicare guidelines above.

- Patients disease has progressed to the point that they may die because of any intercurrent illness, despite having been optimally treated,
- Age of patient: > 65 yrs
- Functional status of the patient as measured by various HRQOL instruments as well as the already utilized Karnofsky scale for general hospice care for malignant disease. That is patients are severely limited in their performance status.
- Number of admissions to hospital for AECOPD; a history of previous intubation during an AECOPD admission carrying with it a higher mortality
- Nutritional status and BMI
- The number of associated comorbidities, especially cardiac comorbidities such as ischemic heart disease and heart failure
- The patient understands that death may be near and does not wish to suffer needlessly

Recommending and electing for palliative care / hospice care in COPD is still studded with controversies including prognostication and cost benefits. Prognosticating as to which patient will survive for less than six months (as we have seen) has proven to be inaccurate. It is important to recognize that patients with COPD follow a dying trajectory different from those with cancer. Thus they may have prolonged courses prior to death in what is known as entry re-entry pattern. This pattern of uncertainty as well as the lack of ability to accurately predict mortality in COPD, should not exclude patients from the benefits of palliative and hospice care services. In fact the group of patients and their families may benefit more from palliative care enrollment from a psycho-social and spiritual standpoint. (Rabow *et al*., 2004) Frank discussions about patterns of dying and likely prognosis should be done in patients at risk.

The cost benefit of electing hospice care is still debated, since patients with COPD who elect hospice seem to live longer than patients with terminal cancer. This seems to be directly related to the length of hospice care. Although the expenditures are relatively higher compared to cancer patients the benefits may offset this. Patients in these programs either at home, in nursing homes, or in hospitals, are provided with comprehensive care to address their physical, emotional, spiritual and family needs. This in itself may prove to be a life prolonging measure while promoting all around increase in the quality of life.

5. Conclusion

In summary identifying the appropriate COPD patient who will benefit from a palliative care approach is to say the least challenging. None the less palliative therapy is a much underutilized path of therapy for this population. Prognostication of patients is still imperfect and there is a great need to have better models. Palliation for the COPD patient as well as other diseases with this reentry type of dying trajectory can become confusing for the family, patient and the physician. However by discussing the probabilities of various outcomes with the patient, identifying their preferences for measures such as intubation and other advance directives will help as guides. Emotional, spiritual and physical relief of symptoms should be the focus of the interventions offered by the palliative care team as opposed to only specific laboratory and physiologic measurements.

Glossary

Parenchyma: the functional parts of an organ such as the alveoli of the lungs (final portions of the respiratory tree which are involved in gas exchange), in contrast to the stroma which refers to the supporting tissues of organs.

Bronchodilator: an agent/ medication that reduces narrowing of the airways and obstruction of the airways in asthma and COPD.

FEV_1: The volume of gas exhaled during the first second of expiration.

FVC: The total volume of gas exhaled during expiration.

Hypercapnia: elevation of the carbon dioxide content of the blood above the upper limit of normal (the normal upper limit of carbon dioxide in arterial blood is 40mmHg) which may occur in respiratory insufficiency or hypoventilation.

Intubation: insertion of an endotracheal tube for the purpose of mechanical ventilation.

Pulmonary Embolism: an often fatal blood clot in the blood vessels of the lungs.

Cardiac Arrhythmia: an abnormality of the heart rhythm which is often accompanied by abnormality of the blood pressure or cardiac arrest.

Cor pulmonale: right sided heart failure secondary **to** pulmonary hypertension.

Opioid medications: narcotic medications such as morphine, oxycodone, fentanyl or hydromorphone which are most commonly used to treat pain but can also be used to relieve shortness of breath.

Vagotomy: surgical interruption of the vagus nerve.

Hypercarbic respiratory failure: respiratory failure that is accompanied by respiratory failure.

Albumin: a protein that is predominantly synthesized in the liver and maintains oncotic pressure and is reduced in cachexia, advanced medical illnesses and chronic liver disease. Normal values for serum albumin range from 3.5-5.5g/dl.

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