Asian Biomedicine Vol. 8 No. 2 April 2014; 229-236 DOI: 10.5372/1905-7415.0802.283

Original article

Precipitating causes and outcomes of chronic obstructive pulmonary disease exacerbation at a tertiary care center in northeast Thailand

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Background: Acute exacerbation of chronic obstructive pulmonary disease (COPD) is a leading cause of hospitalization and economic burden. Frequent exacerbations impair quality of life and effect decline of lung function.
Objective: We evaluated characteristics of COPD patients with frequent exacerbations. The precipitating causes, outcomes, hospital stay, and cost of admission were also determined.
Methods: The study population included COPD patients admitted because of acute COPD exacerbation at Srinagarind Hospital between 1 January 2006 and 31 December 2010.
Results: Over the 5-year period, 183 patients were admitted. Their mean age was 74.9 (SD 9.28) years and the male to female ratio was 170:13. Most patients (144; 79%) had one exacerbation per year and 39 (21%) had more than one per year. The group with more exacerbations, had a higher stage of the disease than those with only one exacerbation (p = 0.023), but there was no significant difference in the mortality rate (18% vs 14%, p = 0.53). A total of 245 episodes of acute exacerbation of COPD occurred in 183 patients. The mean duration of symptoms was 4.1 (SD 3.46) days. Forty-seven percent presented with Anthonisen type III, 42.4% with Anthonisen type II, and 10.6% with Anthonisen type I exacerbations. For 44 exacerbations (18%), the precipitating causes were not determined. The most common precipitating cause was pneumonia, which occurred in 90 episodes (36.7%). The second common was bronchitis (27.8%); followed by heart failure (8.2%), infected bronchiectasis (5.3%), diarrhea (1.2%), acute urinary retention (0.8%), unstable angina (0.4%), pneumothorax (0.4%), urinary tract infection (0.4%), atrial fibrillation (0.4%) and drug induced cough (0.4%). The organisms responsible for respiratory tract infection were identified in 31% cases of pneumonia and 18% of bronchitis cases. The top three common pathogens for pneumonia were *Pseudomonas aeruginosa* (9%), *Acinetobacter baumannii* (8%), and *Klebsiella pneumoniae* (8%). The top three common pathogens for bronchitis were *P aeruginosa* (7%), *Haemophilus influenza* (6%), and *K pneumoniae* (4%). About one quarter (25.3%) of acute exacerbations were complicated by respiratory failure. The mean duration of admission was 17.3 days (range 1–682 days). The mean cost of admission per exacerbation was 80,010 Thai baht (US $2,666) (range, 2,779–3,433,108 baht). The total cost for 245 exacerbations was 19.6 million baht ($653,000).
Conclusion: Respiratory tract infections were common causes of COPD exacerbation and one quarter of which developed respiratory failure. Preventive measures such as vaccination, smoking cessation, lung rehabilitation, and appropriate drug use are helpful.

Keywords: COPD exacerbation, precipitating causes, outcomes

Chronic obstructive pulmonary disease (COPD) is the only leading cause of death that still has a rising mortality rate. It has been estimated that by the year 2030 COPD will be the third among the conditions with a high burden to society [1]. Acute exacerbation of COPD represents the most important single factor for deterioration in quality of life and decline in pulmonary function [2, 3]. Furthermore, exacerbations are a major cause of unscheduled physician visits, contributing 25%–50% of COPD-related healthcare expenses [4, 5].

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Frequent exacerbations contribute to an increased morbidity and mortality [6, 7]. One-third of the precipitating causes for COPD exacerbations are unknown [8]. It has been reported that 50%–70% of exacerbations are because of respiratory tract infections; however, the role of antibiotics in the treatment of exacerbation is controversial [9]. In a subset of patients whose exacerbations were characterized by a combination of increased dyspnea, increase in sputum volume and purulence in sputum quality, antibiotic therapy was found to be of benefit [10].

The core pathogens of respiratory tract infections in COPD exacerbation are *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. However, these pathogenic organisms may differ with severity of COPD, repeated exacerbation, current antibiotic use in 3 months and common pathogens at the respective admitting center [11, 12]. Several reports have suggested that in patients with advanced stages of COPD and with severe exacerbation, Gram-negative bacilli (including *Pseudomonas aeruginosa*) were more common [12, 13].

In addition to knowing the cause of respiratory tract infections, other precipitating causes may improve the treatment outcome [14]. COPD exacerbation treatment outcomes vary, depending on aggressiveness of the approach [8, 15]. Future exacerbations should therefore be avoided by using lifestyle modification, long-term appropriate medical treatment, pulmonary rehabilitation, and long-term home oxygen therapy where indicated [16].

The purpose of this study was to evaluate patient characteristics and outcomes between a group with one exacerbation and a group with more than one exacerbation per year. The clinical features, precipitating causes and acute management of COPD exacerbation that needed hospitalization were recorded. In cases precipitated by respiratory tract infections, the pathogens were identified by culture. Hospital stay, mortality rate, and cost of admission for COPD exacerbation were evaluated.

Materials and methods

This cross-sectional study enrolled hospitalized patients diagnosed with acute exacerbation of COPD at Srinagarind Hospital between 1 January 2006 and 31 December 2010. The diagnostic criteria for acute exacerbation of COPD were acute worsening of respiratory symptoms beyond normal day-to-day variations leading to a change in medication [8]. Patients who had underlying COPD, but were admitted with other conditions or illness were excluded. Demographic data were collected, including: age, sex, occupation, medical comorbidity, and smoking status. COPD staging was classified according to spirometry as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [8]: obstructive airway pattern (FEV1/FVC < 70%) and not fully reversible with bronchodilator (% change of FEV1 post bronchodilator less than 12%). The patients were classified as: Stage I, if the postbronchodilator FEV1 ≥ 80% of the predicted value; Stage II, if it was 50% ≤ FEV1 < 80% of the predicted value; Stage III, if 30% ≤ FEV1 < 50% of the predicted value; and, Stage IV, if the FEV1 < 30% of the predicted value or FEV1 < 50% of the predicted value and presented with corpulmonale [8]. Patient characteristics, COPD staging, and mortality rates were compared between a group with one exacerbation and a group with more than one exacerbation.

Episodes of exacerbation during this 5-year period were reviewed. Data collection included: duration of symptoms, severity of exacerbation by clinical presentation defined according to Anthonisen's criteria [10], precipitating cause of each exacerbation, and acute management that patients received. The patients were defined as having Anthonisen type I exacerbation if they had 3 of the 3 cardinal clinical symptoms; (1) increased dyspnea, (2) increased sputum volume, and (3) increased sputum purulent. If they had 2 of the 3 symptoms, exacerbation was defined as Anthonisen type II, and if 1 of the 3, it was defined as Anthonisen type III.

If exacerbation was precipitated by pneumonia or bronchitis, the pathogenic organisms were reviewed by culture results. Management of each acute exacerbation was reviewed, including: oxygen therapy, ventilator support, systemic corticosteroid, short-acting bronchodilators, and antibiotics. The outcomes of treatment, hospital stay, cost of admission and complication were analyzed. Long-term treatments for surviving patients at discharge were also recorded; that is, which one, or combination of, long-acting bronchodilators was prescribed. If the patients received inhaled corticosteroid (ICS) alone or in combination with a long-acting β_2-agonist (ICS/LABA), the dose of inhaled corticosteroid was evaluated. ICS alone was defined as budesonide 800

μg/day or beclomethasone 1,000 μg/day. ICS/LABA was considered a moderate dose ICS if the combination was budesonide 164/formoterol 4.5 μg per inhalation or fluticasone 125/salmeterol 25 μg per inhalation and the patients used 2 inhalations in the morning and 2 in the evening. ICS/LABA was defined as high-dose ICS if the combination was budesonide 320/formoterol 9 μg per inhalation or fluticasone 250/salmeterol 25 μg per inhalation and the patients used 2 inhalations in the morning and 2 in the evening.

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Khon Kaen University. Statistics were used to describe the data. Means and SD were calculated for the continuous data, while number and percentage were calculated for the categorical data. Student's *t* test and a chi-square test were used to compare characteristics between the group with one exacerbation group and the group with more than one exacerbation. A $p < 0.05$ was considered statistically significant.

Results

Over the 5-year period, 1,654 patients were diagnosed with COPD and received treatment at Srinagarind Hospital. Of these, 183 patients were hospitalized with acute exacerbation of COPD. One hundred forty-four patients (78.7%) had one exacerbation and 39 patients (21.3%) had more than one exacerbation per year. Twenty-four patients (13.1%) had two, 8 (4.4%) had three, 6 (3.3%) had four, and 1 (0.5%) had five exacerbations per year. Thus, there were 245 acute exacerbations needing hospitalization.

The mean age of the 183 hospitalized patients was 74.9 (SD 9.28) years, and the male to female ratio was 170:13. Fifty-nine percent of the patients were elderly (60 and over) and not working. Eleven percent were monks, 13% civil servants, 9% farmers, 3% were in business, 3% employees, and 2% were housemaids. Twenty percent of the patients had no other medical comorbidity. The major underlying diseases were: hypertension (40%), diabetes mellitus (26%), old pulmonary tuberculosis (23%), benign prostatic hypertrophy (17%), and coronary heart disease (14%). Most (149 patients, 81%) were ex-smokers of ≥20 pack-years, 13% (23 patients) nonsmokers, 3% (6 patients) were ex-smokers <20 pack-years, and 3% (5 patients) were current smokers ≥20 pack-years. Spirometry was performed on 115 patients (63%) for COPD staging while in 68 patients (37%) it was not, so staging was not determined. According to the GOLD guidelines: 10 (5%) patients were Stage I, 28 (15%) were Stage II, 42 (23%) were Stage III, and 35 (19%) were and Stage IV. Twenty-seven patients (15%) died from acute exacerbation.

When we divided the patients into two groups according to the frequency of acute exacerbation (**Table 1**): 39 patients had more than one exacerbation per year and 144 patients had just one exacerbation per year. There was no significant difference between the two groups for mean age, sex ratio, occupation, or smoking status, but in the group that had more than one exacerbation per year, there was a greater proportion of severe COPD stages, especially Stages III and IV ($p = 0.023$). The mortality rate was higher in the group with more than one exacerbation per year than the group with one exacerbation per year (18% vs 14%), but this was not significant ($p = 0.53$).

The mean duration of symptoms for the 245 COPD exacerbation episodes was 4.1 (SD 3.46) days (**Table 2**).

The initial management during acute exacerbation included oxygenation and ventilator support, bronchodilator, systemic corticosteroids, and antibiotics. One-hundred forty episodes (57.1%) needed oxygen cannula 3–5 L/min, while 4 episodes (1.6%) needed noninvasive mechanical ventilation and 56 (22.8%) needed endotracheal intubation with mechanical ventilation. Systemic corticosteroid was given in nearly 80% of episodes. Bronchodilators with Berodual (ipratropium bromide/fenoterol) nebulization were prescribed in 95.1% of cases, β_2-agonist nebulization in 62%, while 147 episodes (60%) used Berodual together with a β_2-agonist nebulization. Antibiotics were prescribed for 217 episodes (88.6%) of acute exacerbation.

Pneumonia and bronchitis were the most common respiratory tract infections precipitating exacerbations of COPD. The causative organisms were identified in only 31% cases of pneumonia and 18% cases of bronchitis (**Table 3**).

About one quarter (25.3%) of acute exacerbations were complicated by respiratory failure (**Table 4**).

The mean duration of hospital admission was 17.3 days (range, 1–682 days) (**Table 5**). The total cost for the 245 exacerbations over five-year period was 19.6 million baht (US$ 653,000).

Medications prescribed for long-term management at discharge are presented in **Table 6**.

Table 1. Demographic data of 183 patients hospitalized with COPD exacerbation

Patient characteristic	One exacerbation (n = 144)	More than one exacerbation (n = 39)	*p*
Age, mean (SD) years	75.0 (9.78)	74.6 (7.22)	0.77
Male:female	132:12	38:1	0.30
Occupation, n, (%)			
Elderly retired	85 (59)	23 (59)	0.78
Civil servant	19 (13)	5 (13)	
Monk	15 (10)	6 (15)	
Farmer	12 (8)	4 (10)	
Businessperson	6 (4)	0 (0)	
Employee	4 (3)	1 (3)	
Housemaid	3 (2)	0 (0)	
Smoking status, n (%)			
No smoking	20 (14)	3 (8)	0.42
Ex-smoker, ≥20 pack-year	114 (79)	35 (90)	
Ex-smoker, <20 pack-year	5 (4)	1 (3)	
Current smoker, ≥20 pack-year	5 (4)	0 (0)	
Current smoker, <20 pack-year	0 (0)	0 (0)	
COPD staging (n, %)			
Stage I	8 (6)	2 (5)	0.023*
Stage II	23 (16)	5 (13)	
Stage III	32 (22)	10 (27)	
Stage IV	21 (15)	14 (36)	
Not determined	60 (42)	8 (21)	
Death, n (%)	20 (14)	7 (18)	0.53

*p <0.05 (considered significant)

Table 2. Hospitalization of 245 episodes of COPD exacerbation over a five-year period

Characteristic	N = 245
Duration of symptoms (mean, SD), days	4.1 (3.46)
Clinical presentation, n (%)	
Anthonisen type I	26 (10.6)
Anthonisen type II	104 (42.4)
Anthonisen type III	115 (47.0)
Precipitating cause, n (%)	
Not determined	44 (18.0)
Pneumonia	90 (36.7)
Bronchitis	68 (27.8)
Heart failure	20 (8.2)
Infected bronchiectasis	13 (5.3)
Diarrhea	3 (1.2)
Acute urinary retention	2 (0.8)
Unstable angina	1 (0.4)
Pneumothorax	1 (0.4)
Urinary tract infection	1 (0.4)
Atrial fibrillation	1 (0.4)
Drug induced cough	1 (0.4)
Acute management, n (%)	
O_2 cannula	140 (57.1)
Noninvasive ventilation	4 (1.6)
ET-tube with mechanical ventilation	56 (22.8)
Systemic corticosteroid	194 (79.2)
β_2-agonist nebulization	152 (62.0)
Berodual nebulization	233 (95.1)
Antibiotics	217 (88.6)

Table 3. Organisms identified in pneumonia and bronchitis

Organism*	**n (%)**
Pneumonia (n = 90)	
Organism not identified	62 (63)
Identified organism	28 (31)
Pseudomonas aeruginosa	8 (9)
Acinetobacter baumannii	7 (8)
Klebsiella pneumoniae	7 (8)
MRSA	4 (4)
Haemophilus influenzae	3 (3)
Stenotrophomonas maltophilia	3 (3)
Escherichia coli	3 (3)
Influenza virus	2 (2)
H. parainfluenzae	1 (1)
Bronchitis (n = 68)	
Organism not identified	55 (82)
Identified organism	12 (18)
P aeruginosa	5 (7)
H influenzae	4 (6)
K pneumoniae	3 (4)
A baumannii	1 (2)
Influenza virus	1 (2)

*More than one organism may be present in one patient

Table 4. Complications in 245 episodes of COPD exacerbation

Complication	**N = 245**
Respiratory failure	62 (25.3%)
Hospital acquired pneumonia	28 (11.4%)
Septicemia/septic shock	25 (10.2%)
Upper GI bleeding	11 (4.5%)
Right ventricular failure	9 (3.7%)
Cardiac arrhythmia	7 (2.8%)
Acute kidney injury	7 (2.8%)
Hypovolemic shock	5 (2%)
Acute myocardial infarction	4 (1.6%)
Acute urinary retention	4 (1.6%)
Hypokalemia	3 (1.2%)
SIADH	2 (0.8%)
Acute pulmonary embolism	1 (0.4%)

Table 5. Outcomes of treatment in 245 episodes of COPD exacerbation

Outcome	**N = 245**
ICU admission, n (%)	51 (20.8)
Admittance duration, mean (range) days	17.3 (1–682)
Death per exacerbation, n (%)	27 (11.02)
Cost of admission per exacerbation mean (range) baht	80,010 (2,779–3,433,108)

Table 6. Long-term management at discharge

Long-term treatment	N = 245 episodes
Long-acting theophylline	114 (46.5%)
Inhaled corticosteroid (ICS)	27 (11.0%)
ICS/LABA (moderate dose ICS)	128 (52.2%)
ICS/LABA (high-dose ICS)	71 (29.0%)
LAMA	69 (28.2%)
Long-term home oxygen therapy	21 (8.6%)

ICS/LABA = inhaled corticosteroid/long-acting β_2-agonist bronchodilator, LAMA = long-acting muscarinic antagonist

Discussion

Exacerbations of COPD are unfavorable events for patients in the course of chronic obstructive pulmonary disease. However, the severity and outcomes of an exacerbation may vary significantly between patients; as some will recover completely in the short-term while others may succumb and die [17]. Patients with two or more exacerbations per year are defined as having frequent exacerbations. Management of acute exacerbation of COPD remains extremely challenging and it places a heavy economic burden on healthcare institutions. Identification of the precipitating causes could help management, prevent failure, and achieve satisfactory recovery. However, the causes of about one-third of exacerbations cannot be identified.

During the five-year study period, 183 patients needed hospitalization. Most of these patients had stable COPD or mild COPD exacerbations treatable at an outpatient clinic. Even though the absolute number of hospitalized COPD exacerbations were not high, the types of exacerbations had a large impact on morbidity, mortality and cost of treatment. Nearly 60% of hospitalized patients were elderly (mean age 75 years). Approximate 80% were ex-smokers ≥20 pack-year, and the group with more than one exacerbation tended to have a higher percentage of heavy smokers. Frequent exacerbations were found to be related to COPD staging. Those with severe staging (especially Stage III and IV) were prone to have more than one exacerbation per year. The mortality rate for these two groups, however, was not significantly different; perhaps because hospitalized COPD patients in both groups were elderly and had multiple comorbidities. Age and comorbidities have previously been identified as risk factors for in-hospital mortality [18-20]. Advanced age is an adverse prognostic factor, with age over 75 years giving rise to a relative risk of death of 4.9 (95% CI, 2.3–10.8) [19].

Acute exacerbation of COPD patients presenting with worsening dyspnea, increased sputum volume and purulence should be offered antimicrobial therapy [11]. In the current study, more than half of the patients presented with clinical symptoms classified as Anthonisen type I and II and about two-thirds of the precipitating causes were the result of respiratory tract infections: pneumonia (37%), bronchitis (28%), and infectious bronchiectasis (5%). Reported pathogenic bacterial organisms were found in 50% to 80% of patients with COPD during exacerbations [21, 22]. In a previous study, the predominant organisms during acute infective exacerbations were believed to be *S pneumoniae*, nontypeable *H influenzae* and *M catarrhalis* [22]. Gram-negative bacteria may be found in repeated exacerbations or at an advanced stage of the disease [13]. In acute infective exacerbations, Enterobacteriaceae and Pseudomonas species predominate in patients with FEV1 ≤35% of the predicted value [13]. Potential pathogenic microorganisms reported from Taiwan in acute exacerbation of COPD were *K pneumoniae* (19.6%), *P aeruginosa* (16.8%), and *H influenza* (7.5%), followed by *A baumannii* (6.9%), Enterobacter species (6.1%), and *Staphylococcus aureus* (6.1%) [12]. In the current study; *P aeruginosa*, *A baumannii*, and *K pneumoniae* were the common pathogens for pneumonia; and *P aeruginosa*, *H influenza*, and *K pneumoniae* were the common pathogens for bronchitis. It seemed that Gram-negative bacteria and *P aeruginosa* were more commonly related to advanced stage of lung function. This data suggests that physicians prescribe antibiotics for acute exacerbation of COPD.

In acute management of exacerbations, one-fifth needed ventilator support, but few decided to accept support with noninvasive ventilation (i.e., continuous positive airway pressure or bilevel positive airway pressure ventilation). Increased use of noninvasive ventilation is now recommended for ventilator support in acute exacerbation of COPD in the GOLD guidelines [8]. A randomized control trial found that the need for intubation was less in the noninvasive ventilation group (13.5% vs 34%, p <0.01) [23], which may decrease hospital stay and mortality. In addition to oxygen therapy and ventilator support, the three classes of medications most commonly used for exacerbation of COPD are bronchodilators, corticosteroids, and antibiotics [8]. In the current study, most patients were treated with these three classes of medications and commonly used bronchodilators having combination of short-acting inhaled β_2-agonist and a short-acting anticholinergic agent.

The complications that followed acute exacerbations played a major role in the cost of treatment and hospital stay. The three most common complications were respiratory failure, hospital acquired pneumonia, and septicemia with septic shock. The mortality rate per exacerbation was 11%, as similar to previous reports [6, 7, 19]. The costs of treatment per exacerbation was on average 80,000 Thai baht (US $2,666), and calculated to be 19.6 million baht (US $653,000) for the 245 exacerbations over the five-year study period. The costs of hospitalization, especially in the intensive care unit (ICU) were higher than for outpatient treatment [24, 25]. The study of the direct costs of COPD among managed care patients indicated that medical costs comprised 96% of healthcare for the ICU patients. The mean episode-level costs were $305 for an outpatient visit, $274 for an urgent outpatient visit, $327 for an emergency department visit, $9,745 for a standard admission, and $33,440 for an ICU stay [24]. Long-term treatment with long-acting bronchodilators or in combination with inhaled corticosteroids to reduced exacerbation, and long-term home oxygen therapy (in indicated cases) will improve long-term outcomes [16, 26].

In conclusion, acute exacerbation increased morbidity and mortality for COPD patients. Moreover, repeated exacerbations resulted in declined lung function, impaired quality of health, and increased cost of treatment. In the current study, repeated exacerbations occurred commonly at an advanced stage of lung function. The common precipitating causes of exacerbation were respiratory tract infections; including pneumonia, bronchitis, and bronchiectasis. Gram-negative bacteria especially *P aeruginosa* were found to be common pathogens. For hospitalized COPD patients, oxygen therapy and early ventilator support should be considered. Short-acting bronchodilators, corticosteroids and antibiotics are the main treatment during exacerbation periods. Smoking cessation, vaccination against pneumococcus and *H. influenza*, pulmonary rehabilitation, and appropriate maintenance of pharmacotherapies are the long-term treatment strategies for preventing further exacerbations.

Acknowledgements

The author thanks Department of Medicine and Faculty of Medicine at Khon Kaen University for their support and Mr. Bryan Roderick Hamman and Mrs. Janice Loewen-Hamman for assistance with the English-language presentation of the manuscript. The author has no conflicts of interest or financial ties to disclose.

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