Derleme / *Review*

doi:10.5505/sakaryamj.2014.77486

# Kronik Obstrüktif Akciğer Hastalığında Akut Alevlenme: Etyoloji ve Tedavi

## *Acute Exacerbation of Chronic Obstructive Lung Disease: Etiology and Treatment*

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**Başvuru Tarihi:** 17.09.2013 **Kabul Tarihi:** 12.05.2014

**Özet**

Kronik obstrüktif Akciğer Hastalığı (KOAH), tüm dünyada ve ülkemizde sıklığı giderek artan bir küresel sağlık sorunudur. Acil servis başvuruları ve hastane yatışlarının önemli bir nedeni olan akut alevlenmeler, bu sorunun en büyük bileşenidir. Akut alevlenmeler, ağır solunum yetmezliğine gidiş sürecini hızlandırır, yüksek oranda mortalite ve morbidite nedenidir ve ülkelerin sağlık harcamalarında ciddi bir yük oluşturur. Alevlenmelerin etyolojisi ve tedavisi özellikle acil servis-aile hekimleri, evde sağlık hizmeti sunucuları ve göğüs hastalıkları ile ilgilenen hekimlerce iyi bilinmelidir.

**Anahtar Kelimeler:** Kronik Obstrüktif Akciğer Hastalığı, KOAH, akut alevlenme etyolojisi, akut alevlenme tedavisi

***Aplication:*** *17.09.2013* ***Accepted:*** *12.05.2014*

***Abstract***

*Both worldwide and in our country, the increasing incidence of Chronic Obstructive Pulmonary Disease (COPD) is a major health problem. Acute exacerbations, which are a major cause of emergency room visits and hospital admissions, are the largest component of this problem. Acute exacerbations adversely affect the prognosis of the disease and accelerate the process, resulting in severe respiratory failure, and are a cause of morbidity/mortality. Moreover, they cause a considerable load on healthcare expenditures and a significant amount of labor force loss. The etiology and treatment of exacerbations especially must be well understood by family and emergency service physicians, home health care service providers, and physicians dealing with chest diseases.*

***Keywords:*** *Chronic Obstructive Pulmonary Disease, COPD, etiology of exacerbation, treatment of exacerbation.*

**Introduction**

Chronic Obstructive Pulmonary Disease (COPD), quite common both in our country and around the world, is a disease, which despite being both preventable and treatable, has high mortality and morbidity. Moreover, COPD is public health problem that causes a significant healthcare spending and loss of workforce participation.[1]

According to the World Health Organization, in 2011, COPD was the world's fourth leading cause of death.[2] While mortality rates from cardiovascular and cerebrovascular diseases, which are other leading causes of death, have decreased, there has been an increase in the COPD mortality rate, and, in 2020, it is expected to be world's third leading cause of death.[3]

The annual cost of a patient with COPD in the United States is around $10,000.4 Direct costs of COPD are estimated to be 20.[4] billion dollars in the United States and 38.6 billion euros in the European Union.[1] Because of continued exposure to COPD risk factors and aging of the population, in the coming years the global burden of COPD is expected to increase further. The most important parts of the burden are hospitalizations and emergency room visits due to acute exacerbations.[5] Besides the economic burden, acute exacerbations are the most important cause of mortality and morbidity. One-year mortality after COPD exacerbations requiring mechanical ventilation has been reported to be 40%. Also, acute attacks adversely affect the prognosis of the disease and accelerate the process of severe respiratory failure. For these reasons, the prevention and treatment of acute exacerbations of COPD is very important.[6]

**Definition:**

COPD is defined as "progressive airflow limitation" which develops secondary to inflammation and damage of the lungs, and is caused by prolonged inhalation of harmful gases and particles (especially tobacco smoke). In a study performed in our country, the prevalence of COPD in persons over the age of 40 was found to be 28% of males and 10% of females.[7]

Most patients without a diagnosis have experienced shortness of breath for years and often come to the doctor because of an acute exacerbation. During the natural course of the disease, an "acute exacerbation" is defined as increases in shortness of breath, in the amount of sputum and in purulence that reach a level requiring treatment .[8] Patients with COPD undergo, on average, 1-3 exacerbations per year. In some patients, a predisposition to more exacerbations has been shown, with the frequency of attacks usually being associated with the severity of disease. With increasing severity of disease, the frequency of exacerbations also increases; frequent exacerbations contribute to further disease.[9,10]

**Etıology Of Exacerbatıons:**

There have been many etiologically based studies of acute exacerbations of COPD (regional, seasonal), and, although there are relative differences according to the methods used in the diagnosis, infections were shown to be the most common cause of exacerbation. In general, 60-80% of exacerbations are caused by infections.[5] The second most common cause of exacerbations is air pollution (15-20%).[11] The other less common causes of exacerbations are heart failure and arrhythmias, metabolic disorders and electrolyte disturbances, pulmonary embolism, pneumothorax, reflux-aspiration, and drugs.[5,8,11,12] Approximate frequency of causes of exacerbations are given in table 1.

Table 1 Potential indications for hospital admission

| Hospital admission indications |
|---|
| • Severe underlying COPD |
| • Marked increase in intensity of symptoms |
| • Sudden develepment of resting dispnea |
| • Onset of new physical signs (e.g. cyanosis, peripheral edema) |
| • Failure of an exacerbation to respond to initial medical management |
| • Presence of serious comorbidities (e.g. herat failure or arrhythmia) |
| • Frequent exacerbations |
| • Older age |
| • Insufficient home support |

1- Infection-induced exacerbations:

In acute exacerbations of COPD with conventional culture methods of sputum and bronchial lavage, H. influenzae, S. pneumoniae, M. catarrhalis are the most frequently isolated microorganisms. In patients with severe COPD who had frequent exacerbations, a history of frequent hospitalizations,

and lower FEV1, P. aeruginosa, S. aureus and Gram negative enteric bacteria were isolated more frequently during acute exacerbations .[19-23] However, during stable periods, in terms of exacerbation etiology, the colonization by these bacteria raises doubts. Although the lower airways of healthy people are sterile, airways of patients with stable COPD are known to be colonized by bacteria.[13] Harmful particles and cigarette smoke disrupt airway defense mechanisms through chronic exposure. Reduction in mucociliary clearance, increase in the viscosity of mucus as a result of epithelial injury, and inflammation result in bacterial colonization of the distal airways. In comparative studies with healthy control groups, in protected brush biopsy specimens and sputum of patients with stable COPD, H. influenzae, S. pneumoniae, M. catarrhalis, P. aeruginosa and S. aureus colonizations were found.[14-16] Although the effect of colonized bacteria on acute exacerbations is not yet clear, more recently, in the relationship between acute exacerbation and increased bacterial burden, the proliferation of new strains has been suggested.[17-18] From studies evaluating the parameters associated with bacterial colonization, a significant relationship was found between the frequency of exacerbations and increased colonization.[14,19] There are studies showing correlation between the decrease in FEV1 and the colonization.[16] As a result, in patients with frequent exacerbation, bacterial colonization seems to be more common. However, whether colonization often leads to exacerbation, or if colonization results in patients who had frequent exacerbations is not clear.

Viral factors are responsible for approximately 15-30% of exacerbations.[5] Most commonly rhinoviruses, followed by metapneumovirus, influenza A and B, parainfluenza, coronavirus, adenovirus, and RSV were isolated from patients with exacerbations.[24,25] Viral factors show a different distribution over the seasons and years.[26] Similar to bacteria, it is difficult to distinguish colonization-infection in nasopharyngeal swab samples. Also, from a significant proportion of patients, both bacterial and viral agents can be isolated. Mixed infections are more frequent in patients with severe COPD.

In studies investigating atypical agents, a wider distribution according to methods is observed. In our country, the four studies performed by serological methods were evaluated and atypical agents were found to be responsible in 22-38% of cases. Most commonly, Chlamydia pneumoniae, followed by Mycoplasma pneumoniae and Legionella pneumophilia were encountered. However, atypical factors are known to be part of colonization, and the role of atypical factors in polymicrobial infections in acute exacerbations is not clear.[27-30]

Sputum culture is often used in clinical trials to determine the infectious agent. However, because of selective culture conditions, the proliferation of many species in the sample is prevented. In addition, most patients have previously used antibiotics, and this causes a decrease in sensitivity and specificity of determination. Because of difficulties in the production of the agent by culture method and the need to use a different media for different microorganisms, in infections in which more than one agent is responsible, only one factor can be determined. In recent years, the polymerase chain reaction (PCR) method was developed. PCR replicating very low amounts of microbiological DNA or RNA to unlimited amounts is a new method that provides faster and more accurate diagnosis. It also can detect more than one agent in microbiological samples; and it can also detect nonliving microorganisms that are not affected by antibiotics.[31] In recent studies of COPD, in addition to identified by culture, the persistence of other potentially pathogenic bacteria was showed only by molecular methods and has been associated with severe attacks.[32] In studies with the PCR method, isolation of the bacterial agent and mixed infectious agents demonstrated a significant increase in the culture. Compared to serological methods, the frequency of atypical agents was found to be less and the use of antibiotics for atypical pathogens with no change in clinical results was observed.[24,31,33- 36]

2 - Non-infectious exacerbations:

In our country, especially in urban areas where air pollution is dense, admissions to the hospital because of acute exacerbations has increased significantly. Sulfur dioxide and nitrogen dioxide, exhaust fumes, and coal combustion product carbon compounds from industrial pollution are causes of acute attacks. A correlation between exacerbations and the amount of particles smaller than 10 microns in diameter in the air has been observed. [37,38]

Heart failure and arrhythmias, lung congestion and pulmonary pressure changes, and disruption of pulmonary vascular dynamics cause acute exacerbations. Another rare cause of exacerbations is the increased susceptibility to pulmonary embolism due to immobilization in patients with severe COPD and embolic episodes. In patients with emphysematous and bullous lung pneumothorax, comorbid conditions especially diabetes, eating disorders and electrolyte imbalances, reflux-aspiration and respiration suppressive drug usage can be considered.[5,12,39]

**Treatment Of Acute Exacerbatıons:**

1 – First evaluation and triage:

First, the patient's general and mental status (confusion, lethargy), hemodynamic stability (hypotension) and respiratory pattern (tachypnea, involvement of accessory respiratory muscles) and signs of right heart failure were evaluated. Arterial blood gas, chest X-ray and ECG, followed by glucose, urea, BUN, AST, ALT, blood biochemistry including electrolytes, and total blood counts were performed. Since CO2 retention can develop, blood gas measurement should be repeated 30-60 minutes after initiation of oxygen therapy.

The aim of treatment in exacerbated COPD is to minimize the risks of morbidity and mortality of those exacerbations. In this case, the first decision that must made is whether to treat the patient with outpatient treatments or to hospitalize the patient. Approximately 80% of exacerbation cases may be treated with outpatient therapies.10 The characteristics that may be effective in making the decision to hospitalize are given in table 2.

Table 2 Potential indications for ICU admission.

| İndications for ICU admission |
|---|
| • Changes mental status (confusion, lathergy, coma)<br>• Persistant or worsening hypoxemia (PaO2< 40 mmHg)<br>• Severe respiratory acidosis (Ph<7,25)<br>• Hemodinamic instability (need for vasopressors)<br>• Severe dyspnea that responds inadequality to initial emergancy therapy |

Another immediate decision to be made in the emergency department is whether the patient has indications for admittance to the intensive care unit. The indications for admittance to ICU are given in table 3.

2- Oxygen treatment:

The first approach to acute exacerbations is to provide supplemental oxygen to correct hypoxemia in patients. To reach the target of 88 to 92% saturation, oxygen is given by facemask or nasal cannula. Nasal cannula is inexpensive, safe and well tolerated. Its flow rate is 1-6 liter/min and FiO2 can be between 22-44%. It does not interfere with movement, eating, drinking or talking but can come off easily. Nasal cannulas cannot be used in cases of nasal congestion, and some patients continue to breathe through the mouth during their attacks. It is difficult to hold the oxygen concentration steady with the nasal cannula. A simple facemask provides 6-12 liter/min flow rate and FiO2 between 35-55%. However, it is not suitable for long-term therapy and interferes with eating, drinking, and talking and may cause skin irritation. In addition, a high flow rate is required to avoid inhaling the CO2 that is exhaled back into the mask. Reservoir masks provide 4-15 liter/min flow rate and FiO2 between 40-100%. In high-flow facemasks (venturi), the flow rates and FiO2 can be adjusted by tubes, and oxygen can be provided at the desired constant rate independent of the patient's breathing pattern.45 These masks are ideal for acute attacks but are less likely to be tolerated by patients.

3 - Antibiotic therapy

Infections are the most common cause of acute attacks. Infections are responsible for 60 to 80% of episodes and of those, 60-70% are due to bacterial factors. However, in which attacks and which antibiotics should be given remains controversial. Except for isolation of the pathogen, there is no definite parameter indicating whether the attack is caused by infection. While culture results are available in two days, results from serological methods result take fifteen days. The PCR method is expensive and has not yet entered into routine use. For all these reasons, clinicians' empirical antibiotic therapy begins. The best method for an indication for the initiation of antibiotic therapy is the assessment of the amount of sputum and the increase in the purulence.[40] In meta-analysis as sign of successful treatment, use of short-term antibiotics reduced the mortality risk 53% (initial mortality rate was 77%

before treatment).[41,42] For this reason, in patients with three main symptoms: dyspnea, increased sputum volume, and purulence of sputum; in patients with purulence of sputum and other one main symptom; in patients in whom mechanical ventilation is required; and in patients in whom severe exacerbations is observed, antibiotic therapy should be started.[1] In initiating empiric antibiotic, the frequency of exacerbations of the microbiological agent and the specific resistance of that bacterial population should be known in order to make rational antibiotic selections and increase treatment success. In our country, in those patients with mild-to-moderate COPD and without a history of frequent exacerbations and hospitalizations with the three most common causative agents (H. influenzae, S. pneumoniae, M. Catarrhalis), amoxicillin (which is effective), amoxicillin-clavulanic acid, ampicillin-sulbactam or second generation cephalosporins should be suggested. For patients with a history of more severe and frequent exacerbations enteric Gram negative bacteria and pseudomonas, an effective third generation cephalosporin or fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin) should be given and parenteral treatment options should be considered.[43] A treatment duration of 5-10 days is usually sufficient.1 Microbiological samples should be obtained during severe attacks in patients who suffer from frequent attacks and/or if the patient is not responding to the initial antibiotic therapy. Based on the examination of microbiological samples, the antibiotic therapy should be revised.

### 4 - Bronchodilator therapy

In the treatment of exacerbations, short-acting bronchodilators (salbutamol) alone, or in combination with short-acting anticholinergics (salbutamol+ipratropium), are given via inhalation (during heavy attacks, they may be given via nebulizer).[1] Short-acting bronchodilators may be repeated after 20 minutes according to the condition of patient. When long acting beta-mimetic (salmeterol, formoterol) and/or long-acting anticholinergics (tiotropium) are prescribed as maintenance therapy, the use of inhalation devices is described and explained. Because of insufficient instruction in the use of inhalation devices, approximately half of patients have used inhalation devices incorrectly.[44]

### 5 - Corticosteroid therapy

With corticosteroid treatment, shorter recovery times, improvements in lung function and hypoxemia, shorter durations of hospitalization, and reductions in recurrences were shown. For prednisolone treatment, during an attack, according to the level of exacerbation, a 40-80 mg parenteral dose followed preferably by a 30-40 mg oral dose for 10-14 days is recommended. Budesonide, which is a nebulized form of steroid, can also be used to treat attacks.[1]

### 6- Other pharmacological therapies:

Methylxanthines (theophylline) are less effective than inhaled bronchodilators and are less tolerated. They are not recommended for use in stable COPD. Intravenous methylxanthines are the second choice treatment in acute attacks and can be used in patients who had inadequate response to primary short-acting beta-mimetic treatment. Mucolytic and antioxidant (acetyl cysteine, erdosteine, ambroxol) drugs are not recommended for the treatment of stable COPD due to poor total benefits. However, they are beneficial during acute attacks for patients who have viscous sputum and have difficulty clearing it.

### 7 - Other supportive therapies

Treatment of comorbidities, especially in evaluating heart failure, should be focused on issues such as appropriate fluid and electrolyte balance, diuretics, and anticoagulant therapy, calcium channel blockers for the treatment of often seen arrhythmias, diabetes and blood sugar regulation, nutrition and closing the gap in protein.

There is some evidence from clinical trials that pulmonary rehabilitation programmes reduce hospital stay.

If there is no response to the initial treatment, standard treatments for dyspnea and oxygen support (the evaluation of arterial blood gas) are provided; if respiratory acidosis (pH <7.25), and hypoxemia (PaO2<40 mmHg), confusion, and lethargy are present, and/or in conditions where hemodynamic stabilization cannot be maintained, patients should be admitted to the intensive care unit and should be assessed for noninvasive or invasive mechanical ventilation support.[1]

**Preventıon Of Copd Exacerbatıons**

Conducting necessary studies to prevent future exacerbations in COPD should form the last link of acute attack treatment. Quitting smoking is the most important factor in preventing attacks. Every patient should be evaluated in terms of smoking and should be persistently advised in cessation. All patients should be carefully observed for correct use of their inhaler devices and their errors should be corrected. Influenza infection often causes acute attacks in patients with moderate and severe COPD. Therefore, annual influenza vaccination and pneumococcus vaccination should be recommended, especially for patients older than 65 years. Patients should be encouraged to continue their physical activities and pulmonary rehabilitation program should be provided within the facilities. Epidemiological studies in COPD patients have provided some evidence that long-term oxygen therapy and noninvasive ventilatory support may reduce hospital admission and prevent exacerbations, but controlled trials have not yet addressed these issues.

**Conclusıon:**

With an increased frequency in our country and around the world, COPD will continue to be a major health problem. True treatment and preventing of exacerbations, but you may be able to increase their level of knowledge on this subject. Should be given the necessary training especially emergency services, family physicians and home health care servers. Reducing the incidence of attacks and rapid treatment of exacerbations are positively affected by the progression of COPD patients. So both the process of going into end-stage respiratory failure is decelerated as well as a major contribution to the national economy is provided.

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