Review

COPD exacerbation in ICU

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SUMMARY. Exacerbations affect the progression of COPD, especially when hospitalization is required. During COPD exacerbation, patient has increased respiratory effort, which sometimes can lead to fatigue of respiratory muscles and finally respiratory failure requiring mechanical support and ICU admission. The prognosis of patients with COPD exacerbation admitted in ICU is disappointing. Clinicians often face difficulty in taking the decision for intubating patients with COPD exacerbation, mainly because these patients usually have prolonged stay in ICU, difficult and prolonged weaning, many complications and finally poor outcome. In this review will be analyzed the indications for mechanical ventilation, pathophysiology, the clinical characteristics of COPD patients admitted in ICU, factors that affect outcome, and treatment of them in accordance with current guidelines. *Pneumon 2014, 27(3):242-248.*

INTRODUCTION

According to the definition set by Global initiative for chronic Obstructive Lung Disease (GOLD updated 2014), chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual cases[1]. COPD has been estimated to become the third leading cause death worldwide by the year 2020, while in the United States COPD is the fourth cause of death and the 12th cause of morbidity[2].

A variety of clinical factors are considered to influence the natural history and prognosis of patients with chronic obstructive pulmonary disease. These factors include among others, airway obstruction (FEV_1), weight (BMI), chronic hypercapnia and frequency of acute exacerbations[3].

Acute exacerbations manifest as gradually worsening respiratory symptoms (such as dyspnea, increased sputum production and increased sputum purulence), which lead to increased respiratory effort and respiratory failure, sometimes requiring ICU admission and mechanical support. Exacerbations affect the progression of COPD, especially when hospitalization is required[1,2]. Patients with frequent COPD exacerbations have faster and greater decline

in FEV1[3], reduced activity in their daily life and increased mortality[4]. Exacerbations have the largest share of the total costs of providing health care services for COPD[1].

In this review analysis will be analyzed clinical characteristics of COPD patients admitted in ICU, prognostics factors, indications for mechanical ventilation, pathophysiology, treatment and outcome.

DECISION FOR INTUBATION AND CLINICAL CHARACTERISTICS OF COPD PATIENTS ADMITTED IN ICU

Acute exacerbations of COPD are the main reason of ICU admission for a COPD patient[5]. During COPD exacerbation, patient has increased respiratory effort, which sometimes can lead to fatigue of respiratory muscles and finally respiratory failure requiring mechanical support and ICU admission. Other causes of admission in ICU are community-acquired pneumonia, cardiovascular events and acute on chronic respiratory failure from other causes: sedatives, pneumothorax and pulmonary embolism[6]. Several studies showed that, the majority of patients admitted in ICU are patients aged 70 ± 10 years, with mean APACHE II score 22, with severe COPD (stages C and D), usually on home long-term oxygen therapy, with previous hospitalizations, receiving inhaled or systematic steroids and have two or more comorbidities[7]. Elsewhere is shown that among the characteristics of patients with COPD exacerbation admitted in ICU, FEV_1 is an independent predictor factor of the need of mechanical ventilation[8]. It is evident, that the need of mechanical ventilation is related to functional respiratory reserve of patient.

Indications for ICU admission, according to GOLD guidelines for management of exacerbations, are: a) severe dyspnea that doesn't respond to initial emergency therapy, b) changes in mental status, c) persistent or worsening hypoxemia (PaO_2 <40 mmHg) and/or severe or worsening respiratory acidosis pH <7,25 despite supplemental oxygen therapy and noninvasive ventilation, d) need for intubation and mechanical ventilation e) hemodynamic instability and need for vasopressors[1].

MANAGEMENT OF COPD EXACERBATIONS IN ICU

Role of non-invasive mechanical ventilation (NIV)

According to Canadian guidelines, the use of NIV plus standard treatment is a recommendation with level 1A evidence in patients with exacerbation of COPD have hypercapnia and pH <7.35 and should be the first choice for ventilatory support in these patients[9].

It is well know that, the use of NIV in patients with COPD exacerbation and moderate or moderate to severe respiratory acidosis prevents endotracheal intubation and improves survival[10]. Even in severe respiratory acidosis when ventilatory support is required, the use of NIV prevented endotracheal intubation in 48% of the cases. This was the conclusion of a randomized prospective study, which compared NIV with conventional mechanical ventilation. The ICU mortality was the same in both groups of patients, but patients who improved with use of NIV had shorter duration of stay in ICU, while fewer patients of this group re-admitted to hospital or needed supplementary oxygen therapy at 1 year follow up[11].

As shown in a previous review, the application NIV plus standard treatment reduces the need for intubation compared with standard treatment only in COPD exacerbation (RR 0,41 [95% CI 0.33-0.53]). Additionally, the same review stated that the mortality was decreased by applying NIV in combination with standard treatment compared to the usual single treatment in COPD exacerbations (RR 0,52 [95% CI 0.35-0.76])[12]. However, benefits of NIV are similar to the mechanical ventilation's in reducing work of breathing and in improving gas exchange[13]. Additional advantages of NIV are the fewer complications compared to invasive mechanical ventilation. Avoiding the complications of intubation prevents the increased risk for ventilator associated pneumonia and the complications associated with prolonged stay in ICU (for example: deep venous thrombosis)[14]. Nonetheless, approximately 50% of patients will finally need intubation due to adverse effects, intolerance or failure of NIV. The contraindications for use of NIV are shown in Table 1. Predictors of failure of NIV are pneumonia, inability to remove secretions, alterations in mental status and severe acidosis, particularly if pH is not improved after 1 hour of NIV[15].

Another important role of NIV is to facilitate weaning in intubated patients with COPD exacerbation. Several studies have used NIV in patients who failed spontaneous breathing trials. The authors found shorter ventilator time, decreased incidence of ventilator associated pneumonia, reduced ICU mortality and need for tracheotomy[16]. Patients with hypercapnic respiratory failure due to COPD exacerbation had a higher risk for extubation failure but responded better using NIV immediate after extubation[17].

Nava et al[18], randomized 50 patients with COPD exacerbation, who failed spontaneous breathing trial after 48 hours of invasive mechanical ventilation, extubated

TABLE 1. Contra-indications for non-invasive ventilation (NIV) use

Contra-indications for NIV use
1 Cardiac or respiratory arrest
2 Non respiratory organic failure • Severe encephalopathy (GCS<10) • Severe haemorrage of upper gastrointestinal tract • Haemodynamic instability or severe arrythmia
3 Upper airways obstruction
4 Surgical intervention or facial trauma
5 Lack of co-operation
6 Increased risk for bronchial aspiration
7 Copious secretions

them and applied NIV or continued invasive mechanical ventilation. They found that the group of NIV had greater rate of successful weaning (88% vs 68%), shorter length of stay in ICU, better survival at 60 days and no ventilator associated pneumonia[18]. A recent meta-analysis of the use of NIV as a tool of weaning from mechanical ventilation which included 16 randomized trials with 994 patients, confirmed the advantages of this procedure in patients with COPD: greater probability of liberation of mechanical ventilation, shorter duration of mechanical ventilation and stay in ICU, lower incidence of ventilator associated pneumonia, less need of tracheostomy and re-intubation, better survival[19].

Invasive mechanical ventilation

Indications for mechanical ventilation in acute severe COPD exacerbation are shown in Table 2[1].

TABLE 2. Indications for invasive mechanical ventilation (IMV) in COPD acute exacerbations

Indications for invasive mechanical ventilation
1 Failure or intolerance of non-invasive ventilation (NIV)
2 Cardiac or respiratory arrest
3 Impaired consciousness or delirium non controlled with medication in need for sedation
4 Increased risk for bronchial aspiration
5 Copious secretions
6 Severe ventricular arrythmia
7 Severe hypoxemia
8 Severe haemodynamic instability non responsive to fluids and vasopressors

Clinicians often face difficulty in taking the decision for intubating patients with COPD exacerbation, mainly because these patients usually have prolonged stay in ICU, difficult and prolonged weaning, many complications and finally poor outcome[20]. According, to the recommendations of UK guidelines for the management of COPD in adults, the most important variables that can affect the decision for ICU admission are: age, FEV_1, previous ICU admissions, prior functional status, body mass index, requirement for oxygen when stable and co-morbidities[21]. As shown by a study conduced in nine ICUs and related 95 imports of patients with COPD exacerbation, after standardization of variables associated with invasive mechanical ventilation, found that BMI was the only factor correlated with immediate invasive mechanical ventilation in the multivariable analysis. Also, founded that some other factors are important as the doctor of ICU, the presence of specified protocol and the work load of ICU[22].

To optimize the settings of mechanical ventilation is very important to understand the pathophysiology of COPD exacerbation. The basic abnormality in COPD exacerbation is the expiratory airflow limitation and dynamic hyperinflation.

The objectives of mechanical ventilation in COPD exacerbation are:

A) reduction of dynamic hyperinflation and air trapping. This is achieved with bronchodilators and appropriate ventilator settings including long expiratory time, high inspiratory flow, low respiratory rate and titration of Positive End Expiratory Pressure (PEEP) in 80% of endogenous PEEP[24].

B) Adequate gas exchange. Adequate oxygenation is achieved with relatively low O_2 mixtures as the primary pathophysiological mechanism of hypoxemia in these patients is V/Q disorder. The correction of PCO2 is aiming to return to PCO2 values of the patient at rest, before the exacerbation, and not normocapnia.

C) Prevention of lung injury ventilator (Ventilator - Induced Lung Injury, VILI), should therefore be applied small tidal volumes (5-7 ml/kgr). This is called controlled hypoventilation and can result in respiratory acidosis, which tolerate if the pH >7.25 (permissive hypercapnia).

D) Avoiding respiratory alkalosis. The alkalosis may cause a decrease in cardiac output, constriction of blood vessels in the brain, a shift to the left of the release curve of oxyhemoglobin disrupting the release of O_2 in the tissues and depression respiratory drive led to weaning failure[25]. The results of a study showed that respiratory alkalosis associated with prolongation of

mechanical ventilation and length of stay in ICU[26].

E) Resting respiratory muscles. This is achieved by models of controlled ventilation and maintains sedation for 24-48 hours. However, prolonged mechanical ventilation can lead to weakness and even atrophy of the respiratory muscles, making the weaning difficult[27,28].

Weaning from mechanical ventilation

Weaning from mechanical ventilation is a process where mechanical ventilation is gradually withdrawn and the patient resumes spontaneous breathing. For the weaning of mechanical ventilation most often is used the pressure support ventilation (PSV) and, spontaneous breathing trial (SBT)[29].

Patients with COPD have high weaning failure. The main pathophysiologic mechanism of weaning failure in COPD patients with prolonged mechanical ventilation is the failure of respiratory muscles across the increased workload[30]. According studies done in patients that failed to be extubated independent predictors of extubation failure were APACHE II score >35 and prior use of NIV at home. Furthermore, sterile endotracheal secretions were predictors of extubation success[31].

A different approach for difficult weaning in COPD patients is the early extubation with immediate application of NIV. This method showed benefits on outcome, decreased duration of mechanical ventilation, decreased ventilator- associated pneumonia, decreased length of stay in ICU and hospital stay[18].

ANTIBIOTICS

American Thoracic Society and European Respiratory Society recommend the use of antibiotics, in severe exacerbations of COPD requiring admission in ICU. However, in many cases bacteria are not detected in endotracheal secretions while in several cases, viral infections are the cause of severe exacerbations[32]. On the other hand, many of the patients admitted in ICU with severe exacerbation of COPD have bacterial colonizations and it is very difficult to differentiate bacterial colonization from bacterial infection.

The recommendation about the use of antibiotics based on a study done by Nouira et al, who randomized 93 patients with COPD exacerbation admitted in ICU and were in NIV (20%) or invasive mechanical ventilation (80%) and were treated with ofloxacin or placebo. Patients who received antimicrobial therapy had lower mortality (4 vs 17%), shorter duration of mechanical ventilation (6 vs 10 days) and shorter duration of ICU stay and hospital stay[33]. In a recent review of the use of antibiotics had a significant and sustained beneficial effect in patients with exacerbation of COPD admitted to the ICU, as opposed to those who were hospitalized in hospital ward[34].

STEROIDS

The use of corticosteroids in COPD exacerbations is indicated by GOLD guidelines. Recommended dose is 40 mg Prednisolone per day for 5 days[35]. The use of systemic corticosteroids shortens the recovery time, improves lung function (FEV_1), improves arterial hypoxemia (PaO_2) and also, reduces risk of early relapse, treatment failure and length of hospital stay[1]. This is probably based on meta-analyses, which showed that corticosteroids play an important role in the inflammatory response, accelerating thus recovery and improving the lung function. However, these studies excluded patients with severe COPD exacerbations who were in need of mechanical ventilation[36].

In a recent randomized double blind control trial of patients with severe COPD exacerbation that required ventilator support, patients who received systemic steroids had successful non-invasive mechanical ventilation and shorter duration of mechanical ventilation. Patients treated with corticosteroids had a decline in C-reactive protein. This shows a change in immune response and probably explains the reduction of duration of mechanical ventilation[37]. On the other hand, in a recent study of patients with COPD exacerbation requiring mechanical ventilation, the treatment with corticosteroids did not improve mortality or the outcome[38].

Regarding the dose of corticosteroids, in a retrospective observational study found that two thirds of patients admitted to ICU for COPD exacerbation treated with high doses of systemic corticosteroids (>240 mg methylprednisolone intravenously on the first two days) and this was associated with poor outcome frequent side effects. So, the authors recommend low-dose corticosteroids (<240 mg methylprednisolone intravenously on the first two days), although more studies are needed to document this[39].

FACTORS AFFECTING THE OUTCOME OF COPD PATIENTS IN ICU

The variables, that predict outcome in patients with AECOPD, are very important as they affect the decision

about intubation and ICU admission. It is reported that a high APACHE II score and low Glasgow Coma Scale (GCS) are independent predictors for intubation of patients with a COPD exacerbation[40].

A study about the outcome of patients with COPD after hospitalization in general ICU revealed that the risk factors that are associated with increased hospital mortality are: advanced age, severe respiratory disease, length of stay in hospital before admission in ICU, cardiopulmonary arrest before the admission in ICU, low pH (acidosis), low PaO_2/FiO_2 gradient, low serum albumin, and multiple organ failure[41].

A recent review conduced by Messer et al, examined the predicting factors of intermediate mortality (up to 6 months after admission to ICU with an acute exacerbation of COPD). Low GCS on admission in ICU, cardio-respiratory arrest prior to ICU admission, cardiac dysrhythmia prior to ICU admission, length of hospital stay prior to ICU admission and higher values of acute physiology scoring systems have proven to be statistically significant and were associated with higher intermediate mortality[42].

COPD is frequently associated with other diseases. Comorbidities[43] such as heart failure, lung embolism[44], depression[45], metabolic syndrome[46] have a negative impact in exacerbation of COPD. In an interesting study by Divo et al[47], a comorbidity risk index (COTE) was developed, based on a multivariate analysis of comorbidities that increase mortality. Although a large number of comorbidities may be present in COPD patient, a limited number of them are independently associated with mortality. These are malignancies (lung, pancreatic, esophageal and breast cancer), cardiac diseases (atrial fibrillation, congestive heart failure, coronary artery disease), gastric ulcer, liver cirrhosis, diabetes with neuropathy and anxiety. Increases in the COTE index were associated with increased risk of death[47].

LONG-TERM SURVIVAL OF COPD PATIENTS ADMITTED IN ICU

The prognosis of patients with COPD exacerbation admitted in ICU is disappointing. Data on long-term survival after leaving the hospital are insufficient. In-hospital mortality rates vary in different studies because of differences of disease severity.

In a retrospective cohort study, mortality rate 5 years after discharge of hospital was 69.6%. At the same study, as risk factors associated with increased mortality were identified age, higher APACHE II score, hypoalbuminemia and long-term steroid use. Previous intubation and duration of hospital stay were considered independent predictors of hospital mortality[48].

Another retrospective study showed that the long-term survival of patients admitted in ICU for COPD exacerbation was very low[49]. Five-year survival was 13%. In this study, COPD patients had longer ICU duration of stay and higher ICU mortality compared to non-COPD patients[49].

However, in the literature also appear encouraging studies, in which the mortality of ventilated patients due to respiratory failure caused of COPD is lower than mortality of ventilated patients with non-COPD respiratory failure[50]. In a retrospective observational study during 10 years, the hospital mortality of patients with severe COPD exacerbation who required invasive mechanical ventilation and hospitalization in ICU was <30%[51]. Elsewhere, 43% of COPD patients admitted to ICU survived for 3 years and 55% of patients were liberated from mechanical ventilation. The possible explanation is the use of NIV for facilitating weaning[52].

CONCLUSIONS

COPD exacerbations lead to the progression of disease severity and may lead the patient in ICU. The use of NIV in COPD exacerbations is crucial because it improves survival, and prevents intubation in almost 50% of the cases. When required mechanical ventilation is important in maintaining patient's life with the risk however of many life-threatening complications. Although the indications for mechanical ventilation are specific, the poor prognosis of these patients makes it imperative to evaluate other parameters too, such as the age, disease severity, and prior functional status of the patient. Except for the bronchodilators, the etiologically correct and early use of antibiotics in COPD exacerbation with bacteriological feedings is recommended by GOLD. On the other hand, the use of steroids is controversial due to adverse effects, although they decrease the duration of ventilatory support. It is evident, that the appropriate treatment of COPD exacerbation admitted in ICU is essential for patient's life.

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