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Management of Acute Exacerbations

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1. Introduction

American Thoracic Society (ATS) and European Respiratory Society (ERS) define an exacerbation as an acute change in a patient's baseline dyspnea, cough, or sputum that is beyond normal variability, and that is sufficient to warrant a change in therapy (Celli MacNee 2004). Exacerbations have a negative impact on mortality and morbidity and as the disease progresses, the frequency and severity of exacerbations increase, leading to a fall in the quality of life of COPD patients. There is no standard method or tool for the diagnosis of an exacerbation. The changes in the clinical status of the patient should be taken into account.

The most important parameters predicting mortality in patients who are hospitalized due to an acute exacerbation are; severity and stage of COPD, advanced age, co morbidities such as diabetes mellitus or cardiovascular disease, need of intubation and mechanical ventilation, high APACHE II score, presence of sepsis and multi organ failure (Groenewegen et al. 2003).

2. Etiology of exacerbations

Tracheobronchial infections (40-50% bacterial, 30-40% viral, 5-10% atypical bacteria) are involved in 50-70% of COPD exacerbations. Another factor is air pollution that is thought to be involved in 10% of exacerbations. In about 30%, the etiologic factor cannot be identified (Sapey Stockley 2006). Other medical problems, such as congestive heart failure, nonpulmonary infections, pulmonary embolism, and pneumothorax, can also lead to a COPD exacerbation.

Infections:

Bacterial: (Streptococcus pneumonia, Haemophilus influenza, Moraxella catarrhalis, Chlamydia pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus)

Viral: (Rhinovirus, influenza, adenovirus, parainfluenza, coronavirus, respiratory syncytial virus)

Environmental factors:

Indoor and outdoor air pollution

Patients who are known to have COPD are defined as an exacerbation when they are admitted to the emergency departments with increased dyspnea during fall and winter. The main issue is the underestimation of non-infectious causes such as pulmonary embolism, pleural effusion, pneumothorax, thoracic traumas, inappropriate use of sedatives, narcotics and beta blockers, arrhythmias, cardiac failure or problems in the use of long term oxygen therapy. Therefore, in a COPD patient with increased dyspnea, first the diagnosis of exacerbation should be established correctly and then the etiology should be identified as infectious or non-infectious.

Potentially pathogen bacteria are identified in 30% of sputum cultures in mild exacerbations, while this rate can be up to 70% in severe exacerbations in patients who need ventilatory support (Sapey Stockley 2006; Siddiqi Sethi 2008).

3. Initial evaluation of an exacerbation

There are two main steps in the evaluation of a COPD exacerbation. The first step is the determination of severity of the disease that will guide the physician about the treatment approach and hospitalization decision. The second step is the identification of the etiologic cause and decide whether to initiate antibiotherapy or not.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies COPD exacerbations as mild, moderate or severe, based on the intensity of the medical intervention required to control the patient's symptoms (Table 1)(Rabe et al. 2007).

Clinical history	Mild (home treatment)	Moderate (hospital treatment)	Severe (ICU treatment)
Comorbidity	+	+++	+++
Frequent exacerbation history	+	+++	+++
COPD stage	Mild/Moderate	Moderate/Severe	Severe
Hemodynamic status	Stable	Stable	Stable/Unstable
Accessory respiratory muscle use, cyanosis, paradoxal breathing, cyanosis, tachypnea	No	++	+++
Change in neurologic status	No	No	Yes
Symptoms of right heart failure	No	++	+++
Persistence of symptoms despite drug therapy	No	++	+++

+: probably doesn't exist, ++: probably exists, +++: strongly may exist, ICU: intensive care unit

Table 1. Classification of COPD exacerbations

Another classification approach is suggested by Anthonisen and colleagues (Anthonisen et al. 1987). According to this approach, severe exacerbations requiring antibiotherapy are characterized by the presence of increase in all of the 3 criteria: dyspnea, sputum production and sputum purulence. Moderate exacerbations show only the 2 of these criteria, while in mild exacerbations, only one of these criteria is present with a recent history of upper airway infection or fever or symptoms like wheezing, cough, tachypnea and tachycardia.

Diagnostic evaluation of a suspected COPD exacerbation varies whether the patient will be treated in the hospital or at home. Routine sputum culture evaluation is not recommended for mild exacerbations. In case of a severe exacerbation, oxygen saturation must be measured by a pulse oxymeter. Patients who are referred to a hospital must be evaluated by advanced diagnostic tests such as arterial blood gas analysis, chest x-ray, sputum gram staining and cultures, electrocardiography and blood drug levels if possible (Table 2).

Diagnostic procedures	Mild	Moderate	Severe
Oxygen saturation	Yes	Yes	Yes
Arterial blood gas analysis	No	Yes	Yes
Chest X-ray	No	Yes	Yes
Blood tests *	No	Yes	Yes
Serum drug concentrations**	If possible	If possible	If possible
Sputum gram staining and cultures	No	Yes	Yes
ECG	No	Yes	Yes
BNP †	No	No	Yes
Cardiac enzyme measurement ‡	No	No	Yes

*: blood cell count, serum electrolytes, urea, creatinine, liver function tests.

** : theophylline, warfarin, carbamazepine, digoxin

†: One third of dyspnea in chronic lung disease may be attributable to congestive heart failure.

‡: Cardiac ischemia (myocardial infarction is underdiagnosed in patients with COPD).

Table 2. Diagnostic evaluation of patients with suspected COPD exacerbation

About 50% of COPD exacerbations are not reported to physicians (Seemungal et al. 2000). This suggests that half of the exacerbations are mild and do not require hospitalization. Indications for hospitalization of a patient with COPD exacerbation are as follows:

1. Onset of new physical signs such as cyanosis, peripheral edema, deterioration in the neurological status, arrhythmias etc.
2. Having severe or very severe COPD and being under long term oxygen therapy at home.

3. No response to initial drug therapy.
4. Pulmonary (pneumonia), or non-pulmonary (cardiac disease, diabetes mellitus) comorbidities with high risk.
5. Having exacerbations often.
6. Newly diagnosed arrhythmias.
7. Diagnostic uncertainty.
8. Advanced age.
9. Detour in the arterial blood gas analysis results (pH < 7.35 or PaO₂ < 60mmHg or SaO₂ < 90%)
10. Insufficient home support

4. Treatment of COPD exacerbations

All moderate and severe exacerbations must be evaluated in the hospital and in all severe exacerbations; arterial blood gas analysis must be performed. The patient must be evaluated immediately in terms of respiratory failure and oxygen therapy must be initiated if needed. Life threatening exacerbations should be followed up in the ICU. Respiratory failure with hypercapnia and respiratory acidosis is related with high mortality both at the time of admission and also during the 12 months follow up. While carbon dioxide retention is possible in moderate and severe exacerbations under oxygen therapy, arterial blood gas analysis must be performed every 30-60 minutes in order to detect the PaCO₂ and pH levels.

The inhaled oxygen concentration must be titrated to achieve a SaO₂ > 90% or a PaO₂ > 60 mmHg. High-flow oxygen devices deliver oxygen more effectively than nasal canulas but nasal canulas may be tolerated better. If adequate oxygenation cannot be achieved by high flow masks or if the acidosis begins worsening (pH < 7.35 and/or PaCO₂ > 50mmHg), noninvasive ventilation (NIV) is indicated. Success rates of NIV in COPD exacerbations are reported as 80-85% (Mehta&Hill 2001). The effect of NIV must be evaluated at the end of first and second hour by an arterial blood gas analysis. If there is worsening in the arterial blood gas result or if the patients cannot tolerate NIV, has worsening hypoxemia or has severe comorbidities such as myocardial infarction, hemodynamic instability, severe arrhythmias or sepsis, intubation and invasive mechanical ventilation must be initiated immediately.

Short acting inhaled β-2 agonists are the first line preferred drugs for COPD exacerbations. The dosage and frequency of these drugs must be increased. Another option is to add an inhaler short acting anticholinergic drug or increase the dosage if the patient is already taking the drug. Nevertheless, the effectiveness of this combination still remains controversial. If there is a long acting bronchodilator the patient is not using, it can also be added to the therapy even though there is no clinical evidence showing the benefit of these drugs during an exacerbation. In severe exacerbations if the patient cannot inhale effectively, nebulised forms must be used. The role of theophylline in COPD exacerbations is controversial. If there is not enough response to short acting inhaled β-2 agonists, it can be used as a second choice drug. Serum levels must be obtained and patients must be followed carefully because of its cardiovascular side effects.

Characteristics of the patient and exacerbation	Possible causes	Oral therapy choices	Parenteral therapy choices
Mild exacerbation (no signs of respiratory failure and severe obstruction, no comorbidities, 3 or less exacerbations in the last one year, no antibiotic use in the last 3 months)	<ul style="list-style-type: none"> H. Influenza S. Pneumoniae M. Catarrhalis C. Pneumoniae Viruses 	<ul style="list-style-type: none"> β-lactam (Penicillin, Ampicillin/ Amoxicillin) Tetracycline Trimethoprim/ Sulphamethoxazole β-lactam/ β-lactamase inhibitors (Co-amoxiclav) Macrolides (Azithromycin, Clarithromycin, Roxithromycin) 2nd or 3rd generation cephalosporins Ketolides (Telithromycin) 	<ul style="list-style-type: none"> β-lactam/ β-lactamase inhibitors (Co-amoxiclav, ampicillin/ sulbactam) 2nd or 3rd generation cephalosporins Floroquinolones (Levofloxacin, Moxifloxacin)
Moderate/ Severe exacerbation (complicated exacerbation, risk factors for treatment failure but not for P. Aeruginosa)	<p>Added to above;</p> <ul style="list-style-type: none"> β-lactamase producing enteric gram (-) bacteria (K. Pneumonia, E. Coli e.g) 	<ul style="list-style-type: none"> β-lactam/ β-lactamase inhibitors (Co-amoxiclav) 2nd or 3rd generation cephalosporins Floroquinolones (Gemifloxacin, Levofloxacin, Moxifloxacin) 	<ul style="list-style-type: none"> Floroquinolones (Ciprofloxacin, Levofloxacin-high dose) β-lactams with antipseudomonal activity
Severe exacerbation with a high risk of P. Aeruginosa*	<p>Added to above;</p> <ul style="list-style-type: none"> P. Aeruginosa 	<ul style="list-style-type: none"> Floroquinolones (Ciprofloxacin, Levofloxacin-high dose) 	<ul style="list-style-type: none"> Floroquinolones (Ciprofloxacin, Levofloxacin-high dose) β-lactams with antipseudomonal activity

*Hospitalization in the last one month, frequent antibiotic use in the last one year, exacerbation causing severe respiratory failure, isolation of *P. Aeruginosa* in the sputum culture during stable state or prior exacerbations.

Table 3. Antibiotherapy options in infectious exacerbations of COPD

Adding systemic (oral or intravenous) glucocorticosteroids to other therapies in the hospital management of exacerbations of COPD is recommended (Niewoehner et al. 1999). Systemic use of corticosteroids may lead to fast recovery and improvement in hypoxemia and lung functions in COPD exacerbations. The recommended dosage of prednisolon is 30-40 mg/day for 7-10 days if the patient has an initial FEV1 value below 50%. Prolonged treatment does not have a positive affect, besides it may increase the risk of side effects (e.g. muscle atrophy, hyperglycemia).

Bronchoscopic studies showed that the amount of bacteria is increased nearly in 50% of COPD patients during an exacerbation when compared to the stable state (Sethi 2004). The decision to use antibiotics and the choice of antibiotic should be guided by the patient's symptoms (e.g., presence of purulent sputum), recent antibiotic use, and local microbial resistance patterns. Prophylactic or continuous use of antibiotics does not improve outcome in patients with COPD (Rabe, Hurd et al. 2007).

Even though the most common bacteria responsible for the exacerbations are *H. influenzae*, *S. pneumoniae* and *M. Catarrhalis*; some enteric Gram (-) bacteria and *Pseudomonas aeruginosa* are also isolated in most of the patients with hypoxemia, severe airway obstruction, malnutrition, frequent hospitalization and antibiotic use history and comorbidity (Incalzi et al. 2006). There are some studies suggesting that atypical bacteria can also be an etiologic reason for an exacerbation but antibiotherapy targeting these bacteria showed no positive affect on clinical outcomes (Diederer et al. 2007; Tasbakan et al. 2007). Viruses can also be responsible in 15-40% of all exacerbations. Most of these are present with a bacterial infection.

Antibiotherapy reduces the mortality rates and treatment failure especially in severe exacerbations of COPD (Puhan et al. 2007). Antibiotics also decrease the relapse rates of exacerbations in outpatients (Adams et al. 2000). Therefore, antibiotherapy is strongly indicated especially if the patient has purulent sputum and increase in dyspnea. Treatment options according to clinical status is summarized in Table 3.

5. Preperation for hospital discharge

In order to qualify for a discharge, the patient must have stable clinical conditions and a stable or improving arterial PaO₂ of greater than 60mmHg. The patient should not require short acting β -agonist more often than every 4 hours. If the patient is stable and can use a metered dose inhaler, there is no extra benefit of using nebulised forms (Jenkins et al. 1987). Patient education including topics such as medical treatment, nutrition, rehabilitation and physiotherapy programs and when to seek for professional medical help may improve the response to future exacerbations. Home support such as home mechanical ventilation, long term oxygen therapy, nebulisers or similar equipments should be arranged before discharge.

6. Preventing future exacerbations

Pulmonary rehabilitation, smoking cessation and immunization against influenza and pneumonia have been shown to improve health quality and reduce exacerbations in COPD

patients. There are also some data showing that long term oxygen therapy reduces the risk of hospitalization and shortens hospital stays in severely ill COPD patients. Long-acting inhaled bronchodilators and inhaled corticosteroids to improve symptoms and reduce the risk of exacerbations in patients with stable COPD are reviewed elsewhere with promising results.

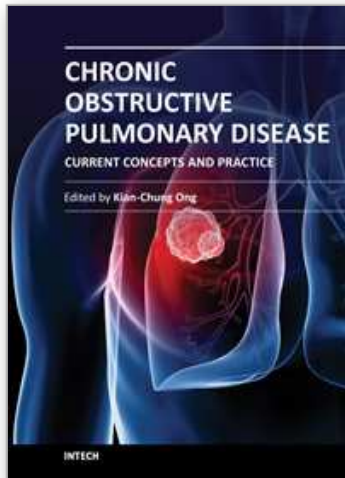
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A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

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