REVIEW

COPD exacerbations: management and hospital discharge

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Received 18 May 2018; accepted 17 June 2018

KEYWORDS
COPD; Exacerbation; Hospitalization; Management; Discharge

Abstract Chronic Obstructive Pulmonary Disease (COPD) is a serious pulmonary condition. Many patients experience exacerbations and some require Emergency Room visits and hospitalization. In Portugal, hospitalizations due to COPD between 2009 and 2016 decreased by 8%, but they still represented 8049 hospitalized patients in 2016. Appropriate management of COPD exacerbations presents a clinical challenge and, in order to guide therapy, it is important to identify the underlying cause; however, this is not possible in about a third of severe COPD exacerbations. There are several diagnostic tools that can be used to assess an exacerbation and its severity, which will in turn guide treatment, and prognostic scores should be used to predict the risk of future exacerbations. After an exacerbation is appropriately managed, a suitable discharge plan should be prepared. This should generally include reclassification of the patient according to GOLD criteria, optimization of pharmacological therapy, management of comorbidities, patient (or caregiver) education on the correct use of medications, referral to a Pulmonology Outpatient Clinic, if they are not already attending one, and a smoking cessation and respiratory rehabilitation program. In this paper, we will focus on the pharmacological strategies for the management of COPD exacerbations, risk stratification and a hospital discharge plan proposal.

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https://doi.org/10.1016/j.pulmoe.2018.06.006
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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a serious pulmonary condition, which is slowly progressive with systemic repercussions; it mainly affects people over 40 years old. However, COPD is preventable and treatable. Many patients experience COPD exacerbations and some of these require Emergency Room (ER) visits and hospitalizations. In Portugal, and although hospitalizations due to COPD between 2009 and 2016 have decreased by 8%, they still represented 8049 hospitalized patients in 2016. Hospitalizations of patients aged 80 years or more increased from 28.4% in 2005 to 38.0% in 2014, reflecting an aging population, with potentially more comorbidities.

Appropriate management of COPD exacerbations represents an important clinical challenge. In 70% to 80% of COPD exacerbations, the precipitant factor is a respiratory tract infection, but in about a third of severe exacerbations of COPD a cause cannot be identified, which hampers proper guidance of the therapeutic strategy. There are several diagnostic tools to assess an exacerbation and its severity, which will help in decisions like whether patient can be managed at home or in a primary care setting or if he/she should be referred to an ER and eventually hospitalized. The severity of an exacerbation will inform its treatment, and prognostic scores should be used to predict the risk of a future exacerbation. Three prognostic scores have been proposed based on biological and clinical characteristics of exacerbations: the BAP-65 score, the DeCOPD score and the score proposed by Roche et al.

After an exacerbation is appropriately managed, a suitable discharge plan should be prepared. This will depend on the severity of the exacerbation, but should generally include reclassification of the patient according to the GOLD criteria, optimization of pharmacological therapy, management of comorbidities, patient (or home caregiver) education on the correct use of medications, referral to a Pulmonology Consultation if they are not already attending one, and a smoking cessation and pulmonary rehabilitation program.

Exacerbations

Definition, causes and etiology

Definition

Currently, there is no exact or consistent definition of a COPD exacerbation. The definition of exacerbation in the 2016 GOLD update, "an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication", was simplified in the GOLD 2017 document to "an acute worsening of respiratory symptoms that results in additional therapy".

Causes and etiology

Several factors that can lead to a worsening of symptoms have been identified, and in 70% to 80% of COPD exacerbation cases, the precipitant factor is a respiratory tract infection, either viral or bacterial, but in about a third of severe exacerbations of COPD a cause cannot be identified.

It is important to identify the underlying cause of an exacerbation as this will guide the therapeutic strategy.

Classification

As with the lack of definition of an exacerbation, there is no consensual classification system to assess the exacerbation severity, although some have been proposed. Some of these scores will be discussed further.

In mild exacerbations there is a worsening of symptoms which can be managed at home, with an increase in dosage of regular medications. Moderate exacerbations do not respond to an increased dosage of bronchodilators and therefore require treatment with systemic corticosteroids and/or antibiotics. Severe exacerbations require hospitalization or evaluation in the ER and have a severe impact on physical activity. Very severe exacerbations require admission to an Intensive Care Unit (ICU) and have a very severe impact on physical activity. Infectious exacerbations are characterized by increases in volume and purulence of the sputum associated with aggravated dyspnea and should be treated with antibiotics.

Diagnostic tools

The assessment of an exacerbation and its severity is based on the patient’s medical history, e.g., airflow limitation, duration of worsening of symptoms and number of previous episodes (total/hospitalizations). Symptoms such as breathlessness, cough or sputum, oxygen saturation levels, new limitation of daily activities, clinical signs of severity such as use of accessory respiratory muscles, paradoxical chest wall movements, worsening or new onset central cyanosis, development of peripheral edema, hemodynamic instability, deteriorated mental status and comorbidities should all be assessed. Pulse oximetry should be performed on all patients. If a patient is referred to a hospital, arterial blood gases should be measured and a chest radiography should be done to exclude comorbidities and/or other pulmonary diseases. In these cases, it is also recommended that patients should have an ECG, whole blood count and basic biochemical tests, including electrolyte concentrations, urea, glycemia and metabolic panel. Theophylline levels should be measured in patients on theophylline therapy at admission and blood cultures should be taken if the patient has fever. Culture of sputum samples is not recommended in routine practice, only if sputum is purulent, and the GOLD 2018 document recommends sputum culture and an antibiotic sensitivity test only if an infectious exacerbation does not respond to the empirical antibiotic treatment. Some authors mention eosinophilia blood count as an advisable procedure to guide COPD exacerbations therapy since it has been suggested that eosinophilic exacerbations may be more responsive to systemic steroids.

If the exacerbation is severe and the patient hospitalized, brain natriuretic peptide and cardiac enzyme
measurements levels should be considered, especially if
the patient is not responding to conventional treatment.6
Also, pharyngeal swab or sputum should be tested for
viruses and bacteria4,14,20,23 and serum C-reactive protein
measured.4,10,24 Procalcitonin may guide antibiotic ther-
apy since it has been suggested as a more specific marker
for bacterial infections and that may be of value in
deciding on antibiotics prescription.1 The Charlson comor-
bidity index,5,10,21,23 the modified Medical Research Council
(mMRC) dyspnea scale5,20,21,23 physical activity4 and general
health9 should be assessed. The authors do not advise
the use of COPD Assessment Test (CAT) score25 routinely in
Portugal as it is not validated for the Portuguese population.
If the patient is admitted to the ICU, besides the tests recom-
manded in severe exacerbations, the Glasgow Coma Scale4
should be used, respiratory tract infections investigated25
and a hemoculture performed.24 According to the GOLD 2018
document only patients requiring non-invasive ventilation
(NIV) or invasive ventilation (IV) should be hospitalized.1

Pharmacologic strategies

LABA + LAMA

Short-acting inhaled β2 agonists (SABAs) and short-acting
muscarinic antagonists (SAMAs) remain the mainstay in the
treatment of symptoms and airflow obstruction during COPD
exacerbations.1,4,6 Although at the time of publication of the
GOLD 2018 document there were no clinical studies eval-
uating the usefulness of long-acting β2 agonists (LABA) or
long-acting muscarinic antagonists (LAMA) in exacerbations,
the recommendation is to continue this medication during
the exacerbation or to start it as soon as possible before hos-
pital discharge.1 The LABA + LAMA combination does have
a documented benefit in the reduction of exacerbations
when prescribed to patients in the stable phase of COPD,26
particularly the indacaterol/glycopyrronium combination as
demonstrated in the SPARK27 and FLAME28 studies. More-
over, the recent FLAME study,28 the first prospective study
evaluating blood eosinophilia as a biomarker of therapeutic
response, showed that indacaterol/glycopyrronium demon-
strated a significant improvement in lung function compared
with salmeterol/fluticasone for all the cutoffs analyzed.29
A recent post hoc analysis of the WISDOM study identified a
subset of patients – patients with ≥2 exacerbations and
≥400 cells/μL – that seem to be at increased risk of exacer-
bation when discontinued from ICS.30 In fact, and according to
the most recent version of the GOLD document,1 symp-
tomatic patients in the stable phase of COPD and a history
of ≥2 moderate exacerbations, or 1 with hospital admis-
sion, in the past year, may benefit from an ICS on top of
LABA/LAMA. However, it is yet to be established whether
blood eosinophils can be used as a biomarker to predict ICS
efficacy in terms of exacerbation prevention, as suggested by
the WISDOM post hoc analysis.1

Antibiotics, corticosteroids and xanthines

When treating an exacerbation adding oral or intra-
venous corticosteroids and/or antibiotics is recom-
ended, depending on symptom severity and the presence
of infection.1,4,6-8,31 Antibiotics should only be used for the
treatment of infectious5,6,8,31 or severe exacerbations.31 The
GOLD 2018 and NHS 2014 documents recommend antibi-
tics for patients with COPD exacerbations who have three
cardinal symptoms – increase in dyspnea, sputum vol-
ume, and sputum purulence (Evidence B)1; have two of the
cardinal symptoms, if increased purulence of sputum
is one of the two symptoms (Evidence C)1; or
require mechanical ventilation (invasive or non-invasive)
(Evidence B).1

Antibiotics have been shown to reduce the risk of short-
term mortality, treatment failure and sputum purulence,
and a study in COPD patients with exacerbations requiring
mechanical ventilation (invasive or non-invasive) indicated
that not treating with antibiotics was associated with
increased mortality and a greater incidence of secondary
nosocomial pneumonia.1 A Cochrane review concluded that
antibiotics for very severe COPD exacerbations showed wide
and consistent beneficial effects across outcomes of patients
admitted to an ICU,31 but this conclusion was based on data
from a single study.32

The NHS protocol for management of COPD exacer-
bations in primary care states that bronchodilators and
corticosteroids are the mainstay of exacerbation treat-
ment.7 However, a systematic review of 19 COPD
guidelines reported that the criteria for treating patients
with antibiotics were largely based on an increase in
respiratory symptoms, while systemic corticosteroids were
often universally recommended for all patients with acute
exacerbations.13 The authors also concluded that current
COPD guidelines are of little help in identifying patients
with acute exacerbations who are likely to benefit from
treatment with systemic corticosteroids and antibiotics in
primary care, which might contribute to overuse or inap-
propriate use of either treatment.

Some biomarkers have been suggested as useful for opti-
mizing antibiotic treatment. The GOLD 2018 document does
not recommend that CRP be used routinely but state that
several studies have suggested that procalcitonin-guided
antibiotic treatment reduces antibiotic exposure and side
effects with the same clinical efficacy. This observation
is corroborated by a Cochrane review demonstrating that
procalcitonin can guide antibiotic therapy.12 In contrast,
other authors reported that CRP might be a more valu-
able marker,34 and a real-life primary care study concluded
that performing CRP rapid tests led general practition-
ers to prescribe fewer antibiotics than those who did not.35

For all patients, the choice of antibiotic should be guided
by the local bacterial resistance pattern,7,8 the microbiology
story of the patient and his/her risk factors.

Usually initial empirical treatment encompasses
aminopenicillin with clavulanic acid, a macrolide, or a
tetracycline.1,8 However, the long-term use of macrolides
may be associated with important side-effects and the
risk of developing bacterial resistance.34 Sputum should
be sent for culture (in the case of patients with frequent
exacerbations, severe airflow limitation, and/or exacerba-
tions requiring mechanical ventilation), as gram-negative
bacteria (e.g., Pseudomonas species) or resistant pathogens
that are not sensitive to the above-mentioned antibiotics may be present.8

Although the most effective duration of treatment is still to be defined,9,10 the recommended length of antibiotic therapy is usually 5–7 days (Evidence D)11 but treatment duration will depend on the antibiotic used.

The management of exacerbations in primary care should include maximization of bronchodilator therapy and systemic corticosteroids if not contraindicated (30 mg prednisolone) for 7 days.1,7,8 Therapy with oral prednisolone is equally as effective as intravenous administration.1 The GOLD 2018 document recommends a dose of 40 mg prednisone per day for 5 days whilst NICE 2016 recommends a dose of 30 mg for 7–14 days, and further recommends that a course of corticosteroid treatment should not be longer than 14 days as there is no advantage in prolonged therapy.8

The use of systemic corticosteroids in COPD exacerbations have been shown to shorten recovery time, improve lung function, improve oxygenation, decrease the risk of early relapse and treatment failure, and decrease the length of hospitalization.1

A meta-analysis confirmed that the rate of treatment success increased with systemic corticosteroids in comparison to usual care of COPD exacerbations. Corticosteroids seem to be beneficial to the whole population in terms of treatment success rate.7,11

Some studies suggest that corticosteroids may be less efficacious in treating acute COPD exacerbations in patients with lower levels of blood eosinophils.14,28

As for methylxanthines in the management of COPD exacerbations, current evidence does not support their use, given that the possible beneficial effects in lung function and clinical endpoints are modest and inconsistent, whilst adverse events are significant.1,4,6,31 Intravenous methylxanthines (theophylline or aminophylline) may be considered second-line therapy and used as an add-on when there is insufficient response. When using theophylline, it is necessary to monitor blood levels, side effects and potential drug interactions.9,31

Therapeutics – risk stratification

Exacerbations of COPD may be classified as mild, moderate, severe12 and very severe. Very severe exacerbations require admission to the ICU, with invasive ventilation, and are outside the scope of this paper.

As previously mentioned, exacerbations of COPD are very heterogeneous making it particularly relevant to determine their etiology, pathology, severity and risk as all of these factors will have implications in the prognosis, pharmacological treatment and place of treatment.

In terms of pharmacological treatment and place of treatment, if exacerbations are mild and non-infectious,1,4,7,8,31 they may be treated at home with an increase in the dosage of maintenance bronchodilators.8,17 If the exacerbation is infectious,4,8,31 an antibiotic should be given.5,9

Moderate exacerbations should be treated in the ER and the patient then discharged as these exacerbations do not require hospitalization, unless the hospitalization occurs for socioeconomic reasons. The dosage of maintenance bronchodilators should be increased4,17 and the patient been given an oral corticosteroid6,17,18 for 5 days.1,38,39 If the exacerbation is infectious4,8,31 an antibiotic should be given.1,7

In the case of a patient who has had a severe exacerbation, requiring hospitalization, the patient should be reclassified as a frequent exacerbator. Usually, hospitalization due to a severe exacerbation requires modification of inhaled maintenance treatment including O2 if the patient is hypoxic and non-invasive ventilation if patient has hypercapnia, greater than 52 cm H2O and/or acidemia,1,4,6,9 oral or intravenous corticosteroids (for 5 days)1,38,39 and antibiotic if infectious,1,7 xanthines if there is an inadequate response to treatment4,8,16,31 and prevention of pulmonary thrombembolism.

Discharge – action plan

Patients with mild exacerbations should be re-assessed after three months, with spirometry and a re-evaluation of the GOLD degree and, when appropriate, reclassification.

On discharge from a moderate exacerbation, bronchodilation should be optimized, anti-pneumococcal vaccination should be prescribed, and a smoking cessation and respiratory rehabilitation plan should be prepared.

On discharge after a severe exacerbation, optimal maintenance therapy1,4,8 with LABA, LAMA and ICS should be prescribed. Patients who have had an episode of respiratory failure should have satisfactory oximetry or arterial blood gas results before discharge. Patients (or home caregivers) should be given appropriate information to enable them to fully understand the correct use of medications, including inhalers and oxygen, and, if necessary, arrangements for follow-up and home care (such as visiting nurse, oxygen delivery, referral for other support) should be made. The patient, patient’s caregiver and the physician should be confident that he or she can successfully manage the new treatment plan. When there is any doubt about the patient’s capacity to manage his/her therapy, a formal activities of daily living assessment may be helpful.1 The GOLD 2018 document provides a list of discharge criteria.1 For patients who are hypoxic during an exacerbation, arterial blood gases and/or pulse oximetry should be evaluated prior to hospital discharge and in the following 3 months. If the patient remains hypoxic, long-term supplemental oxygen therapy may be required.1 Also, patients should be given clear instructions about when and how to stop their corticosteroid treatment.1,8 Concerning the need for individualized care, a Canadian study in which the patients were offered a post discharge phone call, a home visit and continued care concluded that although there was no reduction in 30- and 90-day readmission rates, a decrease in 90-day total mortality was seen. These data suggest that the individualized care undertaken in this study can impact COPD morbidity and mortality after an acute exacerbation.40 All patients who have had a severe exacerbation should be reassessed 4–6 weeks after discharge from hospital,1 given an anti-pneumococcal vaccination prescription, and a smoking cessation and respiratory rehabilitation plan should be prepared – Fig. 1.

The authors propose that the patient should be prescribed an anti-pneumococcal vaccine 10 to 20 days after discharge from the ER or Hospital.
**Fig. 1** Proposed therapy, discharge and follow-up of mild, moderate, severe and very severe COPD exacerbations.

During the follow-up consultation (three months for moderate exacerbations and 4–6 weeks for severe exacerbations), spirometry and arterial blood gases should be measured. Symptoms, correct use of inhaled therapy and adequate management of comorbidities should be reassessed. Pharmacological treatment should be optimized. The smoking cessation and respiratory rehabilitation plan should be evaluated. A new follow-up consultation should be scheduled within the next 30–60 days.

**Conclusions**

Identification of the underlying cause of COPD exacerbations and assessment of their severity is fundamental to guiding treatment. After an exacerbation is appropriately managed, a suitable discharge plan that will depend on its severity should be prepared. A proper discharge plan will decrease symptom burden, contribute to a faster recovery, increase the patient’s quality of life, and prevent or delay future exacerbations. Referral to a Pulmonology Consultation if the patient is not already attending one is of the utmost importance.

**Conflicts of interest**

AR declares having received speaking fees from AstraZeneca, Boehringer Ingelheim, Diater, Immunotec, Menarini, Mundipharma, Mylan, Tecnifar and TEVA, and participating in advisory boards of Bial, GSK and Novartis. MD declares having received fees for talks from AstraZeneca, Boehringer Ingelheim, Bial, GSK, Menarini and Novartis and for participation in advisory boards of Bial, GSK and Novartis. CRC declares speaking fees from Boehringer Ingelheim, Roche, Novartis, AstraZeneca, Pfizer vaccines, Teva, Menarini, Medinfa and Tecnifar, and participating in advisory boards of Boehringer Ingelheim, Roche, Novartis, GSK, AstraZeneca and Pfizer vaccines.

**Acknowledgements**

Funding for this paper was provided by Novartis Portugal. Funding was used to access all necessary scientific bibliography and cover meeting expenses. Novartis Portugal had no role in the collection, analysis and interpretation of data, in the writing of the paper and in the decision to submit the paper for publication.

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