

Hospital Treatment of Chronic Obstructive Pulmonary Disease Exacerbations: an Evidence-Based Review

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Introduction

This article presents an integrated overview of treatment of patients admitted to hospital for chronic obstructive pulmonary disease (COPD) exacerbations,¹⁻⁵ based on the best scientific evidence available (Table 1).

Hospital treatment of COPD exacerbations has several aims,^{2,5} namely: *a*) to stabilize the patient's respiration and hemodynamics; *b*) to improve or, if possible, normalize the clinical state of the patient; *c*) to diagnose the cause or causes of the exacerbation; *d*) to assess the severity of COPD and identify other concurrent diseases; *e*) to educate the patient on how to take medication and use therapeutic equipment (nebulizers, inhalers, oxygen therapy devices, etc) correctly, and to promote a healthy lifestyle before discharge; and, finally, *f*) to evaluate the need for additional home treatment such as respiratory rehabilitation and/or home oxygen therapy. If these aims are to be achieved, the patient must be managed at different levels of care, that is, in the emergency room, the hospital ward, and the intensive care unit (ICU).

This review will cover the following: *a*) initial clinical management of patients with COPD exacerbations in the emergency room; *b*) the criteria for admission to hospital; *c*) treatment for COPD exacerbations in a conventional hospital ward; *d*) management of COPD exacerbations in the ICU; and *e*) the criteria for discharge from each of these levels of care. We will then identify aspects that we consider unresolved and in need of further investigation.

Management in the Emergency Room

Initial Assessment

Table 2 shows the main components of the initial assessment in the emergency room of a patient with a

suspected COPD exacerbation. The information provided by the clinical history, physical examination, chest x-ray, and arterial blood gas analysis can provide the basis for the diagnosis of a COPD exacerbation, determine its severity, and indicate whether hospitalization, oxygen therapy, and/or ventilatory support are needed (level D evidence).^{6,7} The severity of airflow obstruction determined when the patient is clinically stable (before the exacerbation) is not useful for assessing the severity of the current exacerbation, the need for admission to hospital, or when the patient should be discharged.⁶⁻⁸ Finally, other concurrent processes that may contribute to a deterioration in the clinical state of the patient should be discarded (or treated if necessary). The most important such processes, because of their high prevalence and/or their seriousness, are heart failure, pulmonary embolism, pneumonia, and/or use of sedatives. None of these should, however, be considered as the cause of the COPD exacerbation.⁹

Therapeutic Measures

Oxygen therapy. Arterial blood gas analysis is recommended, clinical state of the patient permitting, before starting oxygen therapy. Oxygen therapy will then be started with the inspiratory oxygen fraction needed to raise PaO₂ above 60 mm Hg (8.0 kPa) or to reach arterial oxygen saturation (SaO₂) greater than 90% without provoking acidosis due to an increase in PaCO₂ (level A evidence).^{2,5,10}

Bronchodilators. Short-acting β_2 agonists in the form of aerosols are the bronchodilators of choice in the initial treatment of a COPD exacerbation (level A evidence)^{2,3,10} (Table 3). If this treatment does not lead to a rapid response at high doses, it is recommended to add anticholinergic agents (level B evidence).^{2,5,8,10} Subcutaneous or intravenous administration of β_2 agonists should only be considered if the patient cannot take the drug by inhalation or if the patient's life is at risk.

Glucocorticoids. Whether administered orally or intravenously, glucocorticoids are effective in the treatment of COPD exacerbations (level A evidence).^{6,7,10} Empirical recommendations are for

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TABLE 1
Level of Evidence for Recommendations*

Levels of Evidence	Source of Evidence	Definition
A	RCT, much data available	Evidence is derived from a large number of RCTs, which include a substantial number of patients and whose findings are consistent in the population for whom the recommendation is being made
B	RCT, limited data	Evidence is derived from a limited number of RCTs, which are small, include a population that differs from the population for whom the recommendation is made, or have findings that are inconsistent
C	Nonrandomized trials Observational studies	Evidence from observational studies or uncontrolled trials
D	Opinion of consensus groups	This category includes recommendations based on the opinions of expert groups about topics for which there is insufficient information in the scientific literature to justify inclusion in any of the above categories

*RCT indicates randomized controlled trial.

initial doses of 0.5 mg/kg of prednisolone every 6 to 8 hours (level D evidence).^{3,4,10}

Antibiotics. The use of antibiotics in the treatment of COPD exacerbations is controversial. When invasive and sophisticated diagnostic techniques (such as

protected specimen brushing of the tracheobronchial tree with endoscopy) are used, potentially pathogenic bacteria are only isolated in about 65% of exacerbations. Only in these cases (and possibly not in the remaining 35%) would the use of antibiotics be indicated for exacerbations of COPD. However, invasive diagnostic techniques are rarely used in everyday clinical practice. Thus, in accordance with the guidelines of Anthonisen et al,¹¹ treatment of COPD exacerbations with antibiotics is recommended provided 2 of the following criteria are met: *a)* increase in the usual dyspnea of the patient; *b)* fever; *c)* increased volume of sputum; and *d)* increased purulence of sputum. These criteria have subsequently been extended to include all COPD exacerbations that are accompanied by acute respiratory insufficiency (or a relapse of chronic respiratory insufficiency) (level B evidence).^{3-5,7,10}

Other measures. For treatment in the emergency room, prescription of diuretics and anticoagulants, administration of fluids and electrolytes, and therapy for any other associated disease that requires treatment should be considered.

Criteria for Admission to Hospital

As yet, no useful biological markers have been found that allow specific diagnosis of COPD exacerbations or that provide an objective criterion for admission to hospital. Therefore, the need for admission to hospital is based on an assessment of the clinical state of the patient, response to initial treatment, and the presence and severity of concurrent diseases. Table 4 shows the

TABLE 2
Evaluation of Patients With Chronic Obstructive
Pulmonary Disease Exacerbations

Clinical history
Respiratory state before the exacerbation
History of smoking
Previous exacerbations and admission to hospital
Volume and color of sputum
Degree of dyspnea at rest
Previous lung function tests and arterial blood gas analysis
Duration and progression of symptoms
Exercise capacity
Treatment given and degree of compliance
Social conditions of the patient
Concurrent disease
Physical examination
Cor pulmonale
Bronchospasms
Pneumonia
Hemodynamic instability
Clouding of consciousness
Paradoxical respiration
Use of accessory muscles
Uncontrolled associated disease
Diagnostic techniques
Arterial blood gas analysis
Electrocardiogram
Chest x-ray
Basic hematology and serum biochemistry
Sputum cultures

TABLE 3
Main Bronchodilators Used in Exacerbations of Chronic Obstructive Pulmonary Disease

Drug	Inhaler (µg)	Nebulizer (mg)	Intravenous Route (mg/min)	Star (min)	Peak (min)	Duration (h)
Fenoterol	100-200	0.5-2.5	—	—	—	4-6
Salbutamol	100-200	2.5-5	4	3-5	60-90	4-6
Terbutaline	250-500	5-10	0.005	3-5	60-90	3-6
Formoterol	12-24	—	—	5	60-90	11-12
Salmeterol	50-100	—	—	45-60	120-240	11-12
Ipratropium	40-80	0.25-0.5	—	05-15	060-120	6-8

TABLE 4
Criteria for Admission to Hospital for Chronic Obstructive
Pulmonary Disease (COPD) Exacerbations

Poor response to outpatient treatment
Severe COPD with home oxygen therapy
Severe dyspnea that hinders eating, speaking, or mobility at home.
Social difficulties that prevent home treatment
Altered mental state
Cyanosis
Sudden onset of symptoms
Prolonged and deteriorating symptoms
Serious concurrent disease or poor general state of health
Appearance or worsening of cor pulmonale
Acute x-ray abnormalities
pH<7.5
Body temperature >38.5°C
Respiratory rate >25 breaths/min
Heart rate >110 beats/min
Acute respiratory insufficiency
Uncertain diagnosis
Need for diagnostic or surgical procedures requiring analgesics or sedatives that may cause deterioration in lung function

most common criteria for admitting patients with COPD exacerbations to hospital.^{2-5,10} None of these criteria can be taken as an absolute indication, but the case for hospital treatment is strengthened if several of them are met (level D evidence).

Treatment of Patients in the Hospital Ward

In this section, we distinguish between pharmacological treatment (bronchodilators, glucocorticoids, antibiotics, etc) and nonpharmacological therapeutic measures (oxygen therapy, noninvasive ventilation, etc).

Pharmacological Treatment

Bronchodilators. The main bronchodilator drugs available for treatment of COPD exacerbations are short-acting β_2 agonists and anticholinergic agents (level A evidence).^{7,12} Although the potency of the two drugs is similar,^{6,7,13} it is recommended to start treatment with short-acting β_2 agonists because the onset of treatment effect is faster (level A evidence).^{2,10} If the clinical response to high doses of short-acting β_2 agonists is not satisfactory, the recommendation is to add anticholinergic agents,^{2-5,10} but there is no firm evidence that a combination of the two drugs is better than an increase in the dose of one of them.^{10,13}

Short-acting β_2 agonists and anticholinergic agents (Table 3) are usually administered every 4 to 6 hours, although they can be given more frequently if necessary. Inhalation is the most effective route of administration and the one with least side effects (level A evidence).^{6,7} Patients in hospital usually receive bronchodilators from a nebulizer, but inhalation devices are just as effective if the patient is in a sufficiently good state of health for proper coordination of inhalation (level A evidence).^{2,7}

If severe COPD exacerbations are not satisfactorily controlled with short-acting β_2 agonists and anticholinergic agents, methylxanthines as a continuous infusion (aminophylline bolus, 2.5-5 mg/kg over 30 minutes, followed by a maintenance perfusion of 0.5 mg/kg/h) can be added (level B evidence).^{2,3,10,14-16} The serum concentrations of this drug need to be closely monitored during use.^{2-4,10,14} There is still not enough evidence to recommend use of long-acting β_2 agonists or tiotropium for COPD exacerbations.

Glucocorticoids. Systemic glucocorticoids are effective in treatment of COPD exacerbations (level A evidence).^{6,7,10,17} They accelerate the recovery of forced expiratory volume in 1 second, shorten the stay in hospital, and reduce the number of readmissions due to exacerbations.^{7,18-21} However, conclusive studies on optimal dose and duration of glucocorticoid treatment have not been carried out in patients with exacerbations. A dose of 0.5 mg/kg of prednisolone every 6 to 8 hours, either orally or intravenously, is normally recommended during the first 72 hours, with subsequent progressive dose reduction^{3,4,10,22} until complete withdrawal after 2 weeks (level D evidence).^{3,7,10,20} For patients with COPD exacerbations and no acidosis, nebulized glucocorticoids may be as effective as systemic ones, but with a lower risk of side effects.²³ The evidence, however, is as yet insufficient to justify their use in COPD exacerbations.

Antibiotics. As discussed earlier, the use of antibiotics in the treatment of COPD exacerbations is controversial. Viral and bacterial infections of the tracheobronchial tree are an important cause of exacerbations, but probably not the only one.²⁴ With the use of invasive techniques, potentially pathogenic bacteria have been isolated in 65% of the patients with COPD exacerbations,²⁵ but around 35% of these patients are chronically colonized by bacteria when clinically stable,^{8,25} suggesting that new bacteria are identified only in 30% of the exacerbations. Viruses may also be a notable cause of exacerbations and, in fact, techniques using polymerase chain reaction to detect viral genomes have identified the presence of a virus in around 30% of COPD exacerbations.²⁶ The coexistence of viruses and bacteria is common. In general, bacterial infection is probably important in some (but not all) COPD exacerbations and, in theory, antibiotics should be indicated only in such cases. Of course, the problem is to identify exacerbations due to bacterial infection and, therefore, those susceptible to antibiotic treatment. Extensive research is needed on this question. For the moment, antibiotic treatment is recommended for COPD exacerbations that meet at least 2 of the following criteria: *a*) increase in normal dyspnea in the patient; *b*) fever; *c*) increased volume of sputum; and *d*) increased purulence of sputum (evidence B).^{3,4,7,10,11} Antibiotics are also indicated when the natural course of the exacerbation coincides with acute respiratory insufficiency or relapse of chronic respiratory

insufficiency (level B evidence).^{3,6,7,27} The bacteria most often isolated in a COPD exacerbation are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.²⁵ In patients with severe COPD (forced expiratory volume in 1 second less than 35% of the reference value), infections with gram-negative bacteria, particularly enterobacteria and *Pseudomona* species, are common.²⁸ Cephalosporins, broad-spectrum penicillins, or antipseudomonal quinolones are recommended in accordance with these epidemiological and spirometric data.^{2,8,12,28,29} In any case, the choice of antibiotic should be based on whether the aforementioned bacteria have developed resistance in the clinical setting and on the antibiotics given to the patient before admission.

Other Pharmacological Measures

– *Low molecular weight heparin.* Subcutaneous administration of heparin is recommended in bedridden, polycythemic, or dehydrated patients, or those with a history of previous thromboembolic disease.

– *Diuretics.* When clinical signs of right heart failure, such as malleolar edema or jugular venous distension, are present, then diuretics are indicated.

– *Liquid and electrolyte balance.* Magnesium, calcium, phosphate, and potassium deficiencies are relatively common in patients with COPD and may worsen during an exacerbation.^{2,30,31} Monitoring the electrolyte balance during the stay in hospital (and correcting any imbalances if necessary) is important in the clinical management of COPD exacerbations.^{2,10}

– *Nutritional supplements.* Often, patients with COPD are malnourished and have lost weight.³² They may become further malnourished during exacerbations that require admission to hospital.³² Nevertheless, enteral nutrition is only recommended in patients who are too dyspneic for oral intake.¹⁰

– *Respiratory stimulants.* There is no evidence that drugs such as doxapram, almitrine, protriptyline, medroxyprogesterone, or acetazolamide are useful for treatment of COPD exacerbations³³⁻³⁵ and, in general, physicians are advised against prescribing them.²⁻⁵

Nonpharmacological Therapeutic Measures

Oxygen therapy. Respiratory insufficiency is almost always present in patients admitted to hospital for COPD exacerbations; therefore, oxygen therapy is one of the corner stones of hospital treatment of such patients. Oxygen therapy aims to raise PaO₂ above 60 mm Hg (8.0 kPa) or SaO₂ above 90%, without causing CO₂ retention or acidosis (level A evidence).^{2-5,10} These goals can usually be achieved with an inspiratory oxygen fraction of 24% to 28%.^{3,4,12} Oxygen therapy can be administered by nasal prongs, which are more

comfortable, or by Venturi masks, which allow better control of inspiratory oxygen fraction pressure.^{3,10,36} For patients who require inspiratory oxygen fraction above 40%, nonbreathing masks with one-way valves are recommended.²

Given that the inspiratory oxygen fraction is chosen empirically and that the effects on PaO₂, CO₂ retention, and pH cannot be readily predicted, arterial blood gases should be monitored until 30 minutes after the start of oxygen therapy. The effects of the inspiratory oxygen fraction administered can then be properly evaluated and titrated (upward or downward) as necessary. Likewise, arterial blood gases should be reanalyzed whenever the inspiratory oxygen fraction is changed (or when the clinical state of the patient changes significantly).³⁵ Monitoring of SaO₂ by pulse oximetry is only acceptable once arterial blood gas analysis has shown that pH and PaCO₂ are normal.³

Chest physiotherapy. We have no firm evidence that patients admitted to hospital due to a COPD exacerbation benefit from physiotherapy, and it may even be harmful.^{3,6,7,37} Techniques such as huff coughing, postural drainage with or without vibration, and chest percussion are only applicable in certain patients with sputum production in excess of 25 mL/day (level D evidence).^{2,10} Mucolytics, expectorants, and overhydration in nondehydrated patients have not been shown to be useful in patients with COPD exacerbations.^{6,7}

Noninvasive ventilation. The use of noninvasive ventilation (NIV) outside the ICU is a controversial aspect of the treatment of COPD exacerbations.³⁸ Its advantages and drawbacks, as well as criteria for prescribing or ruling out use of NIV, are discussed in the following section.

Treatment in ICU

General Measures and Pharmacological Treatment

Measures for general care and the different pharmacological options presented earlier for treatment of COPD exacerbations in the hospital ward (bronchodilators, glucocorticoids, antibiotics, oxygen therapy, etc) are all applicable to patients who require intensive care (Table 5), and so we will not discuss them here again, but rather focus on the therapeutic options more specific to the ICU.

TABLE 5
Criteria for Admission to the Intensive Care Unit

Intense dyspnea that does not respond to initial treatment in the emergency room
Confusion, lethargy, or fatigue of the respiratory muscles
Persistent or progressive hypoxemia despite receiving optimal treatment and supplementary oxygen
Intense respiratory acidosis (pH<7.30) or progressive respiratory acidosis despite receiving optimal treatment
Need for mechanical ventilation

Mechanical Ventilation

Patients with COPD exacerbations may require ventilatory support, which can either be invasive (that is, through an endotracheal tube connected to a ventilator) or noninvasive (with a nasal or face mask so avoiding the need for an endotracheal tube). Both types of ventilation have the same therapeutic goals, that is, to reduce the morbidity and mortality associated with the exacerbation and to improve the symptoms of the patient.

Noninvasive ventilation. NIV is an effective first-line treatment (added to conventional treatment) for patients with COPD exacerbations and respiratory failure³⁹⁻⁴² (level A evidence). In such patients, NIV can *a*) lower PaCO₂ and increase arterial blood pH; *b*) improve symptoms (such as dyspnea) derived from fatigued respiratory muscles; *c*) reduce the mean length of stay in hospital (level A evidence); and *d*) reduce the need for intubation, the number of complications, and hospital mortality.^{40,42-45} Table 6 shows the screening criteria for deciding whether NIV is indicated.

A recent consensus meeting concluded that NIV should be used only in the ICU and other units that can guarantee close monitoring (level D evidence).³⁹ Contradictory evidence is available on use of NIV in hospital wards.^{46,47} Currently, it is accepted that NIV

outside the ICU is indicated in patients with COPD exacerbations who have not responded to initial treatment and who either have PaCO₂ leading to pH of 7.30 or greater (level D evidence)³⁹ or who cannot be admitted to the ICU for clinical reasons (age and concurrent disease) or logistic ones (lack of beds). NIV can be started in the emergency room only if personnel trained in this technique are on hand with suitable equipment for monitoring the patient.³⁹

The correct use of NIV requires close monitoring of SaO₂, arterial blood gases, and vital signs; correct adaptation of the patient to NIV to avoid leaks and ensure that he or she can expectorate; and the necessary personnel with sufficient experience to deal with possible complications, backed up by sufficient technical resources.

In the treatment of patients with COPD exacerbations, 4 different types of NIV can be used, namely *a*) volume-cycled assist-control ventilation⁴³; *b*) pressure-support ventilation⁴⁴; *c*) pressure-cycled ventilation⁴⁵; and *d*) bilevel positive airway pressure ventilation, with one inspiratory setting and one expiratory setting.^{46,48} The choice of type of ventilation will depend on the experience of the staff who attend the patient.

NIV should be adjusted individually in each patient in order to improve symptoms, improve gas exchange, and prevent undesired effects.³⁹ NIV requires a mask as an interface with the ventilator. Two types exist, face masks, which cover the nose and mouth, and the nasal masks, which only cover the nose. Existing evidence cannot indicate which type of mask is better (or worse) than the other, but the face masks allow higher pressures to be applied with fewer leaks, and less cooperation is required from the patient. In contrast, such masks are less comfortable than the nasal masks and hinder other body functions such as eating and speaking. The nasal mask, on the other hand, requires strict cooperation of the patient, who must keep his or her mouth closed to avoid leaks. The choice of mask for a given patient depends on availability, the experience of the medical team and, importantly, the degree of adaptation of each patient to a certain type of mask. Continuous NIV for 24 hours a day may be desirable, but in practice, it is administered 6 to 12 hours a day, depending on the tolerance of each patient.

TABLE 6
Criteria for Indication or Contraindication of Noninvasive Ventilation

Criterion for indication
pH<7.35 and PaCO ₂ >45 mm Hg
Criteria for contraindication (at least one)
Cardiac or respiratory arrest
Failure of nonrespiratory organs
Severe encephalopathy (Glasgow score <10)
Severe hemorrhage of upper digestive system
Hemodynamic instability or unstable arrhythmia
Facial surgery, trauma, or deformity
Obstruction of the upper airway
Inability to cooperate/protect the airway
High risk of aspiration, unable to expel secretions, presence of abundant secretions
Extreme obesity

TABLE 7
Indications for Invasive Mechanical Ventilation

Absolute indications	Relative indications
Cardiac or respiratory arrest	Severe dyspnea with use of accessory muscles
Failure of noninvasive ventilation or presence of exclusion criteria	Respiratory rate >35 breaths/min
Persistent hypoxemia (PaO ₂ <40 mm Hg) despite receiving optimal treatment	Vascular complications (hypotension, shock, heart failure)
Worsening of respiratory acidosis (pH<7.25) despite receiving optimal treatment	Other complications (severe pneumonia, pulmonary thromboembolism, etc)

Invasive Mechanical Ventilation

Despite the benefits of NIV with respect to invasive mechanical ventilation,⁴⁴ specific indications have been determined for use of invasive mechanical ventilation (Table 7). In patients with COPD exacerbations, the aims of mechanical ventilation are to correct the pulmonary gas exchange and respiratory acidosis⁴⁹; to administer life support while the patients are receiving treatment to correct the cause of the exacerbation; and to rest the respiratory muscles to give them a chance to recover from fatigue.⁵⁰ Complications associated with mechanical ventilation include barotrauma,⁵¹ ultrastructural lesions with changes in the permeability of lung tissue,⁵² and

ventilator-associated pneumonia. Mortality in patients with COPD exacerbations and respiratory failure who require invasive ventilation is no greater than in patients ventilated for other reasons.¹⁰ Certain aspects of mechanical ventilation of patients with exacerbations of COPD should be considered individually:

– *Tracheal intubation.* In acute clinical situations such as COPD exacerbations, tracheal intubation through the mouth is the technique of choice.⁵³ If the nasal route is used, the risk of sinusitis increases,⁵⁴ airway resistance increases,⁵⁵ and bronchial release of the aerosol medication decreases.⁵⁶ Fiberoptic bronchoscopy can be useful for endotracheal guidance in the presence of difficulties (such as in patients with abnormal facial anatomy).

– *Types of ventilation.* Two types of ventilation can be used in patients with exacerbations of COPD: volume or pressure-cycled assist-control ventilation, or pressure-support ventilation. As yet, no studies have compared these different types of mechanical ventilation in COPD exacerbations.

In patients with an exacerbation, invasive mechanical ventilation reduces the intrinsic positive end-expiratory pressure (iPEEP) and the degree of dynamic hyperinflation. For this to be achieved in assist-control ventilation, low tidal volumes (between 8 and 10 mL/kg) are combined with a large expiratory/inspiratory time ratio. This in turn requires low respiratory rates and high inspiratory flows.⁵⁷ Furthermore, the iPEEP level can be balanced by applying extrinsic positive end-expiratory pressure (ePEEP),⁵⁸ thus reducing both respiratory work and the degree of air trapping (and therefore, iPEEP).^{59,60} The applied ePEEP should be lower than the iPEEP so as not to accentuate dynamic hyperinflation.^{59,60} Another ventilatory strategy that can be used in patients with a COPD exacerbation is the so-called controlled hypoventilation with permissive hypercapnia, which is widely used in acute respiratory distress to limit complications derived from mechanical ventilation.⁶¹ Controlled hypoventilation with permissive hypercapnia in patients with COPD exacerbations and severe airway obstruction helps reduce dynamic hyperinflation and iPEEP (level D evidence).⁵³ In any case, regardless of the type of assist-control ventilation used, iPEEP and peak and plateau pressures should both be monitored—iPEEP indicates changes in respiratory mechanics and airway resistance, whereas peak and plateau pressures reflect the extent of insufflation and pulmonary distensibility.⁴⁹

Pressure-support ventilation is more comfortable than assist-control ventilation because the patient (and not the ventilator) controls the tidal volume. Dynamic hyperinflation and iPEEP can also be reduced with this arrangement. Pressure adjustment in pressure-support ventilation will depend on the tidal volume and respiratory rate (which should be less than 30 breaths/min).⁶² This type of ventilation is used in patients with COPD exacerbations who can maintain sufficient tidal volumes and respiratory rates. Assist-control

ventilation should be used in patients whose respiratory muscles require absolute rest and in those who have difficulty adapting to pressure-support ventilation.

– *Sedation, analgesia and paralysis.* Patients with COPD exacerbations who are mechanically ventilated require a certain degree of sedation and analgesia to help them adapt to the ventilator, and to reduce dynamic hyperinflation, oxygen uptake, and CO₂ production.⁵³ Propofol is recommended, provided there are no specific contraindications against its use, because this drug has some bronchodilatory effect,⁶³ and use of muscle relaxants should be avoided.⁶⁴ Benzodiazepines and opiates, alone or in association, are alternative drugs. Haloperidol is the most suitable drug for weaning because it does not depress respiratory drive. Intermittent administration of these drugs (on demand) is the most appropriate approach, as continuous sedation prolongs time on invasive mechanical ventilation and increases treatment costs.^{65,66} Muscle relaxants are only administered for extreme dynamic hyperinflation and when ventilation is ineffective because the patient has not adapted to the ventilator.

– *Administration of bronchodilator treatment during invasive mechanical ventilation.* Bronchodilator treatment, administered with either an inhaler or a nebulizer, has been shown to be effective in mechanically ventilated patients⁶⁷⁻⁶⁹ and is a treatment of choice despite being less effective in this clinical setting. The benefits are the same regardless of whether administered with an inhaler or a nebulizer.⁷⁰ Bronchodilators and glucocorticoids administered systemically have the same indications and the same favorable and undesired effects as when administered outside the ICU.

– *Weaning from the mechanical ventilator.* Patients can be extubated when the cause of the COPD exacerbation has been corrected (or significantly improved) and the patient is clinically stable. Premature extubation can cause an increase in mortality (due to heart arrest, pneumonia, and/or aspiration),⁷¹ prolong the stay in the ICU, and increase the need for long-term physical rehabilitation.⁷² The use of T-tubes⁷³ or NIV⁷⁴ can help in the weaning process. To wean patients with COPD exacerbations, NIV techniques offer advantages with respect to invasive pressure-support, namely they a) reduce the weaning time; b) shorten the stay in the ICU; c) reduce the risk of nosocomial pneumonia; and d) improve survival in the first 60 days after discharge from the ICU (level B evidence).⁷⁴

Criteria for Discharge From Hospital Units

Discharge From the ICU

There are no definite criteria for discharging a patient from an ICU, but in accordance with clinical experience it is advisable to consider discharging patients who

meet the following criteria: *a)* the cause of the exacerbation has been corrected (or significantly improved); *b)* relevant medical complications that might interfere with the stability of the patient are not present; *c)* ventilatory support is not required; and *d)* close monitoring is not required.

Discharge From the Hospital Ward

The ideal length of stay in hospital for a patient with a COPD exacerbation is not known, essentially because there are no objective criteria for determining the moment of discharge from hospital. The criteria that are available are based solely on the opinion of a group of experts.^{2,10} Table 8 presents the criteria recently proposed by the GOLD initiative (Global Initiative for Chronic Obstructive Lung Disease) (level D evidence).¹⁰

Early Discharge and Home Support Programs

The criteria for discharge from hospital shown in Table 8 will probably change in the future with the appearance of early hospital discharge programs and home support. An increasing number of studies have been published investigating the availability, safety, acceptance, and cost-effectiveness of these alternative programs.⁷⁵⁻⁸⁰ These studies have shown that around 20% to 30% of the patients with a COPD exacerbation who come to the emergency room, and who would otherwise be admitted to hospital, can be sent home directly and treated safely and efficiently there if suitable nursing support is available.^{75,76,81} Furthermore, studies have highlighted the possibility of combining short stays in hospital with early discharge and home support for such patients.^{77,78} This latter alternative can be offered to a broad group of patients with good results.^{77,78}

Outpatient Monitoring

It is recommended that patients discharged from hospital after a COPD exacerbation have an outpatient visit scheduled for 4 to 6 weeks later (level D

TABLE 8
Criteria for Discharge From Hospital

<p>Clinical stability for more than 24 hours Arterial blood gases stable for more than 24 hours Patient fully understands application of home treatment Outpatient clinical follow-up and home care well established Patient, family, and physician should agree that the patient can cope satisfactorily as an outpatient</p>

TABLE 9
Follow up at 4 to 6 Weeks After Discharge From Hospital for Exacerbation of Chronic Obstructive Pulmonary Disease

<p>Measurement of forced expiratory volume in 1 second Reassessment of inhalation technique Understanding of recommended therapeutic regimen Assessment of home oxygen therapy or home nebulized therapy</p>

evidence).¹⁰ The variables to be assessed at this visit are shown in Table 9. Subsequent monitoring is the same as for any patient with stable COPD.^{3,10} If respiratory insufficiency was present during the exacerbation, pulmonary gas exchange should be assessed to decide whether home oxygen therapy is indicated. This decision should not be guided by analysis of arterial blood gases at the time of discharge¹⁰ but rather by gases measured when the patient is clinically stable (2-3 months after discharge).

Conclusions and Future Lines of Investigation

Despite the improvements in quality of life and life expectancy of patients with COPD exacerbations in recent years,⁸² usage of hospital time remains an important problem for health services throughout the world. This article has reviewed the basic principles of hospital treatment, presenting the level of evidence for each case whenever possible. This approach has also revealed many of the gaps in our knowledge for which evidence is lacking and for which further investigation is required. The following is just an example of the points that, in our opinion, are more pressing or important.

Underlying Mechanisms of COPD Exacerbations

The pathophysiology of many COPD exacerbations remains unknown and, until we understand the underlying mechanisms better, treatment of exacerbations will remain essentially symptomatic.⁸³ Traditionally, the idea has prevailed that COPD exacerbations are due to "airway infection." But pathogens cannot be identified in a substantial percentage of COPD exacerbations (around 50% of them), even with help of sophisticated invasive techniques.²⁵ This finding is often ignored but, in our opinion, it shows that we must keep an open mind on the matter. The "infection hypothesis" is based on the idea that a COPD exacerbation needs an "external" trigger (in this case, a virus or bacterium). In theory, however, at least some of the exacerbations could be due to an "internal" factor. In fact, many noninfectious chronic inflammatory diseases (such as rheumatoid arthritis or ulcerative colitis) also follow a pattern of exacerbations, which, unlike COPD, are normally considered an integral part of the disease. We do not know whether the same might occur with COPD (which is also an inflammatory disease), but a better understanding of the pathophysiology of the exacerbations could help new and more effective alternative therapies to be developed.

Better Definition of the Role of Existing Treatments

Many of the current therapeutic options for treatment of COPD exacerbations have been "inherited" from other respiratory diseases (asthma, pneumonia) and, often, sufficient scientific evidence is still lacking to determine place of such therapies in the in-hospital therapeutic

strategy. For example, the place of long-acting β_2 agonists in the treatment of exacerbations of COPD has not been analyzed. Recently, a new anticholinergic drug, tiotropium, has come onto the market. Tiotropium has a longer half-life than ipratropium bromide and acts more specifically on the different muscarinic receptor subtypes.⁸⁴ Its bronchodilatory potency is therefore enhanced. However, nothing is currently known about what its future role in the treatment of COPD exacerbations might be. In contrast, even though NIV is clearly effective in the ICU,³⁹ no studies as yet have indicated when and how it should be used outside the ICU.^{38,40,46,47,85} Finally, the question of whether antibiotics should be administered to treat COPD exacerbations is as yet unresolved and is likely to remain so until we are able to find a marker of "bacterial airway infection" that can identify patients who will benefit from antibiotic treatment.

Evidence-Based Criteria for Admission and Discharge From Hospital

The criteria for hospital admission and discharge discussed in this article are based on clinical experience and "expert opinion."²⁻⁵ In recent years, reports have been published on new forms of hospital management of COPD exacerbations, including home hospitalization and early hospital discharge with home support.^{75-78,81} These new forms of treatment require a more precise definition of the criteria for hospital admission and discharge. This definition should be evidence-based if possible and, ideally, make use of a biological marker (like the troponin used by cardiologists). With such a definition, patients could receive better and more comfortable treatment, and health resources could be used more rationally.

Intermediate Respiratory Care Units

NIV has been shown to be an effective support treatment for COPD exacerbations.^{39,86} Such evidence has induced the development in recent years of respiratory intermediate care units with a level of monitoring between the conventional hospital ward and the ICU. These units are designed to give high-quality care to patients with single organ failure (in our case, the respiratory apparatus) and respiratory insufficiency.⁸⁷ Such units can offer NIV and continuous monitoring (pulse oximetry, electrocardiogram, vital signs) for patients who are not admitted to the ICU or, alternatively, act as a bridge with the conventional hospital ward during weaning from invasive mechanical ventilation.⁸⁷ These units require fewer nursing staff than the ICUs, which relieves some of the staffing pressure associated with the ICU, and they consume fewer resources and have a lower rate of complications.⁸⁷⁻⁸⁹ Nevertheless, prospective studies are needed to define the criteria for admission to such units,⁸⁹ and their cost-benefit ratio and cost-effectiveness need to be investigated⁸⁷ in the treatment of COPD exacerbations.

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