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Formal Expert Consensus on discharge management protocol for severe and very severe exacerbation of COPD

Consenso Formal de Expertos acerca del protocolo de manejo y cuidados poshospitalarios de la exacerbación grave y muy grave de la EPOC

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ABSTRACT. Introduction: chronic obstructive pulmonary disease alarmingly contributes to mortality worldwide. Severe (requiring admission) and very severe (requiring intensive care) acute exacerbation are relevant events due to their impact on quality of life and survival. Different international guidelines propose recommendations for the in-hospital management of exacerbations, but there is a need to establish guidelines for discharge management protocol. The objective and importance of this consensus is to establish and offer recommendations to be included in a discharge protocol for severe and very severe exacerbation in order to reduce the risk of relapse, readmission or death in short and long term. **Material and methods:** a formal Consensus of experts was elaborated as an initiative of the Mexican Respiratory Society *(Sociedad Mexicana de Neumología y Cirugía de Tórax)* in collaboration with the Ibero-American Agency for the Development and Assessment of Health Technologies. A Development Group was created of multidisciplinary clinical experts and methodologists with experience in systematic reviews and clinical practice guidelines. The Modified Delphi Panel methodology was used, an agreed level was established at ≥ 70% by Likert score for each recommendation. **Results:** nine clinical questions were integrated that reflected the gaps in clinical practice in the management at discharge of exacerbation. The Delphi Panel shows that all recommendations reached a level of consensus (> 70%). Question 1 and 5 showed a mean < 8.0 and the rest a mean > 8.0 at the first panel round (three questions reached > 90%). **Conclusion:** we now have recommendations that provide guidance and information on controversies to integrate an appropriate discharge protocol.

Keywords: acute exacerbation of COPD, discharge protocol for COPD, discharge consensus for COPD.

RESUMEN. Introducción: la enfermedad pulmonar obstructiva crónica contribuye de manera alarmante en la mortalidad a nivel mundial. Las exacerbaciones agudas graves (que requieren hospitalización) y muy graves (que requieren cuidados intensivos) son eventos relevantes por su impacto en la calidad de vida y en la supervivencia. Las diferentes guías internacionales proponen recomendaciones para el manejo hospitalario de las exacerbaciones, pero hay necesidad de establecer lineamientos para el protocolo del manejo poshospitalario. El objetivo y la importancia de este consenso es establecer y ofrecer recomendaciones para incluir dentro del protocolo de alta de la exacerbación grave y muy grave con la finalidad de disminuir el riesgo de recaída, readmisión y muerte a corto y largo plazo. **Material y métodos:** un Consenso Formal de Expertos fue elaborado por iniciativa de la Sociedad Mexicana de Neumología y Cirugía de Tórax en colaboración con la Agencia Iberoamericana de Desarrollo y Evaluación de Tecnologías en Salud. Se integró un Grupo de Desarrollo por expertos clínicos multidisciplinarios y metodólogos con experiencia en revisiones sistemáticas y guías de práctica clínica. Se empleó la metodología de Panel Delphi modificado, se estableció un nivel de acuerdo ≥ 70% por escala de Likert en cada recomendación. **Resultados:** se integraron nueve preguntas clínicas que reflejaron las brechas en la práctica clínica en el manejo al egreso de una exacerbación. El Panel Delphi muestra que la totalidad de las recomendaciones alcanzaron el nivel de acuerdo (> 70%). La pregunta 1 y 5 mostraron una media < 8.0 y el resto una media > 8.0 a la primera ronda del panel (tres preguntas con > 90%). **Conclusiones:** ahora contamos con recomendaciones que dan orientación y aportan información sobre las controversias para integrar un protocolo de alta adecuado.

Palabras clave: exacerbación aguda de la EPOC, protocolo de alta de la EPOC, consenso de alta de la EPOC.

Abbreviations:

95%CI = 95% Confidence Interval
ACIP = Advisory Committee on Immunization Practices
ADO = Age, Dyspnea, and airflow Obstruction
AECOPD = Acute Exacerbations of Chronic Obstructive Pulmonary Disease
BODE = Body-mass index, Obstruction, Dyspnea and Exercise
BTS = British Thoracic Society
CAT = COPD Assessment Test
CODEX = Comorbidity, Obstruction, Dyspnea, and previous severe EXacerbations
COPD = Chronic Obstructive Pulmonary Disease
COVID-19 = COronaVIrus Disease 2019
CPG = Clinical Practice Guideline
DG = Development Group
DOSE = Dyspnea, Obstruction, Smoking, and Exacerbation
FEV_1 = forced expiratory volume in one second
FF = Fluticasone Furoate
GOLD = Global Initiative for Chronic Obstructive Lung Disease
HR = Hazard Ratio
HZ = Herpes Zoster
ICS = Inhaled Corticosteroids
LABA = Long-Acting Beta-Agonist
LACE = Length of stay, Acuity of admission, Co-morbidities, and Emergency visits during last six months
LAMA = Long-Acting Muscarinic Antagonist
MD = Mean Difference
MITT = Multiple Inhaler Triple Therapy
mMRC = modified Medical Research Council
NICE = National Institute for Clinical Excellence
OR = Odds ratio
$PaCO_2$ = Partial Pressure of Carbon Dioxide
PCV = Pneumococcal Conjugate Vaccine
PEARL = Previous admissions, Extended dyspnea, Age, Right-sided heart failure, and Left-sided heart failure
PPSV = Pneumococcal PolySaccharide Vaccine
PR = Pulmonary Rehabilitation
QIV = Quadrivalent Influenza Vaccine
RACE = Readmission, Acuity of admission, Co-morbidities, and Emergency visits during last six months
RCT = Randomized Clinical Trial
RR = Relative Risk
RSV = Respiratory Syncytial Virus
SABA = Short-Acting Beta-Agonist
SAMA = Short-Acting Muscarinic Antagonist
SARS-CoV-2 = Severe Acute Respiratory Syndrome CoronaVirus 2
SGRQ = Saint George's Respiratory Questionnaire
SITT = Single Inhaler Triple Therapy
SR = Systematic Review
Tdap = Tetanus, diphteria and pertussis
TT = Triple Therapy
UMEC = Umeclidinium
VI = Vilanterol
WHO = World Health Organization

INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are the most important episodes in the clinical course of the disease.[1] The GOLD 2025[2] report defines «AECOPD as an event characterized by increased symptoms, dyspnea, cough, and/or sputum, which worsens in less than 14 days and is frequently associated with

increased local and systemic inflammation caused by infection, pollution, or other mechanisms that damage the lungs». Its relevance lies in the impact it has at the local level (amplification of inflammation, alterations in the ventilation-perfusion ratio, pulmonary hyperinflation), increased systemic inflammation (comorbidities, increased cardiovascular risk, musculoskeletal and neurocognitive damage, impact on quality of life), increased use of health resources due to direct and indirect costs, and increased short- and long-term mortality.[3-5] It is one of the leading causes of death globally, with more than three million people reported to have died from the disease in just 2019.[2,5] The global burden of the disease is expected to increase in the coming years due to demographic changes and continued exposure to well-established risk factors.[2,5] A WHO report identified chronic obstructive pulmonary disease (COPD) as the third leading cause of death worldwide, accounting for nearly 90% of deaths in people under 70 years of age and in low- and middle-income countries. Globally, there was a 15.5% increase in the prevalence of COPD between 2007 and 2017.[5] Some systematic reviews report a global prevalence of COPD ranging from 7.6% in 2004 to 11.4% in 2014;[6,7] with higher rates among males, in urban areas, and in high-income countries.[5] Smoking is associated with 70% of COPD cases in high-income countries and 30-40% in middle- and low-income countries,[8] where environmental pollution is a more significant risk factor.

The clinical presentation of exacerbations is usually heterogeneous, varying in severity and phenotype, requiring careful and extensive clinical assessment for management.[9] Unlike mild exacerbations (which can be resolved with rescue bronchodilators) and moderate exacerbations (which can be managed on an outpatient basis because there is no difficulty breathing), severe exacerbations require hospitalization due to respiratory compromise (hypoxemic respiratory failure), and very severe exacerbations require advanced airway management in intensive care (due to respiratory acidosis).

The different phenotypes described for COPD exacerbations (based on severity, frequency, symptom complex, and timing) are determined by inflammatory endotypes: T2, T1, or T17, according to the predominant eosinophilic, neutrophilic, or paucigranulocytic response, and which are associated with different etiological triggers such as bacterial infections, viral infections, or elevated eosinophil counts in the blood; they represent 55%, 29%, and 28%, respectively, of all exacerbations.[9] Viral infections cause more inflammation and last longer; however, there are other triggers of AECOPD (in 50-70%), such as environmental pollution, poor medication adherence, climate change, anxiety, right heart failure (pulmonary hypertension), and gastroesophageal reflux.[9-12] It is difficult to clinically distinguish between the different phenotypes, but with the help of biomarkers it is possible to tell the difference, although they are not fully validated.[9] An increase in total eosinophils in peripheral blood has been shown to be the only reliable and accepted biomarker for exacerbations.[13,14]

The various clinical practice guidelines (CPGs)[1,2,4,15] describe in detail how AECOPD is classified and how it is managed in outpatient and inpatient settings; however, when it comes to managing these patients during the transition from hospital to home, we find many gaps and unresolved needs for the primary care physician or specialist.

The objective of this expert consensus is to develop recommendations based on scientific evidence and the experience of leading experts in the management of COPD patients who have experienced an exacerbation and have been discharged home, with the aim of reducing risks and complications during this critical period.

MATERIAL AND METHODS

This document was produced in accordance with a general model for developing a formal expert consensus,[16] which consists of the following stages: confirmation of the expert group, scope document/clinical questions, literature search/review, consensus on recommendations via the Delphi Panel, and review of the final document. These stages are described below.

The Development Group consensually drew up a list of clinical questions to aid clinical decision-making in the management of patients who have been discharged home from hospital following a severe exacerbation.

The Formal Expert Consensus documents need to be developed using a systematic method to include the best available evidence and combine the best clinical experience. A development group (DG) composed of experts in the diagnosis and management of COPD met to work in a multi-collaborative and interdisciplinary manner, with extensive academic and clinical experience in various specialties such as pulmonology, emergency medicine, and intensive care. Methodological experts with experience in the development of systematic reviews (SR) and CPGs were also included. The DG met on several occasions via online platforms to agree on the work plan, timelines, and distribution of responsibilities, as well as important aspects in defining the general scope of the consensus and the list of structured clinical questions.

On August 28, 2023, a meeting was held to present the general methodology with the objective of agreeing on the scope document and the list of structured clinical questions. Over several weeks, regular remote video-assisted meetings were held via electronic platforms to reach consensus and analyze the results of the systematic searches and the drafting of the initial recommendations.

The scope document was defined by consensus, agreeing on the characteristics of the population to be included in the study, as well as the characteristics of the population that would not be considered in the document. The scope document establishes the general framework for the development of the work. Clinical questions addressing and identifying gaps in knowledge and relevant clinical issues were established in accordance with the members of the development group. It was proposed that clinical questions should be clear, precise, and specific in order to facilitate the search for and identification of scientific evidence, thereby avoiding recommendations that are poorly suited to the clinical problems raised by the project.

Internationally validated algorithms and strategies were assembled for the comprehensive identification of scientific evidence. MeSH (Medical Subject Headings) terms were identified and used in the search strategies to obtain a sensitive and specific search strategy considering the population of patients with severe or very severe COPD exacerbation requiring hospitalization. Systematic reviews and controlled clinical trials to answer questions about therapeutic alternatives; diagnostic test studies to answer questions about the diagnostic accuracy of different diagnostic alternatives; and finally, case-control studies and prospective and retrospective cohorts were searched to answer questions about risk factors and prognostic factors. We searched PubMed, Embase, Cochrane Collaboration, SciELO, Artemisa, and Google Scholar, and no time limit was set for publication.

Formal Expert Consensus

The process of gathering the opinions of all the experts who were part of the DG was carried out under the guidance of a modified Delphi Panel. They were sent an invitation via email to review each of the clinical recommendations suggested by the DG, which were posted on a digital platform designed for this purpose (Survey Monkey - https://es.surveymonkey.com). The experts were asked to assign a rating using a Likert scale according to their assessment of the content, applicability, wording, and timeliness of each of the clinical recommendations, with a lower limit of 1 and an upper limit of 9; the number 1 indicates that the expert «strongly disagrees» with the recommendation, and 9 means the expert «Totally agrees»; in the same way, a score of 5 (in the middle of the Likert scale) would correspond to being indifferent. On this scale of 1-9, levels of disagreement are shown in red, passing through yellow and shades of green, while levels of agreement are shown in shades of blue.[13-18] All members of the DG were asked to include a clinical argument associated with their quantitative response so that adjustments could be made to the recommendation if a satisfactory level of agreement among the experts could not be achieved. The mean, median, standard deviation, and percentage of consensus for each recommendation were calculated from the responses on the Likert scale. A minimum level of consensus was established as a mean of 7.0 and a percentage of at least 70% of responses in the range of 7 to 9 on the Likert scale. The DG members monitored the interaction between participants, processing information and filtering relevant content, as well as modifying recommendations in accordance with the clinical arguments of all panelists in order to send the new text to the next round of the Delphi Panel and have it re-evaluated by the same participants from the previous round.[16-19]

The DG members met repeatedly via remote platforms to review the evidence responding to each of the clinical questions. Both the scientific evidence analyzed and the clinical experience of the DG and the risk/benefit ratio were considered in drafting the recommendations, where we were especially careful to avoid ambiguities. The organizational characteristics and resources available in both public and private hospitals in our country were taken into account. Once the Delphi Panel was completed, a consensus was reached on the clinical recommendations.[16-19]

RESULTS

Clinical recommendations and scientific evidence

Question 1:
What are the criteria for hospital discharge of patients with severe exacerbation of chronic obstructive pulmonary disease?

Recommendation

We recommend complying with the criteria contained in the checklist *(Figure 1)*, as these criteria reflect the patient's improvement and appropriate conditions for reliable discharge. These recommendations are supported by various respiratory societies in relation to hospital discharge. They basically concern home care, and there is a need to have defined criteria at hand to decide on discharge. International documents establish some common criteria. Below is a list of the criteria proposed by different research groups and those proposed by this working group. It should be noted that it is not necessary to meet all the criteria at the same time, as some take longer than others to achieve, but the more criteria that are met, the greater the stability, the better the follow-up, and the less fear of re-entry. The criteria and recommendations may carry specific weight depending on each patient or circumstance *(Figure 2)*.

Supporting text and analysis

The GOLD 2025[2] CPGs state that, to date, there are no universally accepted standards establishing the timing and criteria for discharging hospitalized patients *(Figure 2)*. However, evidence supports the fact that the mortality risks of patients with exacerbations are associated with increased age, the presence of respiratory acidosis, the need for ventilatory support, and comorbidities such as anxiety and depression.[2] Therefore, we suggest that, in addition to confirming respiratory and hemodynamic stability at the time of discharge, depression and/or anxiety should be assessed and, if necessary, treated before discharge *(Table 1)*.

An SR published by Ospina *et al.* in 2017[20] aimed to evaluate the effectiveness of different post-hospitalization care strategies for COPD exacerbations. It has been found that a significant proportion of patients do not receive information about well-established management programs, fail to receive the appropriate vaccinations, do not receive optimal therapeutic management, and do not establish formal smoking cessation treatments. The authors included 14 clinical studies, four of which were RCTs (randomized clinical trials). The elements included in the different programs were: ensuring correct inhalation technique (nine studies), individual drug management strategies (eight studies), assessment and referral to rehabilitation therapy (eight studies), ensuring follow-up (eight studies), and referral to a smoking cessation program (seven studies).[20] The results of the meta-analyses show that of the four RCTs, the hospital readmission rate decreased by 20% with discharge program strategies (relative risk [RR] 0.80; 95%CI 0.65-0.99). This percentage increases in observational studies (range −6.11 to −48.5%).[20] However, with regard to secondary outcomes, the implementation of these programs did not demonstrate a reduction in long-term mortality (RR 0.74; 95%CI 0.43-1.28) or in the Saint George Respiratory Questionnaire (SGRQ) scores (mean difference [MD] 1.84; 95%CI −2.13-5.8).[20]

Question 2:
What are the risk factors associated with hospital readmission?

Recommendation

Consider the risk factors described in *Table 2*, as they have been shown to have predictive value for hospital readmissions.

Supporting text and analysis

Patients with COPD have high readmission rates, which can be as high as 50%, so identifying patients who are at increased risk of readmission is an important management goal. Many studies have been published that have evaluated the various risk factors associated with hospital readmission in patients with COPD. A systematic review published by Chow *et al.* in 2023[21] aimed to evaluate predictors of readmission and included 242 studies with 16,471,096 participants. The results of the meta-analyses showed that the predictors that were significantly associated were: patient characteristics (male gender, previous hospitalization, comorbidities, poor physical condition evidenced by high SGRQ (> 50 points), sedentary lifestyle, and use of supplemental oxygen), previous hospitalization (length of stay, use of corticosteroids (CES), and use of mechanical ventilation), laboratory markers and lung function (anemia, low forced expiratory volume in one second [FEV_1 < 30% p], elevated total blood eosinophils (> 200 cells/mm^3), neutrophil/lymphocyte ratio > 7, elevated blood carbon dioxide pressure ($PaCO_2$) (> 45 mmHg), elevated bicarbonate > 25 mEq/L) and specific characteristics at discharge (home oxygen and discharge to long-term care or specialized clinics). Other well-identified factors for readmission are the presence of comorbidities, exacerbations (≥ 2) and previous hospitalizations (≥ 1), use of systemic corticosteroids, and prolonged hospital stay for readmission at 30 and 90 days.[21,22]

According to GOLD 2025[2] and in line with the findings reported by Chow *et al.*,[21] the main factors contributing to readmission are: comorbidities, previous exacerbations (≥ 2), hospitalization (≥ 1), and prolonged hospital stay.[2] Similarly, in 2023, Ruan *et al.*[23] published a meta-analysis of 46 studies in which (in addition to identifying the same risk factors already mentioned), the presence of comorbidities such as diabetes mellitus and specifically cardiovascular comorbidities such as heart failure and hypertension were associated with a higher risk of hospital readmissions (38%) in the following year; on the other hand, obesity was identified as a protective factor.[23] The specific combination of heart failure and osteoporosis is associated with worse clinical outcomes, probably due to an increase in the systemic inflammatory response.[24] In this same study, low physical activity levels, musculoskeletal dysfunction, and frailty syndrome were other factors associated with worse clinical outcomes and a higher readmission rate *(Table 2)*.[23]

Biomarkers associated with readmissions in COPD

- Persistently elevated C-reactive protein (CRP) > 10 mg/L (> 14 days after exacerbation).[25]
- Eosinophils: the presence of elevated eosinophils (> 200 cells/μL) has been consistently associated with an increase in short-term (30 days) hospital readmissions with an odds ratio (OR) of at least 3.59, as well as hospital readmissions for any other cause unrelated to COPD (OR 2.32)

Checklist for discharge of hospitalized patients with COPD exacerbations

	Yes	No
Arterial blood gas analysis or oximetry normal or at levels similar to those prior to the exacerbation		
Complete review of all clinical and laboratory parameters, in other words, disease stability		
Check maintenance therapy and understanding of home care instructions		
Does not require short-acting bronchodilators less frequently than every four hours		
The patient is able to walk around the room		
The patient is able to eat and sleep without frequent awakenings due to dyspnea		
Correct use of medication by the patient and/or caregiver		
Guaranteed continuity of care		
Exclude depression and/or anxiety		

Figure 1: Discharge checklist.
Recommendations proposed by different respiratory societies regarding hospital discharge. These criteria basically include home care, as there is a need for clear criteria to decide on discharge. International documents establish some common criteria reflected in this checklist.
COPD = chronic obstructive pulmonary disease.

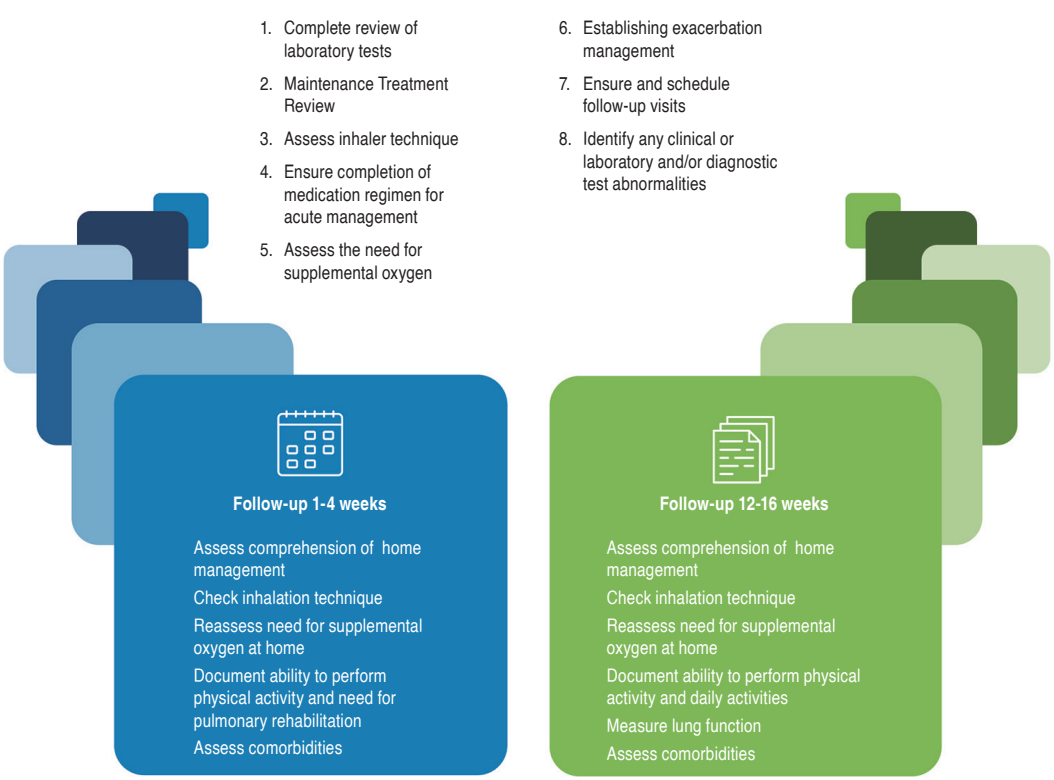

Figure 2:

GOLD 2025 - Criteria for discharge and recommendations for follow-up.[2]
Modified from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Bethesda: GOLD Global Strategy for Prevention, Diagnosis and Management of COPD: 2025 Report. Available from: https://goldcopd.org/2025-gold-report/

Table 1: Discharge parameters according to different international guidelines.

Parameter	NICE	ATS	TSANZ	GOLD	GesEPOC	SMNCT
Arterial blood gas or oximetry normal or at levels similar to those prior to exacerbation	XXX				XXX	XXX
Complete review of all clinical and laboratory parameters, that is, disease stability	XXX		XXX	XXX	XXX	XXX
Check maintenance therapy and understanding of home management instructions	XXX	XXX	XXX		XXX	XXX
Short-acting bronchodilators less frequently than every four hours			XXX		XXX	XXX
The patient is able to walk around the room		XXX	XXX		XXX	XXX
The patient is able to eat and sleep without frequent awakenings due to dyspnea			XXX	XXX	XXX	XXX
Correct use of medication by the patient and/or caregiver	XXX	XXX	XXX	XXX	XXX	XXX
Guaranteed continuity of care	XXX	XXX		XXX	XXX	XXX
Depression and/or anxiety assessed and, where appropriate, treated						XXX
Re-stablish maintenance bronchodilator treatment	XXX					

This table summarizes the criteria considered in various international guidelines for deciding on the discharge of COPD patients hospitalized for exacerbation of the disease. ATS = American Thoracic Society. COPD = Chronic Obstructive Pulmonary Disease. GesEPOC = Spanish guide for COPD. GOLD = Global Initiative for Chronic Obstructive Lung Disease. NICE = National Institute for Clinical Excellence. SMNCT = Mexican Society of Pulmonology and Thoracic Surgery. TSANZ = Thoracic Society of Australia and New Zealand.

and shorter intervals between each exacerbation and readmission (OR 2.78), without a statistically significant association with the length of hospital stay.[26]

- Markers of myocardial dysfunction: The two markers of acute myocardial dysfunction that have been evaluated in the context of stable COPD and COPD exacerbation are troponin I and B-type natriuretic peptide, with elevated troponin I levels being associated with worse clinical outcomes. A troponin I level above the reference cutoff point at hospital admission is associated with a higher number of hospital readmissions due to COPD exacerbation at 90 and 180 days, as well as an increase in adverse outcomes of all-cause mortality or major cardiovascular events (except myocardial infarction) with a risk ratio (RR) of 2.88.[27]

Predictive models for hospital readmission

Clinical prediction scales with multiple variables are not new in COPD and have proven their usefulness over time in multiple clinical studies. These scales allow us to determine the severity of the disease, predict future exacerbations, and now also predict the risk of short-, medium-, or long-term hospital readmission. These scales, whose names are acronyms are represented by: ADO (risk of exacerbations: Age, Dyspnea, airflow Obstruction), BODE (disease severity: Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity), DOSE (disease severity: Dyspnea, Obstruction, Smoking, and Exacerbation), CODEX (risk of exacerbations: Comorbidity, Obstruction, Dyspnea, and previous severe EXacerbations), PEARL (readmission at three months: Previous admissions, Extended dyspnea, Age, Right-sided heart failure, and Left-sided heart failure), CORE the COPD-REadmission (readmission at 12 months: eosinophil count, lung function, triple inhaler therapy, previous hospitalization, and neuromuscular disease), RACE (readmission at 30 days: Readmission, Acuity of admission, Co-morbidities, and Emergency visits during last six months), LACE (Length of stay, Acuity of admission, Co-morbidities, and Emergency visits during last six months). In most scales, the variable that carries the most weight when combined with the rest and that is repeated in virtually all clinical trials is the history of previous exacerbations or hospitalizations. Some clinical scales use biomarkers such as eosinophils (CORE) and some other comorbidities (CODEX or PEARL).[28,29]

Possible interventions to reduce readmission rates

Just as risk factors for readmissions have been identified, various studies[30,31] have also proposed preventive measures

that can help reduce the readmission rate. These measures are summarized below:

1. Early diagnosis.
2. Optimal treatment for stable COPD.
3. Specific management of comorbidities and risk factors (exposures).
4. Early identification and appropriate management of exacerbations.
5. Establish individual action plans.
6. Prevention of bacterial and viral infections.
7. Early pulmonary rehabilitation.

A large number of hospital programs have been incorporated and evaluated to reduce readmission rates for patients discharged after an exacerbation requiring hospitalization. In 2021, Press *et al.*[32] published the results of a program implemented in various hospitals in the United States. The elements that make up the different programs have some similarities, in particular, that they have been led by health professionals trained in the disease, medications, and patient education, as well as visits and close follow-up in the weeks following discharge. Some of these programs have reported decreases in hospital readmissions ranging from 23% to 15%. These programs include: 1) an appropriate inhaled medication regimen, 2) a month's supply of inhaled medications, 3) personalized education on the use of inhalers, 4) instructions for home use with education for patients and caregivers, and 5) follow-up after two weeks.[32]

Question 3:

What is the efficacy and safety of different types of nebulized bronchodilators and steroids in the post-hospital management of severe COPD exacerbation?

Recommendation

Short-acting bronchodilators and nebulized corticosteroids are safe and effective in treating patients following a severe exacerbation, especially in patients with cognitive or neuromuscular impairment or those who do not reach 30 L/min of inspiratory flow. Since they reduce medical visits and hospital readmissions, they are recommended to be administered for an average of up to 30 days while the patient recovers or learns to use their inhalation devices correctly. However, their use is not sufficient for the maintenance treatment of patients with COPD and they should not be used as monotherapy. Therefore, an appropriate device should be used for each individual patient on an individual basis with long-acting beta-2 agonists/long-acting muscarinic anticholinergics (LABA/LAMA) and, if required, inhaled corticosteroids (ICS), including the use of spacer devices for administration that are not inferior to nebulized therapy.

Supporting text and analysis

The inhaled route is considered the preferred route of administration in the treatment of COPD due to the high

Table 2: Factors associated with an increased risk of presenting a new exacerbation.

Patient-specific factors	Clinical factors associated with the patient	Factors associated with disease severity	Biomarkers
Advanced age (> 65 years)	More than two comorbidities	Low FEV_1 (< 30%)	Eosinophilia > 200 cells/µL
Male gender	Cancer	Moderate or severe exacerbation in the last 12 months	CRP > 10 mg/L
Malnutrition	Diabetes	Hypercapnic respiratory failure	Elevated troponin I and BNP
Reduced physical activity	Heart failure	Severity of disease at admission (GOLD 1 versus 4)	PCO_2 > 45 mmHg
SGRQ > 50	Depression and anxiety	High scores on multidimensional scales (BODE, ADO, CODEX)	HCO_3 > 25 mEq/L
Functional class mMRC 3-4	Muscle dysfunction/osteopenia		

This table summarizes the different factors associated with an increased risk of presenting a new exacerbation. Risk factors associated with readmission. The most significant variables are a history of previous exacerbations (especially moderate or severe) and previous hospitalization. Persistent elevation of biomarkers (eosinophils, C-reactive protein) indicates airway inflammation and is associated with an increased risk of readmission. The use of clinical prediction scales allows patients to be stratified into different risk levels and may benefit from early interventions identified in previous documents and listed in this one to achieve better outcomes with these patients. ADO = Age, Dyspnea, and airflow Obstruction. BODE = Body-mass index, Obstruction, Dyspnea and Exercise. CODEX = Comorbidity, Obstruction, Dyspnea, and previous severe EXacerbations. GOLD = Global Initiative for Chronic Obstructive Lung Disease. HCO_3 = Bicarbonate. mMRC = Modified British Medical Research Council Scale. PCO_2 = carbon dioxide in blood pressure. CRP = C-reactive protein. BNP = Brain Natriuretic Peptide. SGRQ = Saint George's Respiratory Questionnaire. FEV_1 = forced expiratory volume in one second.

local concentration that can be achieved in the airway, offering greater efficacy and fewer systemic adverse effects compared to other routes of administration. The deposition of inhaled medication may be affected by factors associated with the particle or the patient: airway geometry, presence of moisture, particle size, pathological processes that alter airway permeability, breathing patterns, and pulmonary clearance mechanisms. Therefore, these factors could influence the therapeutic effectiveness of inhaled therapies. Particle size is one of the most important determinants of pulmonary deposition, with particles between 1-5 mm being optimal; however, medium-sized particles (around 3 mm) may be more effective for bronchodilation than smaller particles. Devices with particles larger than > 5 mm will be less effective and are associated with greater oropharyngeal deposition and decreased pulmonary deposition.[33]

According to a comprehensive structured survey, 77% of patients and caregivers generally prefer nebulized therapy in COPD patients in terms of easier inhalation, a feeling of well-being, and fewer visits to the doctor and hospitalizations. On the other hand, two other global surveys published by Sharafkhaneh *et al.*[34] and Barta *et al.*[35] found that nebulized therapy offers better breathing and symptom control in 95% and 59% of cases, respectively. It is important to note that in both cases, a reduction in hospitalization was observed *(Figures 3 and 4)*.

Internationally renowned institutions such as the UK's National Institute for Clinical Excellence (NICE) and the British Thoracic Society (BTS) have established home care programs such as those described above. Where nebulized therapy and education on the use of inhalers are the cornerstone of these programs.[36] A study published by Maietta and colleagues[37] in 2023 evaluated a home care protocol consisting of an appropriate regimen of inhaled medications, 30-day doses of medications, education for patients and caregivers, and a 15-day follow-up appointment. Readmissions decreased at 30 days from 49% to 30% (p = 0.003).[37]

It is important to note that patients who have suffered an exacerbation must generate a peak inspiratory flow (PIF) that is compromised by muscle wasting, resulting from hyperinflation, hypoxemia, and muscle atrophy. With PIF compromised, nebulized therapy plays an important role in bronchodilator and steroid treatment for the post-hospital management of patients discharged after a severe exacerbation of COPD.[38]

Parikh *et al.* published a clinical study in 2016 comparing a home care program for patients discharged from hospital due to COPD exacerbation.[39] The study was conducted at a university hospital in the United States, and the outcomes evaluated were days of hospitalization, readmission rate, and hospital costs. Home care protocols included various inhaled medications. In general, the medications considered for home use were anticholinergics (ipratropium bromide), ICS/beta 2 agonists (budesonide/formoterol, albuterol), and other systemic medications, systemic corticosteroids (prednisone, methylprednisolone), and antibiotics in patients with purulent sputum. The results of the study showed a total of 44 patients (22 protocol and 22 control group) and the outcomes reported a significant decrease in readmission rates at 30 days (9.1% protocol versus 54.4% control group, p = 0. 001) and at 60 days (22.7% protocol versus 77% control group, p = 0.0003). Health service costs also decreased significantly in patients in the protocol group.[39]

Another study published by Zafar *et al.* evaluated another discharge protocol in patients with COPD exacerbations.[40] The authors interviewed patients who were readmitted after a COPD exacerbation, and a multidisciplinary team created a discharge protocol for these same patients. The authors reported that the most prevalent failures in readmitted patients were: poor inhalation technique, lack of short-term patient follow-up, and suboptimal patient education instructions. The results of incorporating a discharge protocol (education, appropriate inhaled medication regimen, provision of inhaled medication for 30 days, and follow-up appointment) showed a decrease in the 30-day readmission rate from 22.7% to 14.7%.[40]

Nebulizer therapy is an attractive alternative to handheld devices and has been the mainstay of inhaled therapy for intensive and acute care. Recently published evidence suggests that the efficacy of medications administered via nebulizer is similar to that observed with other devices, given that nebulizers do not require patient coordination for inhalation or any other special inhalation technique. Nebulization devices have a particular benefit in patients with cognitive, neuromuscular, or ventilatory impairment. It is an appropriate inhaled administration strategy in patients with COPD in any of the treatment panels.[41] However, in Mexico, we only have short-acting bronchodilators (SAMA, SABA, SABA/SAMA) and corticosteroids in nebulizer form. In other parts of the world, LABA/LAMA options are available for nebulization, allowing for effective and comprehensive treatment for patients with COPD.[33]

The characteristics of the patient, combination of drugs, as well as their preferences and satisfaction must be considered when making a recommendation on the use of devices for the treatment of patients with COPD.[34,38]

Question 4:

What is the efficacy and safety of systemic corticosteroids for the post-hospital management of severe exacerbation of chronic obstructive pulmonary disease?

Recommendation

Systemic corticosteroids are usually administered during hospitalization, as their efficacy makes them part of standard treatment, and they are generally completed before discharge, so it is not necessary to continue them or restart another course during the post-hospital period, unless the patient has not completed the in-hospital regimen and has to continue it at home.

Corticosteroids (oral prednisone or equivalent) in a shortened regimen of five to 10 days at a dose of 30-40 mg/day have been shown to decrease recovery time, improve lung function and oxygenation, are associated with fewer treatment failures, and decrease adverse effects. It is also not recommended to continue a dose reduction or prolonged duration regimen upon discharge, nor are they recommended as part of the therapeutic regimen in stable patients.

Supporting text and analysis

Corticosteroids are commonly used to reduce inflammation and improve symptoms in patients with AECOPD,[2] and have a favorable impact in the post-hospital phase. The efficacy and safety of corticosteroids for the hospital management of severe AECOPD have

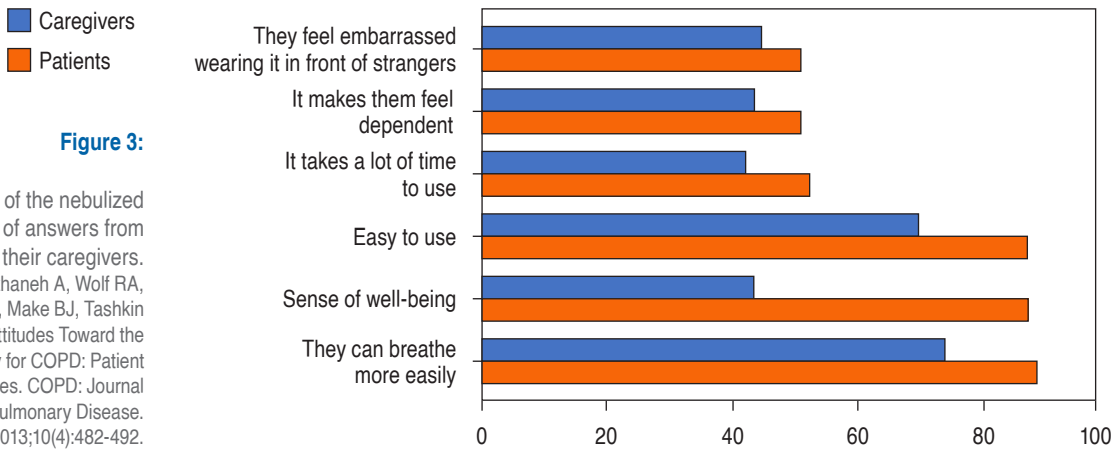

Figure 3:

Benefits and concerns of the nebulized therapy: a comparison of answers from patients and their caregivers.
Modified from: Sharafkhaneh A, Wolf RA, Goodnight S, Hanania NA, Make BJ, Tashkin DP. Perceptions and Attitudes Toward the Use of Nebulized Therapy for COPD: Patient and Caregiver Perspectives. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2013;10(4):482-492.

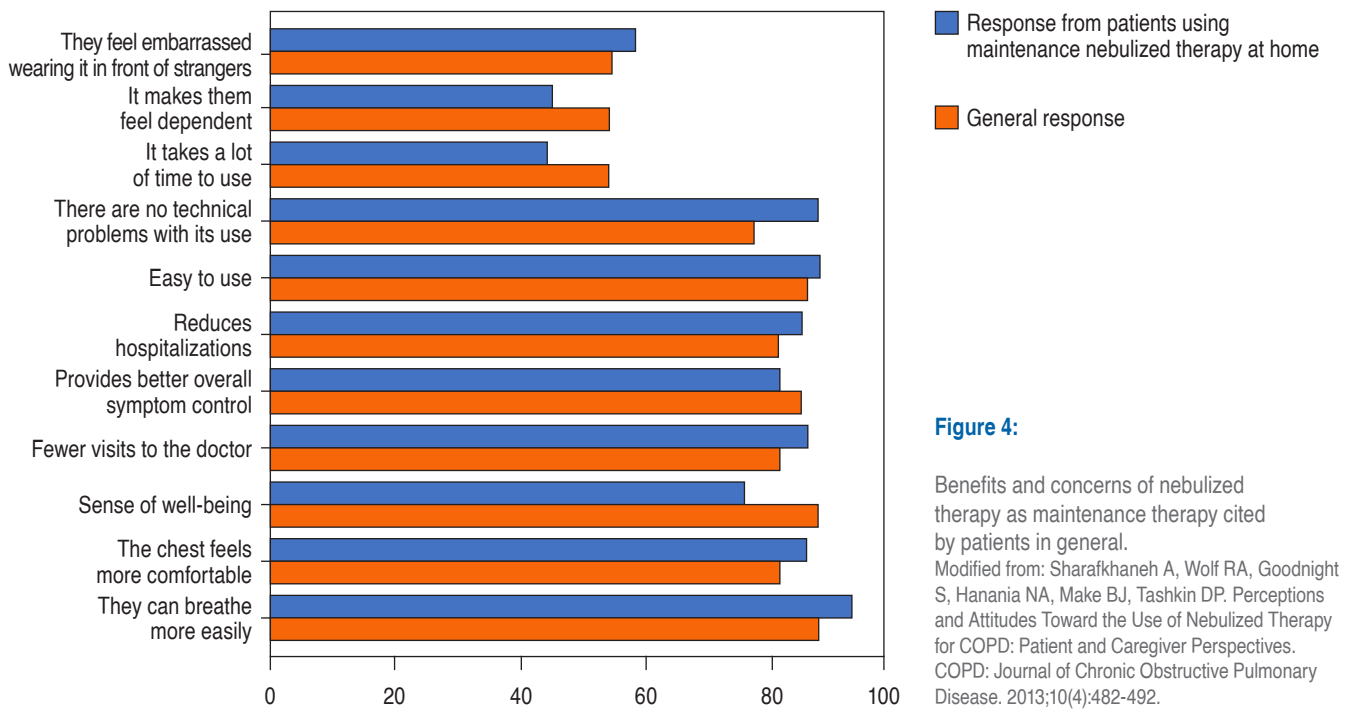

Figure 4:

Benefits and concerns of nebulized therapy as maintenance therapy cited by patients in general.
Modified from: Sharafkhaneh A, Wolf RA, Goodnight S, Hanania NA, Make BJ, Tashkin DP. Perceptions and Attitudes Toward the Use of Nebulized Therapy for COPD: Patient and Caregiver Perspectives. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2013;10(4):482-492.

been evaluated in several clinical trials, meta-analyses, and clinical practice guidelines.

A SR published by Walters *et al.* in 2014[42] in collaboration with Cochrane showed that treatment with corticosteroids was associated with a reduction in treatment failure in more than half of patients with acute exacerbation, with an average treatment duration of 14 days. The authors included 16 clinical studies (1,787 participants) comparing corticosteroids with placebo and four studies (298 participants) comparing oral corticosteroids with parenteral corticosteroids.[42] The authors found moderate-quality evidence showing a reduction in relapse at one month with corticosteroid treatment (RR 0.78, 95%CI 0.63 to 0.97); however, 30-day mortality did not show a decrease associated with corticosteroid treatment in 12 studies (RM 1.00, 95%CI 0.60-1.66).[42] Lung function tests, primarily FEV_1, showed a benefit with systemic therapy (mean difference [MD] of 140 mL, 95%CI 90-200 mL) measured at 72 hours; however, this improvement was not sustained over time. There were more adverse events with corticosteroids (MR 2.33, 95%CI 1.59-3.43) and the risk of hyperglycemia also increased (RM 2.79, 95%CI 1.86-4.19).[42]

The use of prolonged regimens increased the probability of an adverse event (hyperglycemia, infections, weight gain, or insomnia) associated with corticosteroid treatment.[42]

In the REDUCE study, a multicenter, randomized, non-inferiority trial,[43] conducted in five Swiss university hospitals, participants were administered 40 mg of prednisone daily for five or 14 days in a double-blind, placebo-controlled design. The risk indices for relapse at 180 days were 0.95 and 0.93 in the intention-to-treat and per-protocol analyses, respectively, meeting the non-inferiority criterion. Similar relapse rates were observed in both groups, with a difference of –1.2%.[43] The short-term group received a lower cumulative dose of prednisone. The results show that treatment with five days of prednisone in patients with AECOPD does not result in inferior clinical performance compared to conventional 14-day treatment, in addition to reducing adverse effects and hospitalizations at 30 days.[44-47]

Question 5

What is the efficacy and safety of triple therapy (TT) for the post-hospital management of severe exacerbation of chronic obstructive pulmonary disease?

Recommendation

It is recommended that inhaled TT be started within the first 30 days in all patients who will be discharged after hospitalization for severe or very severe AECOPD, regardless of their previous clinical characteristics, with greater benefit observed in those with eosinophils > 150 cells/mL with any previous treatment; even in cases with a history of documented pneumonia, pulmonary tuberculosis, and eosinophils < 100 cells/mL, especially in the presence of cardiovascular comorbidities if the clinical condition permits. Always verify the proper use and understanding of the device.

Supporting text and analysis

Two network meta-analysis studies adequately support this evidence of efficacy and safety for the recommendation.[48,49] COPD guidelines recommend escalating to TT (CEI/LABA/LAMA) after two moderate exacerbations or one severe exacerbation of COPD in the previous year.[2] However, the right time to start it, in whom, and at what time is unclear, although there is information about its effect on some important outcomes. There is no direct comparison with dual bronchodilation in immediate post-hospitalization management, but we assume that, as in AECOPD, TT (corticosteroids and/or nebulized corticosteroids, nebulized SABA/SAMA) is used in some way, the dilemma is how to proceed after hospital discharge.[2]

In a retrospective cohort study in the United States in 2022,[50] the impact of rapid initiation (≤ 30 days) versus delayed initiation (31-180 days) of fixed triple therapy (SITT) based on fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) was evaluated following a moderate or severe exacerbation of COPD, based on a registry of prescriptions issued, where the benefit (reduction in exacerbations, costs, and readmissions) was compared. Early initiation of SITT had significantly lower rates of total exacerbations per patient-year (0.98 versus 1.23; RR 0.79, 95%CI 0.65-0.94), moderate exacerbations (0.86 versus 1.03; RR 0.84, 95%CI 0.69-0.99), and severe exacerbations (0.11 versus 0.20; RR 0.57, 95%CI 0.37-0.79), compared with those who started late. The cost of health resources for all causes and related to COPD was also significantly lower in early starters.[50]

In another more recent study conducted in the United States,[51] using a very similar methodology in 24,770 patients who were prescribed any type of TT, fixed (SITT) or multiple/open (MITT with two or three devices); the important thing was that they had to have had two moderate exacerbations or one severe exacerbation in the last 12 months. Patients were stratified into three groups according to their exacerbation rate and time to initiation of TT (≤ 30 days, 31-180 days, and 181–365 days). It was found that for each month of delay in starting TT, there was an 11% and 7% increase in the risk of any AECOPD and severe AECOPD, respectively (RR 1.11, 95%CI 1.10-1.13 and 1.07, 1.05-1.08), as well as a 4.3% increase (95%CI 3.9-4.6%) in the number of AECOPD, a 1.8% increase (95%CI 1.3-2.3%) in total costs, and a 2.1% increase (95%CI 1.6-2.6%) in COPD-related costs. Evidence IIb.[51]

In a third study comparing the same intervention groups, but in Spain,[52] a retrospective observational real-life cohort (n = 4,625) based on data from the National Health Registry, with any type of TT (SITT or MITT); patients with SITT showed greater adherence to treatment (CR 1.37, 95%CI 1.22-1.53), greater reduction in AECOPD (RR 0.68, 95%CI 0.61-0.77), lower risk of all-cause mortality (RR 0.67, 95%CI 0.63-0.71), and significant reduction in healthcare costs compared to the MITT group. Adherence to any type of TT was associated with protection against AECOPD. Evidence IIb.[52]

In Japan, another retrospective cohort study (n = 1,012) and the EROS study (n = 2,409) evaluated the impact of early initiation (0-30 days) versus late initiation (31-180 days) and very late initiation (181-365 days) of TT after moderate or severe AECOPD in patients from a database who initiated SITT (FF/UME/VIL or budesonide/glycopyrronium/formoterol [BUD/GLI/FOR]) or MITT. Early TT initiators had longer time free of AECOPD (MD 0.77, 95%CI 0.64-0.93); with a rate of 1.52 (1.39, 166); in late initiators, 2.00 (1.92, 2.09); and in very late initiators, 2.30 (2.20, 2.40); and lower use of healthcare resources and lower direct costs for all causes and related to COPD. The longer the delay in initiating TT, the higher the rate of 5% AECOPD. In patients with severe AECOPD, delayed initiation of TT resulted in a significant increase in all-cause readmissions at 90 days (MD 42.1% versus 30.6%; p = 0.0329). Evidence IIb.[53,54]

In addition to the above, and making an indirect comparison of fixed triple therapy (SITT) or mixed multiple/open therapy (MITT), a retrospective study was conducted comparing (BUD/GLI/FOR) versus the initiation of MITT, focusing on reducing mortality and the first serious cardiovascular event. Patients who started SITT had an 18% reduction in mortality (hazard ratio [HR] 0.82 [0.75, 0.91]) and a 12% reduction in risk (0.88 [0.83, 0.93]) for a major cardiovascular event versus patients with MITT.[55]

Question 6

What is the efficacy and safety of supplemental oxygen administration for the post-hospital management of severe exacerbation of chronic obstructive pulmonary disease, and through which device?

Recommendation

It will be prescribed when the patient has not reached acceptable oxygen saturation levels (≥ 88% oxygen saturation or PaO_2 ≥ 55 mmHg at rest and at room air), in those who desaturate with routine physical exertion (nocturnal oxygen therapy and during exertion); and, of course, patients who were already using it prior to the exacerbation. Its requirement will be evaluated between one and four weeks later and, if necessary, between weeks 12 and 16. Among 40 and 80% of patients will not need it in the long term. The type of device used to administer oxygen, as well as the flow rate and number of hours per day, are extrapolated from studies conducted on patients with stable COPD and severe chronic hypoxemia. The flow rate will be that which maintains oxygen saturation between 88 and 92%.

Supporting text and analysis

Most indications for the use of home oxygen in patients with COPD are made after hospitalization (short-term oxygen).[56] A group of patients upon hospital discharge (29%) will have returned to their baseline oxygen saturation levels. In a retrospective cohort of 659 patients with COPD[57] followed up for 90 days after hospital discharge, more than 80% no longer had hypoxemia at rest (SpO_2 > 88% at rest) and therefore no longer required long-term home oxygen therapy.[56] In another retrospective study that evaluated 205 subjects, most of whom had been diagnosed with COPD and required oxygen after hospital discharge, 40% of them no longer met the criteria for continuing home oxygen therapy at 30 days of follow-up.[58]

The need for supplemental oxygen should be reassessed at one month and three months (by measuring oxygen saturation using pulse oximetry or arterial blood gas analysis), because long-term oxygen treatment guidelines will not apply to most COPD patients who required home oxygen use after hospital discharge, with no clinical benefits for those without evidence of hypoxemia at rest and with increased costs.[2]

Oxygen can be administered through various devices, in the form of compressed gas contained in stationary or portable cylinders, liquid oxygen, stationary or portable concentrators;[59] however, most of the evidence regarding the dose and duration of home oxygen use has been generated in patients with stable COPD who have severe chronic hypoxemia, with the recommendation being to use it for 15 to 24 hours a day at a flow rate sufficient to achieve saturation targets of 88 to 90%.[60,61]

A retrospective study found that patients who had lower PaO_2 levels upon hospital discharge were more likely to require long-term home oxygen therapy (OR 0.90, 95%CI 0.84-0.96). In another study that followed up on COPD patients who were prescribed short-term oxygen, mostly because of an exacerbation, those who needed to keep using oxygen for more than 32 days and had more severe obstruction were more likely to need long-term home oxygen.[62]

The one-year survival rate in subjects who required short-term oxygen treatment upon discharge from hospital was 56%. Another follow-up study mentioned that the risk/protection association was not significant after adjusting for age, lung

function, and other confounders such as comorbidities, dyspnea, and oxygenation (CR 1.57, 95%CI 0.87-2.81).[62]

Question 7

What is the efficacy and safety of early pulmonary rehabilitation for the post-hospital management of severe exacerbation of chronic obstructive pulmonary disease and reducing the risk of readmission?

Recommendation

Without a doubt, it is recommended to start a personalized and supervised pulmonary rehabilitation (PR) program as early as possible, even before discharge, once the patient is able or their condition allows it. It should last at least six weeks and then continue indefinitely, as PR is considered a non-pharmacological therapeutic strategy that encompasses education and behavioral intervention, with the main benefits being improvements in:[2,63,64]

Lung capacity: through specific exercises and breathing techniques, it helps increase the lungs' capacity to take in oxygen and eliminate carbon dioxide.

Physical endurance: includes aerobic and resistance exercises that help strengthen the respiratory muscles and improve overall endurance.

Symptoms: as the inflammatory response improves, symptoms such as dyspnea, fatigue, and chronic cough decrease.

Quality of life: by increasing functional capacity and reducing symptoms, it allows people to lead a more active life and participate in daily activities with greater comfort.

Education, nutrition, and support: They also provide education about lung disease, management techniques, and strategies to prevent exacerbations and improve sarcopenia.

Reduction in hospitalizations: helps prevent serious exacerbations and reduce the need for hospitalization.[65,66]

Supporting text and analysis

A review of the literature on controlled studies and meta-analyses related to PR in patients with COPD, especially those who have suffered exacerbations requiring hospitalization, has shown improvements in outcomes in terms of quality of life, improved exercise capacity, reduced dyspnea, and lower healthcare costs and resource use, but without significant changes in lung function or mortality.[65-68]

For COPD patients who have been hospitalized for a moderate or severe exacerbation, there are personalized early PR inpatient rehabilitation programs (recommended to start as soon as the patient is able), which have been shown to reduce the length of hospitalization and accelerate the recovery of lung function, improve quality of life, and decrease hospital readmissions compared to rehabilitation programs after discharge. Therefore, the current recommendation is to start the rehabilitation program early. However, if, due to infrastructure and health resource factors, inpatient rehabilitation programs are not available, it is recommended that they be initiated as soon as possible after discharge.[69-71]

Within the PR protocols, such as those suggested by the American Thoracic Society, which are determined by the type and severity of lung disease, the presence of comorbidities, availability of healthcare resources, etc., they generally recommend supervised rehabilitation programs lasting at least six weeks, followed by continued therapy at home with the implementation of well-defined strategies. Some programs last at least six months, and the patient is monitored during subsequent medical appointments.[72]

One situation that should be noted is that in our environment we lack sufficient PR centers and hospital staff trained to carry it out; in addition, there is a lack of programs with uniform objectives and evaluation parameters that provide us with reliable information on the response to the intervention.[73]

Question 8

Who will remain on TT permanently, and who will remain on dual bronchodilation?

Recommendation

In the absence of studies designed to answer this question, but based on the evidence currently available, it appears that most patients will continue TT indefinitely, given that early initiation within the first 30 days of AECOPD protects against the risk of subsequent exacerbations and reduces healthcare resource use and costs.[50-53] **On the other hand, dual therapy has a similar rate of hospital readmission as monotherapy. Those who could not continue TT for more than three months and would continue with dual bronchodilator or dual therapy (LABA/LAMA) would be cases with contraindications for the use of ICS (documented previous pneumonia, lack of or refusal of pneumococcal vaccination, previous tuberculosis, serum eosinophils < 100 cells/μL), and ICS would be discontinued as soon as possible once clinical stability has been achieved. Always verify the correct use and proper inhalation technique for the device. This question is rounded out with the recommendations from Question 5.**

Supporting text and analysis

AECOPD requiring hospitalization represents an enormous economic burden of the disease. In the outpatient setting, there is strong evidence to justify the use of TT in cases with recurrent exacerbations.

Cases that continue dual therapy (LABA/LAMA) or monotherapy upon hospital discharge after an exacerbation show a similar rate of readmission. Cases that use monotherapy have a higher risk of readmission, particularly when they remain hospitalized for 7-14 days. Therefore, the use of better therapeutic strategies upon hospital discharge after an AECOPD should be promoted.[74]

In the 12-month follow-up after a severe exacerbation of COPD, for every 30 days of delay in starting TT, there was a 13% increase (OR 1.13, 95%CI 1.11-1.15) the risk of any exacerbation and 10% in the risk of severe exacerbations (OR 1.10, 95%CI 1.08-1.12). Similarly, significant increases were observed in the overall costs of care per disease and, specifically, in the costs associated with the care of COPD cases.[75]

The initiation of SITT showed a lower rate of hospital readmissions, a lower frequency of subsequent exacerbations, and significantly lower COPD-related costs per person-year, particularly when the therapeutic strategy was initiated within the first 30 days after discharge from the hospital for a moderate to severe exacerbation.[76]

One of the little-explored factors contributing to the risk of exacerbations is the lack of proper inhalation technique for the various devices used to treat COPD. In a non-randomized trial, the implementation of strategies focused on reducing the risk of errors in the inhalation technique of COPD patients upon hospital discharge through education, providing written guidance on the selection and correct use of the device, and evaluating the inhalation technique during the hospital stay and prior to discharge, it was observed that, compared to the control group (error rate of 61.2%), the group that underwent the intervention had an error rate of 21% (an absolute reduction of 40% in the risk of errors in inhalation technique).[77]

Triple therapy in real-life studies

DACCORD study: results were better with dual therapy versus triple therapy; however, it should be noted that 70% of cases did not experience exacerbations. Therefore, patients discharged from hospital due to an exacerbation will always have to leave with TT.[78]

TT is best for patients with FEV_1 < 50%, who are very symptomatic (CAT > 10 points mMRC 2 or more), have had more than two moderate exacerbations or one severe exacerbation, have eosinophilia 3% or more than 300 cells/μL, significant loss of lung function, and patients recently discharged from the hospital.[78]

Question 9

What is the efficacy and safety of different vaccination schedules in reducing the risk of future exacerbations of chronic obstructive pulmonary disease and reducing the risk of readmission?

Recommendation

All patients with COPD should receive all recommended vaccinations in accordance with relevant local guidelines and as soon as possible *(Table 3)*, since at least 70% of COPD exacerbations are infectious in origin, with respiratory viruses identified in approximately 30% of cases. Vaccination rates remain suboptimal in this population, and COPD exacerbations are associated with worsening and progression of the disease.

Supporting text and analysis[79,80]

The prognosis for patients with COPD depends largely on the frequency of exacerbations, and one of the most common causes of these is respiratory infections. Vaccines are effective preventive measures in patients with respiratory diseases, including those with COPD, because they reduce exacerbations and hospitalizations; however, despite this, their use in these patients is far from optimal.

The following presents evidence of the efficacy of vaccines in patients with COPD.

Pneumococcal vaccine

Pneumococcus is responsible for most community-acquired pneumonia in people over 60 years of age with risk factors, and it is also the cause of acute exacerbations of COPD.

There are two vaccine options: the polysaccharide vaccine (known as PPSV 23), which is administered every five years, and the conjugate vaccines (PCV13, PCV15, and PCV20), which are permanent (once in a lifetime), as they produce an immune response dependent on both B lymphocytes and T lymphocytes, thus generating immunological memory and a longer-lasting effect. The pneumococcal vaccine is conjugated in patients with COPD[79,80] because, in addition, the strains it contains are the most aggressive.

The comparative efficacy of pneumococcal vaccination with PPSV23 and PCV13 in patients with COPD was evaluated in a five-year cohort study. At one year, both vaccines significantly reduced the rate of pneumonia. However, there was a greater difference five years after vaccination. Pneumonia was reported in 47% of patients in the PPSV23 group compared to 3.3% of subjects in the PCV13 group ($p < 0.001$) with similar results for COPD exacerbations (81.3% vs. 23.6%, $p < 0.001$). Randomized controlled trials evaluating the effect of sequential vaccination with PSV13 and PPSV23 in COPD are still scarce.[81]

Vaccination with PPSV23 has been shown to effectively reduce the risk of acute exacerbations (54%), pneumonia (53%), and related hospitalizations (46%) in patients with

COPD. Combinations with other vaccines (trivalent seasonal influenza vaccine) have been shown to improve overall prevention efficacy.

Influenza vaccine

Patients with COPD belong to the population at high risk for influenza infection according to the Centers for Disease Control (CDC) and the WHO, so annual influenza vaccination and vaccines containing dead or inactivated live viruses are recommended.[2]

In terms of preventing flu-related hospitalizations in patients with COPD, flu vaccination has been shown to be up to 38% effective.

There is a moderate average protective effect in preventing this type of hospital and outpatient infection. The effect in unvaccinated patients immunized in previous seasons was 24%, while the efficacy of vaccination in the current season, regardless of previous doses, was up to 40%. Unfortunately, the efficacy of vaccination in patients over 65 years of age with COPD is probably lower and prevents only 22-43% of influenza-associated hospitalizations.[81]

The vaccine significantly reduced the use of healthcare resources (hospitalization) for moderate patients (RM 0.22, 95%CI 0.09-0.51), severe patients (RM 0.19, 95%CI 0.08-0.44), and very severe patients (RM 0.15, 95%CI 0.05; 0.50), compared to mild patients (RM 0.51, 95%CI 0.20-1.26). It reduced emergency room visits for moderate patients (RM 0.33, 95%CI 0.14-0.77), severe patients (RM 0.22, 95%CI 0.10-0.52), and very severe patients (RM 0.72, 95%CI 0.10-0.88), compared to mild patients (RM 0.64, 95%CI 0.30-1.37). Finally, it reduced the incidence of respiratory failure compared to mild patients, showing that influenza vaccination is more effective in patients with moderate, severe, and very severe COPD than in those with mild obstruction.[78,82]

Joint vaccination against pneumococcus and influenza

The administration of both vaccines on the same day (pneumococcal: PCV15, PCV20, or PPSV23) and influenza (QIV) in adult patients has demonstrated a synergistic protective effect, as they are immunogenic and safe, in addition to reducing the risk of acute exacerbation of COPD, pneumonia, and hospitalizations.[2,82]

SARS-CoV-2 (COVID-19) vaccine

COVID-19 represents a serious threat to patients with COPD. Unfortunately, there are no studies investigating the efficacy of the COVID-19 vaccine explicitly in patients with COPD, the impact on the rate of exacerbations.[79]

Some case-control studies suggest that mRNA (messenger ribonucleic acid) vaccines are highly effective for several COVID-19-related outcomes in patients with chronic diseases. The vaccine was highly effective in preventing symptomatic infection, hospitalization, severe illness, and death in people with chronic diseases, but its effectiveness was lower compared to healthy controls. These data did not allow for analysis of the COPD population.[80]

It was recently found that the efficacy of two doses of the vaccine (Corona Vac) against mortality, hospitalization, and severe complications related to COVID-19 was 77% (95%CI 74-80%), 18% (95%CI 6-23%), and 29% (95%CI 12-43%), respectively; while for the two-dose regimen of BNT162b2, it was 92% (95%CI 91-94), 33% (95%CI 30-37%), and 57% (95%CI 45-66%), respectively. The benefit was greater for the same outcomes with a three-dose regimen of CoronaVac (94, 40, and 71%) and BNT162b2 (98, 65, and 83%). Administration of a fourth dose of either vaccine showed an additional positive effect, concluding that COVID-19 vaccines achieved moderate to high efficacy.[83]

Respiratory syncytial virus (RSV) vaccine

RSV is one of the most common causes of respiratory infections in children, but also in adults over 60 years of age; many older people, grandparents who live with their grandchildren (in this sense), are a cause of exacerbation in patients with COPD. Since 2023, a vaccine against RSV has been available, adding to the arsenal of vaccines for chronic respiratory diseases.[79,80,82]

This vaccine is based on the bivalent prefusion protein F of respiratory syncytial virus and the prefusion protein F vaccine for people aged 60 years and older, as recommended by the CDC's Advisory Committee on Immunization Practices (ACIP) and the European Commission. Adults at increased risk for severe RSV disease include adults with chronic heart or lung disease, immunocompromised adults, and those living in nursing homes or long-term care facilities.[2]

Pertussis vaccine

COPD may increase the risk and severity of pertussis infection. In a retrospective study, the incidence of pertussis among people > 50 years of age with COPD was 2.32 times higher than in those without COPD, resulting in significant increases in healthcare resource utilization and direct medical costs surrounding the pertussis event.[79,80]

According to CDC recommendations, the pertussis vaccine is recommended for patients with COPD. It is included in a triple vaccine that also contains diphtheria and tetanus (Tdap); it is usually administered in childhood, so it is not common to recommend this vaccine for patients with newly diagnosed COPD. The vaccine is effective for approximately 10 years on average, but it is important

to consider it for previously unvaccinated patients or for patients at risk as a booster.[79,80]

Herpes zoster (HZ) vaccine

It is estimated that one in three unvaccinated people will develop HZ during their lifetime. The increased risk of HZ is attributed to a decline in cell-mediated immunity, as seen in age-related immunosenescence or in immunocompromised individuals.[79,80]

The risk of HZ in patients with COPD increases up to 2.8 times. Due to the immune dysregulation found in COPD, it exhibits a higher risk of developing it, amplified by the immunosuppressive effect of inhaled or systemic steroids. HZ increases the risk of cerebrovascular and cardiovascular events. The presence of cardiovascular comorbidities in COPD underscores the importance of vaccination against HZ in this group of patients, although there are no data explicitly demonstrating its effectiveness. However, due to their increased risk of HZ, we strongly recommend vaccination, even when they are under 50 years of age.[79,80]

It should be noted that, despite the efficacy and safety of the different vaccines in older populations and those with chronic lung diseases, vaccination rates among these groups remain very low, and strategies have been suggested to strengthen this area. One such strategy is to educate and inform primary care physicians about the benefits of a complete vaccination schedule for both older adults and patients with chronic lung disease or cardiovascular disease, among whom the risk of complications and death is higher than in the general population. Others have developed vaccination programs for individuals who are hospitalized (either in the hospital or in the emergency room), immunizing patients against influenza and pneumococcus (provided there are no contraindications) with favorable results. Therefore, we hope that over time vaccination rates will increase and the risk of exacerbations, hospitalization, and death will decrease, especially in the group of patients with COPD.[79,80,82]

LEVEL OF CONSENSUS

The results of the Delphi Panel show that all recommendations achieved a minimum level of consensus, set at the onset at over 70%. Only questions 1 and 5 showed an average < 8.0, and the rest of the recommendations showed an average > 8.0 in the first round of the Delphi Panel. Questions 4, 6, and 7 achieved «agree» percentages above 90% *(Table 4)*.

DISCUSSION

This consensus document was greatly needed because the questions addressed are not covered in clinical practice guidelines for COPD; there is very little information on discharge protocols for this type of patient, and the information gaps that physicians encounter during this critical period of the disease are not discussed in depth. This gives the document a high degree of originality, and

Table 3: Summary of internationally recommended vaccination schedules in patients discharged from hospital after a severe or very severe exacerbation.

Vaccination for stable COPD		
Vaccine	**Evidence**	**Dose**
Influenza vaccination recommended for people with COPD	B	Annual
The CDC recommends pneumococcal vaccination for patients with COPD	B	One dose of PCV20 or one dose of PCV15 followed by a PPSV23 vaccine PPSV23 every five years or one dose of PCV13
The WHO and CDC recommend vaccination against SARS-CoV-2 (COVID-19)	B	Basic immunization schedule and annual boosters
The CDC recommends the respiratory syncytial virus (RSV) vaccine for people over 60 and/or with chronic heart or lung disease	A	Single dose
The CDC recommends Tdap (dTap/dTPa) vaccination to protect people with COPD against pertussis	B	Single dose for those who were not vaccinated during adolescence
The CDC recommends the Zoster vaccine to protect people with COPD over the age of 50 against herpes	B	Two doses of recombinant vaccine administered 2 to 6 months apart

This table summarizes the criteria considered in various international guidelines for the use of different immunization options against various respiratory microorganisms. CDC = Centers for Disease Control and Prevention. COPD = Chronic Obstructive Pulmonary Disease. WHO = World Health Organization. PCV = Pneumococcal Conjugate Vaccine. PPSV = Pneumococcal PolySaccharide Vaccine. Tdap = Tetanus, diphteria and pertussis.

Table 4: Delphi Panel Results. Modified Delphi Panel Statistics.

Questions	Mean ± standard deviation	Median	Percentage of consensus
Question 1: What are the criteria for hospital discharge for patients with severe exacerbation of COPD?	7.80 ± 1.87	8.5	89
Question 2: What are the risk factors associated with hospital readmission?	8.20 ± 1.32	9	89
Question 3: What is the efficacy and safety of different types of nebulized bronchodilators and steroids in the post-hospital management of severe exacerbation of COPD?	8.30 ± 1.37	9	85
Question 4: What is the efficacy and safety of systemic corticosteroids for the post-hospital management of severe exacerbation of COPD?	8.70 ± 0.56	9	95
Question 5: What is the efficacy and safety of triple therapy for the post-hospital management of severe COPD exacerbation?	7.90 ± 1.79	9	80
Question 6: What is the efficacy and safety of different devices for supplemental oxygen administration for the post-hospital management of severe COPD exacerbations?	8.30 ± 1.28	9	90
Question 7: What is the efficacy and safety of early pulmonary rehabilitation for the post-hospital management of severe COPD exacerbation and reducing the risk of readmission?	8.50 ± 1.17	9	90
Question 8: Who remains on triple therapy permanently and who remains on dual bronchodilators?	8.10 ± 1.35	9	85
Question 9: What is the efficacy and safety of different vaccination schedules for reducing the risk of future exacerbations of COPD and reducing the risk of readmission?	8.40 ± 1.30	9	85

The mean, standard deviation, and interquartile range were calculated, as well as the percentage of agreement among the members of the Development Group. Seventy percent was established as the appropriate percentage of consensus. It was not necessary to conduct a second round of the Delphi Panel, as an adequate level of consensus was achieved in the first round.
COPD = Chronic Obstructive Pulmonary Disease.

one of its strengths is precisely that its recommendations have been drawn up by a group of experts following the Delphi Panel methodology, which rounds off all the evidence presented on the key questions, resulting in a response that is, as far as possible, specific, reasoned, practical, applicable, brief, and concise. We believe that this consensus will also open up another segment of COPD guidelines for future versions.

Among the possible weaknesses is perhaps the omission of some other concerns regarding the management of these patients during the transition from hospital to home; the limited information available on the Latin American population; and the fact that the information available sometimes lacks sufficient evidence to formalize a recommendation. However, this will provide an opportunity to revisit the issue in future updates.

CONCLUSIONS

The relevant clinical questions answered with the evidence found are sufficient to issue recommendations. In some of the questions where there was not as much information, the Delphi Panel was valuable in order to properly ground certain recommendations; Therefore, we consider and conclude that we finally have recommendations that provide guidance and information on controversies to integrate an appropriate discharge protocol that will help improve outcomes for our patients in the hospital-to-home transition in terms of quality of life and reduce the risk of new exacerbations and associated mortality.

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