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NCT
Neumología y Cirugía de Tórax

CONTENTS

Vol. 83 - No. 3 / July-September 2024

EDITORIAL

WHO Framework Convention on Tobacco Control. Impact 20 years after its creation **181**

Jesús Ángel Sigala-Centeno, Valeria Antonia Luna-Bedolla, María Andrea Hernández-Pérez, José Rogelio Pérez-Padilla

ORIGINAL RESEARCH

Formal Expert Consensus on discharge management protocol for severe and very severe exacerbation of COPD **184**

Rafael de Jesús Hernández-Zenteno, Abelardo Elizondo-Ríos, Robinson Emmanuel Robles-Hernández, Ireri Isadora Thirión-Romero, Rafael F. Páramo-Arroyo, Luis Albrecht Septien-Stute, Catalina Casillas-Suárez, Fernando Morett-Vera, Jonathan Álvarez-Pinto, José Luis Mayorga-Butrón, Edgar Zozoaga-Velázquez, Enrique E. Olaya-López, Arturo Cortés-Telles, Alejandra Ramírez-Venegas, Oliver Pérez-Bautista, Jesús J. Vázquez-Cortés, Luis Adrián Rendón-Pérez, Ricardo Lemus-Rangel, Juan Carlos Vázquez-García, Sergio Garza-Salinas, Mario Rodríguez-Vega

Presence of comorbidities and their association with antimicrobial resistance of tuberculosis, in a national reference center in the Bajío region and the north of Mexico **205**

Adrián Rodríguez-Carlos, Juan Valentín Trujillo-Páez, Jesús Núñez-Contreras, Mauricio Regalado-Rodríguez, Bruno Rivas-Santiago

REVIEW

Open access protocol and classification of scientific literature on spirometry **212**

Mario Arturo Flores-Valadez, Layla Michán-Aguirre, Israel Muñoz-Velasco, Minerva Romero-Pérez

CLINICAL CASE OF INTEREST

Empyema secondary to a septic embolus in a patient with septic cavernous sinus thrombosis: a case report and review of the literature **223**

Jesús Alexey Silva Aguilar, Javier Misael Morán Castillo

NCT
Neumología y Cirugía de Tórax

CONTENIDO

Vol. 83 - Núm. 3 / Julio-Septiembre 2024

EDITORIAL

Convenio Marco de la OMS para el Control del Tabaco. El impacto a 20 años de su creación 181

Jesús Ángel Sigala-Centeno, Valeria Antonia Luna-Bedolla, María Andrea Hernández-Pérez, José Rogelio Pérez-Padilla

ARTÍCULOS ORIGINALES

Consenso Formal de Expertos acerca del protocolo de manejo y cuidados poshospitalarios de la exacerbación grave y muy grave de la EPOC 184

Rafael de Jesús Hernández-Zenteno, Abelardo Elizondo-Ríos, Robinson Emmanuel Robles-Hernández, Ireri Isadora Thirión-Romero, Rafael F. Páramo-Arroyo, Luis Albrecht Septien-Stute, Catalina Casillas-Suárez, Fernando Morett-Vera, Jonathan Álvarez-Pinto, José Luis Mayorga-Butrón, Edgar Zozoaga-Velázquez, Enrique E. Olaya-López, Arturo Cortés-Telles, Alejandra Ramírez-Venegas, Oliver Pérez-Bautista, Jesús J. Vázquez-Cortés, Luis Adrián Rendón-Pérez, Ricardo Lemus-Rangel, Juan Carlos Vázquez-García, Sergio Garza-Salinas, Mario Rodríguez-Vega

Presencia de comorbilidades y su asociación a la resistencia antimicrobiana de tuberculosis, en un centro de referencia nacional en la región del Bajío y norte de México 205

Adrián Rodríguez-Carlos, Juan Valentín Trujillo-Páez, Jesús Núñez-Contreras, Mauricio Regalado-Rodríguez, Bruno Rivas-Santiago

ARTÍCULO DE REVISIÓN

Protocolo de acceso abierto y clasificación de la literatura científica sobre espirometría 212

Mario Arturo Flores-Valadez, Layla Michán-Aguirre, Israel Muñoz-Velasco, Minerva Romero-Pérez

CASO CLÍNICO DE INTERÉS

Empiema secundario a embolismo séptico en un paciente con trombosis del seno cavernoso: reporte de un caso y revisión de la literatura 223

Jesús Alexey Silva Aguilar, Javier Misael Morán Castillo

NCT
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Vol. 83 - No. 3 / July-September 2024

Editorial
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WHO Framework Convention on Tobacco Control. Impact 20 years after its creation

Convenio Marco de la OMS para el Control del Tabaco. El impacto a 20 años de su creación

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The World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC)[1] it is the first international public health treaty that addresses all the essential facets for tobacco control, which causes 8 million deaths annually, the highest number of deaths in the 20th century, and premature death in half of the persistent users.[2] The generation and implementation of the FCTC of the WHO strengthened the international collaboration of the public health sectors, with other government sectors, and with civil society organizations.

The main provisions to reduce the demand for tobacco, are contained in articles 6 to 14 and include:

1. Protection against exposure to tobacco smoke, by promoting public spaces free of tobacco smoke and emissions.
2. Regulation of the content of the tobacco products by verifying the ingredients declared on the packaging and the their concentration, and the presence of health warnings.
3. Regulation of tobacco products disclosure. The promotion of tobacco products at public events and in the media is prohibited.
4. Educate, communicate, train and create awareness in the public through public health promotion, of the tobacco control and information campaigns on the risks caused by first- and second-hand exposure to tobacco smoke.
5. Wide access measures that help people who want to quit smoking throughout the health care sector, helplines, tobacco cessation care from the first level of health care, access to medicines to quit smoking, and specialized clinics for tobacco users that require more intensive and comprehensive supports.
6. Periodic surveillance of the state of the tobacco pandemic through systematic and standardized national surveys, in the adult population, in children and youth.
7. The need to legislate to reduce the risks of smoking, without the involvement of the tobacco industry (TI), avoiding conflicts of interest as much as possible, that is, that the economy and profits are not prioritized over public health.

After the ratification of the FCTC, laws for tobacco control, rules or regulations that give precision and detail to the measures according to the FCTC have been managed.

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In Mexico, the General Law on Tobacco Control (GLTC),[3] was published in 2009, achieving most of the objectives described in the FCTC, with some gaps generated by the interference of TI and its defenders, which have been the subject of subsequent efforts to comply with them. Australia, the United Kingdom and Ireland are examples of countries that have excelled in the successful implementation of the effective FCTC policies, which have led to a substantial decrease in tobacco use and an improvement in public health.[4-7]

According to the 2023 report on global progress in the implementation of the FCTC (2023),[7] there is precisely a progressive fulfillment of the postulates over two decades. For example, in Mexico, in 2022, amendments were made to the GLTC regulations, with provisions in the total prohibition of all forms of advertising and promotion of tobacco products, including their display at points of sale, and the expansion of protection against smoke and emissions of any tobacco and nicotine product at national level.[8] It is still pending to achieve advances in so-called generic packs, with neutral packaging, without distinctive details of the brands, which attract consumption by themselves.

There is still a need at the international level to strengthen the implementation of tobacco taxes, the most cost-effective way to reduce tobacco use and health care costs especially among young and low-income people, while increasing government revenues in many countries.[9]

The beneficial impact is not only related to reducing smoking rates, but also to protecting non-tobacco users from tobacco smoke and promoting healthier lifestyles, as well as an improvement in labor productivity. For example, in women in the United States, the odds of achieving a reduction in smoking with the implementation of legislative bans on smoking in public spaces and workplaces were significantly higher at 28%.[10]

The most arduous battle against the tobacco epidemic is the one that, in a practical sense, is carried out against the interests of TI, which defends its profits and frequently relies on free trade agreements or treaties. The strategy is similar to the actions carried out by the food industry, the sugary drinks industry, and the alcohol industry to avoid restrictions that could reduce their very large profits, even if they are implemented in order to favor public health. These powerful industries have influential lobbies, legal departments, and advocates in all government powers, but especially in government areas dealing with commerce and the economy.

TI has sponsored research and investigators, which more frequently than independent findings deny or minimize harms from tobacco use or new tobacco products.[11] Previously, low-tar, filtered, or mentholated cigars were misleadingly promoted as lower risk than regular cigars. There is concern about the growing popularity of e-cigarettes and other novel products among young people and adolescents that increase the likelihood of nicotine addiction, and already installed it is difficult to quit, generating for TI one more customer for life. New products, such as e-cigarettes, heated tobacco, smokeless tobacco, and bagged nicotine, predominantly impact children and adolescents at increased risk of addiction. Many of the new users have never smoked and in this group the risk reduction is ruled out, in addition to a group of them subsequently using regular cigarettes either exclusively, or combined as dual users.[12,13]

The rise of alternative tobacco products is one of the main threats to the continued advancement of tobacco control, as increasing health harms are described over time. There are currently systematic reviews and meta-analyses that have shown that e-cigarette use is associated with an increased risk of initiating subsequent conventional tobacco use (3.62; 95% CI 2.42-5.41) and of continuing smoking during the last 30 days in adolescents and young adults (4.28; 95% CI 2.52-7.27).[14] Additionally, the existing evidence on the risks of dual use is worrying, since the harms of respiratory and cardiovascular diseases are potentiated (range of e-cigarettes: 1.24 to 1.47; dual use, 1.49 to 3.29).[14] It is therefore important to develop updated regulatory frameworks, ensuring that new products receive at least the same restrictions as those of traditional tobacco products, including impeding access to children and adolescents.

The implementation of the FCTC has heterogeneous levels in the different countries of low to middle income secondary to the lack of economic resources, health infrastructure and adequate control, such as those required for adequate surveillance of illicit trade in tobacco products, for which international collaboration is essential.

Despite the FCTC and the gradual reduction in the percentage of smoking prevalence in many countries, the number of tobacco users is still high, which generates disease, high costs in its treatment, disability and deaths. Therefore, the principles of the FCTC remain in force, but they need to be updated to consider new nicotine delivery products, which cannot be achieved without the collaboration of various international organizations, which facilitate the accession of all countries to the FCTC and, in addition, similar internal work in each country and province.

The FCTC celebrates its 20th year of persisting in the fight against tobacco with undeniable achievements and progress, including significant reductions in smoking. In these 20 years, TI, in addition to continuing to sell and promote traditional cigarettes, has managed to put new nicotine-addictive products on the market, trying to avoid the restrictions implemented in order to protect the population from the impacts of smoking. Countering

this influence requires international coordination and cooperation between the public sector, non-governmental organizations and the general population. Fortunately, the strategies have been specified in the FCTC and its MPOWER instrumentation tools, which will also be essential to control new nicotine addiction products.

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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.

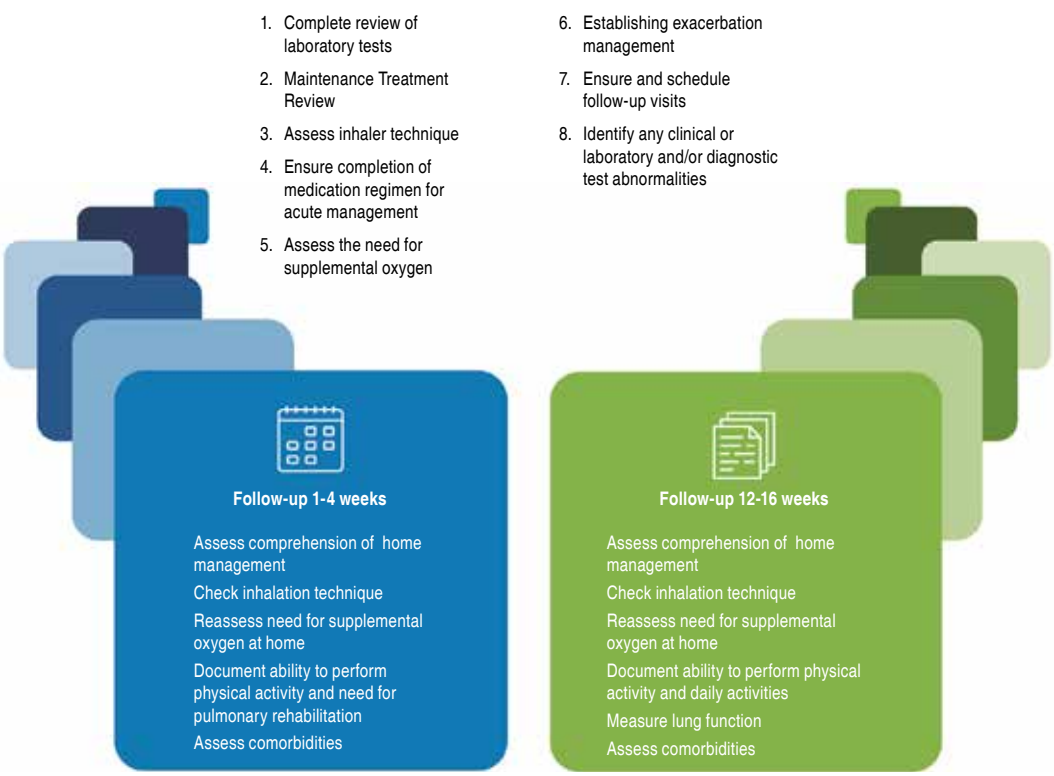

Figure 2:

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

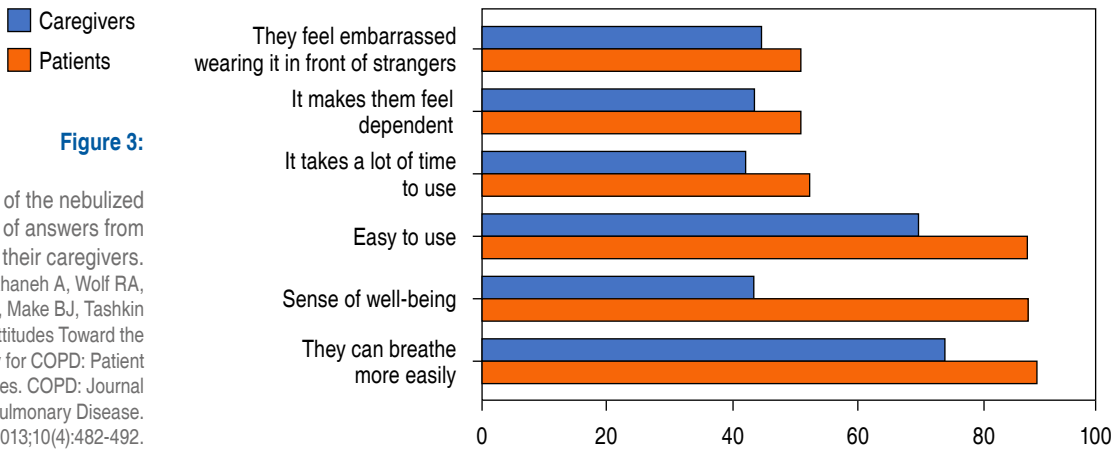

Figure 3:

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.

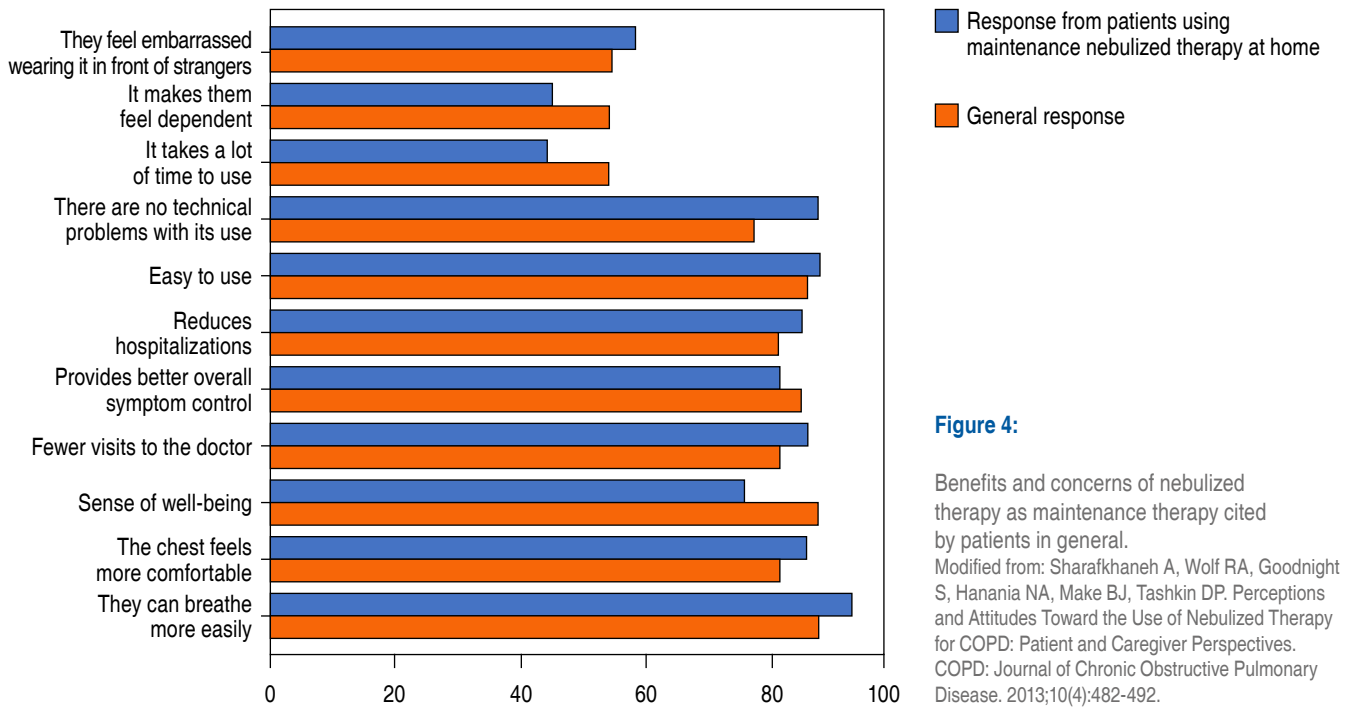

Figure 4:

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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Presence of comorbidities and their association with antimicrobial resistance of tuberculosis, in a national reference center in the Bajío region and the north of Mexico

Presencia de comorbilidades y su asociación a la resistencia antimicrobiana de tuberculosis, en un centro de referencia nacional en la región del Bajío y norte de México

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ABSTRACT. Introduction: although tuberculosis is preventable and curable, this infection represents the leading cause of death from a single infectious agent. The interruption of public health services caused by the COVID-19 pandemic globally reversed the gradual progress that had been achieved in reducing mortality and the incidence of drug-resistant tuberculosis has not been completely determined. **Objective:** to determine the presence of comorbidities and their association with antimicrobial resistance in tuberculosis in 2022. **Material and methods:** a total of 480 cases diagnosed through molecular diagnosis (PCR), microbiological culture, M. tuberculosis isolation, and drug susceptibility testing, reported by UIBMZ-IMSS in the epidemiological surveillance laboratory during the period from January to December 2022. **Results:** a total of 480 tuberculosis cases diagnosed in Mexico in 2022 were analyzed, with 46.88% showing antimicrobial resistance. The most common resistance was to streptomycin (11.67%), followed by pyrazinamide (6.46%), while resistance to isoniazid and ethambutol was lower. It was found that 5.63% of the cases showed resistance to more than three drugs. Resistant tuberculosis was associated with comorbidities such as immunosuppression and drug use. **Conclusions:** the present study emphasizes the need to adjust health policies to control drug-

RESUMEN. Introducción: aunque la tuberculosis es prevenible y generalmente curable, esta infección representa la primera causa de muerte por un solo agente infeccioso. La interrupción de los servicios de salud pública causada por la pandemia de COVID-19 revirtió en el mundo los avances graduales que se habían logrado en la reducción de la mortalidad y la incidencia de tuberculosis farmacorresistente, causando estragos que a la fecha no se han determinado completamente. **Objetivo:** determinar la presencia de comorbilidades y su asociación con la resistencia antimicrobiana de tuberculosis en 2022. **Material y métodos:** un total de 480 casos diagnosticados a través de diagnóstico molecular, mediante cultivo microbiológico, aislamiento de *M. tuberculosis* y prueba de susceptibilidad a fármacos, emitido por la Unidad de Investigación Biomédica de Zacatecas perteneciente al Instituto Mexicano del Seguro Social en el laboratorio de vigilancia epidemiológica durante el período de enero a diciembre de 2022. **Resultados:** se analizaron 480 casos diagnosticados con tuberculosis en México en el año 2022, mostrando resistencia antimicrobiana 46.88%. La resistencia más común fue a la estreptomicina (11.67%), seguida de la pirazinamida (6.46%), mientras que la resistencia a la isoniazida y etambutol fue menor. Se encontró que 5.63% de los casos muestra resistencia a más de tres fármacos. La tuberculosis resistente está asociada con comorbilidades como la inmunosupresión

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resistant tuberculosis, focused on vulnerable populations, mainly immunosuppressed people, or people with addictions.

Keywords: tuberculosis, incidence, *Mycobacterium tuberculosis*, multidrug-resistance, comorbidity.

y el consumo de drogas. **Conclusiones:** el presente estudio enfatiza la necesidad de ajustar las políticas de salud para el control de la tuberculosis farmacorresistente, enfocado en poblaciones vulnerables, principalmente en personas inmunosuprimidas o con adicciones.

Palabras clave: tuberculosis, incidencia, *Mycobacterium tuberculosis*, multidrogorresistencia, comorbilidad.

Abbreviations:

95%CI = 95% Confidence Interval.
IMSS = *Instituto Mexicano del Seguro Social*.
WHO = World Health Organization.
RR = Relative risk.
TB = Tuberculosis.
DR-TB = Drug-resistant tuberculosis.
HIV = Human immunodeficiency virus.

INTRODUCTION

Tuberculosis (TB) is a disease caused by the bacillus *Mycobacterium tuberculosis*. The infection is transmitted almost exclusively through the air, through the inhalation of aerosols generated when a person with active lung disease speaks, coughs, or sneezes. It has been estimated that about a quarter of the world's population is infected by the bacillus in a latent state. It is important to highlight that people infected with the bacillus have a 5-10% chance of becoming ill with TB throughout their life. This risk is increased in people with compromised immune systems, as occurs in cases of human immunodeficiency virus (HIV) infection, diabetes *mellitus*, or in users of tobacco and other drugs.[1] Although TB is preventable and generally curable, this infection represents the first cause of death due to a single infectious agent, causing more than one million deaths and more than 10 million new cases reported by the World Health Organization (WHO) each year.[2]

As a result of the recent COVID-19 pandemic, coupled with the ongoing challenges facing the global health sector, the WHO reported a global reduction of -18% in the number of patients diagnosed with active TB during 2020 compared to 2019, which appears to be due to a lack of funding for TB prevention, diagnosis, and treatment services.[3] In Mexico, the observed reduction in the number of new cases was -22.9% in 2020, with a partial recovery of -9.4% in 2021. This ultimately leads to an increase in deaths, transmission of the infection, and, over time, an increase in the number of patients.[4]

On the other hand, the constant increase in drug resistance has emerged as a significant challenge in recent decades. People with drug-resistant tuberculosis (DR-TB) require treatment with regimens that include second-line drugs such as bedaquiline and fluoroquinolones. The WHO recommends different regimens for rifampicin - single-resistant tuberculosis (RR-TB) or multidrug-resistant tuberculosis (DR-TB, defined as resistance to both rifampicin and isoniazid) and XDR-TB (resistance to rifampicin, any fluoroquinolone, and at least one of bedaquiline or linezolid).[5] Globally, a 15% reduction in the number of people starting treatment for drug-resistant TB was reported during the COVID-19 pandemic.[3] This decline can be attributed to several factors, such as the disruption of health services, the diversion of resources to the COVID-19 response, and mobility restrictions that affected access to health centers.

Therefore, it is essential to conduct targeted epidemiological studies on TB resistance in order to determine the observed local and national impact of the increase in FRTB cases and to demonstrate epidemiological changes following the COVID-19 epidemic.

MATERIAL AND METHODS

This observational, descriptive, and retrospective study was conducted at the Unidad de Investigaciones Biomédica-Zacatecas (UIBMZ) of the Instituto Mexicano del Seguro Social (IMSS) through the diagnostic and epidemiological surveillance program. From a database of 1,900 samples received by the Epidemiological Surveillance Service, 480 cases with primary TB confirmed by molecular diagnosis (PCR) using GeneXpert MTB/RIF™ and microbiological culture on solid Lowenstein-Jensen medium were selected, excluding those that did not present positivity.

Phenotypic susceptibility testing for first-line drugs (rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin) was performed using a BD BACTEC™ MGIT™ 960, following the supplier's instructions. The results were subsequently issued by the UIBMZ-IMSS epidemiological surveillance laboratory. The cases analyzed during the period from January to December 2022 came from various states in Mexico and all corresponded to patients with IMSS benefits. The protocol was approved by the IMSS National Ethics Committee under registration number R-2024-785-014.

Sociodemographic data and the presence of comorbidities, including type II diabetes *mellitus*, HIV, neoplasia, immunosuppression (derived from transplants, use of interferon inhibitors and immunosuppressants), drug use such as alcoholism, smoking, and other substances

(referred to by the physician as recreational substances), were collected as described in the patients' medical records and finally analyzed using SPSS version 24 statistical *software*. Variables were summarized by determining absolute and relative frequencies, which were used as summary measures for analysis and presentation of results. Relative risk (RR) was calculated with its confidence intervals (CI) using Pearson's χ^2 test and Fisher's exact test. Finally, statistical significance was established for p values less than or equal to 0.05.

RESULTS

Total diagnosed cases

The study included a total of 480 individuals diagnosed with TB, of which 37.2% (n = 179) were women and 62.7% (n = 301) were men. Furthermore, the age of the participants was analyzed separately for men and women. In men, the average age was 47.7 ± 17.04 years. On the other hand, the average age of women was 42.98 ± 16.98 years. The distribution of the sample by age and sex is presented in *Table 1*. Finally, the age ranges were categorized as follows: 0-4 years, 5-14 years, 15-24 years, 25-44 years, 45-64 years, and ≥ 65 years. The absolute number of participants is presented for each range. The majority of individuals were between the ages of 45 and 64, representing 43.12% of the total population (n = 207). The specific distribution by sex and age range was as follows: the highest number of women with TB was found in the age range of 25 and 44, representing 35.19% of the sample of female patients with TB (n = 63). The lowest representation was observed in the 5 and 14 age group, excluding younger ages, with 0.55% of the sample of female patients (n = 1). Similarly, the highest number of men with TB was found in the age range of 45 and 64, representing 48.83% of the sample of male patients (n = 147). The lowest representation of these groups was the 5 and 14 age group, representing 0.33% of the sample (n = 1), excluding unrepresented groups. The distribution of the sample according to age range and sex is presented in *Figure 1*.

Table 1: Distribution of study participants by age and sex (N = 480).

Sex, n (%)	
Male	301 (62.7)
Female	179 (37.2)
Edad (años), media ± DE	
Male	47.70 ± 17.04
Female	42.98 ± 16.98

SD = standard deviation.

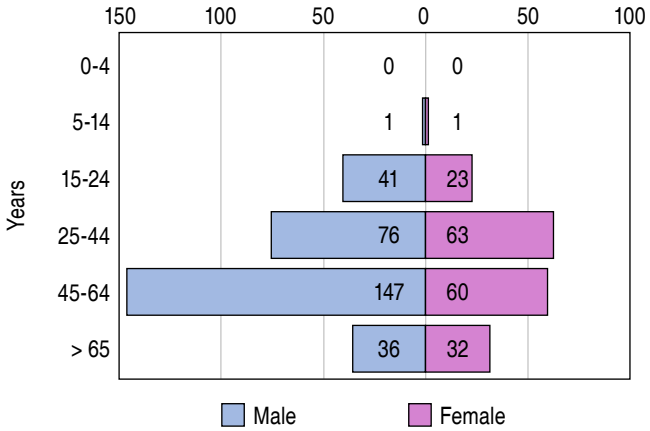

Figure 1: Distribution of diagnosed tuberculosis cases by age group and sex in 2022 (N = 480).

Prevalence of tuberculosis cases

The distribution of cases diagnosed by the tuberculosis epidemiological surveillance laboratory in 2022 shows a marked concentration in Nuevo León, which reported 316 of the 480 total cases, representing 66% of the total reported. Other states with relevant prevalence include Tamaulipas, Veracruz, and San Luis Potosí, with 45, 25, and 23 cases, respectively. Most of the remaining states report fewer than 10 cases, indicating a lower prevalence of cases reported by the unit. States such as Baja California, Campeche, Chiapas, Coahuila, Mexico City, Jalisco, Michoacán, Oaxaca, Quintana Roo, Yucatán, and Zacatecas report between two and 10 cases each. States such as Baja California Sur, Chiapas, Sonora, Nayarit, Puebla, Sinaloa, and Tabasco only reported one to two cases of the total evaluated at the UIBMZ-IMSS *(Figure 2A)*.

Distribution of DR-TB cases in Mexico in 2022

Of the total diagnosed TB cases, 225 (46.88%) were resistant to anti-TB drugs. The geographic distribution of these resistant cases showed a notable concentration in certain states. According to the data analyzed, the state of Nuevo León has the highest number of cases, with a total of 154, representing a considerable concentration of the disease burden in this region. In contrast, most states report considerably lower numbers of cases. Tamaulipas (17 cases) and San Luis Potosí (16 cases) are the states with the highest number of reports, followed by Veracruz and Zacatecas, both with six cases each. Other states such as Jalisco and Michoacán reported four cases each, while Mexico City recorded three cases. States such as Coahuila and Oaxaca recorded two cases each. Finally, the states of Baja California, Baja California Sur, Campeche, Chiapas, Quintana Roo,

and Yucatán have only one reported case. Sonora, Nayarit, Puebla, Sinaloa, and Tabasco reported TB cases overall, but no cases of drug-resistant TB were recorded. It is important to note that data on the incidence of drug-resistant TB are not available in other states in the country *(Figure 2B)*.

These results suggest that drug-resistant TB affects the entire country; however, in the present study, we can only make inferences about those who send samples to the UIBMZ/LAVE-IMSS. *Figure 2C* presents the distribution of total and drug-resistant cases in different states of Mexico, along with the percentage of drug-resistant cases in each state.

Percentage of DR-TB cases during 2022

Streptomycin resistance has a resistance rate of 11.67%, indicating that a considerable percentage of TB strains in the country are resistant to this key drug. Pyrazinamide resistance shows a relatively high resistance rate of 6.46%, suggesting a significant prevalence of strains resistant to this essential drug in the initial phase of treatment. On the other hand, the resistance rates to isoniazid and ethambutol were 3.96 and 0.83%, respectively, while resistance to rifampin was 0.83%. Analyzing drug combinations, resistance to rifampin in combination with streptomycin is 4.38%, to pyrazinamide 0.42%, and to isoniazid 2.91%. Combinations with isoniazid show a resistance rate of 3.75% with streptomycin. Finally, 5.63% of cases show resistance to more than three drugs, the most common drug being rifampicin with 2.5% of the total representation, which is substituted as a marker of DR-TB *(Figure 3)*.

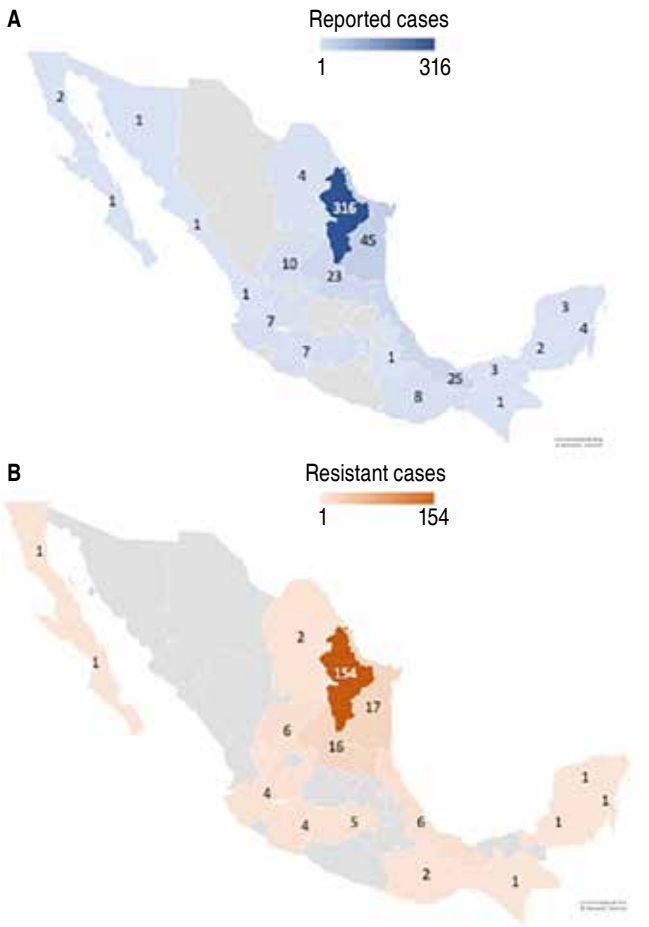

Figure 2: Distribution of total and resistant cases by state in 2022. The map shows the total number of cases per state. **A)** Number of cases with reported antimicrobial resistance. **B)** The gray areas indicate states for which data are unavailable (N = 480). **C)** The percentage of treatment-resistant cases in various states of Mexico.

C

	Cases	
State	Total	Resistant n (%)
Baja California	2	1 (50.00)
Baja California Sur	1	1 (100.00)
Campeche	2	1 (50.00)
Chiapas	1	1 (100.00)
Coahuila	4	2 (50.00)
CDMX	4	3 (75.00)
Jalisco	7	4 (57.14)
Mexico	11	5 (45.45)
Michoacán	7	4 (57.14)
Nuevo León	316	154 (48.73)
Oaxaca	8	2 (25.00)
Quintana Roo	4	1 (25.00)
San Luis Potosí	23	16 (69.57)
Tamaulipas	45	17 (37.78)
Veracruz	25	6 (24.00)
Yucatan	3	1 (33.33)
Zacatecas	10	6 (60.00)
Sonora	1	0 (0.00)
Nayarit	1	0 (0.00)
Puebla	1	0 (0.00)
Sinaloa	1	0 (0.00)
Tabasco	3	0 (0.00)

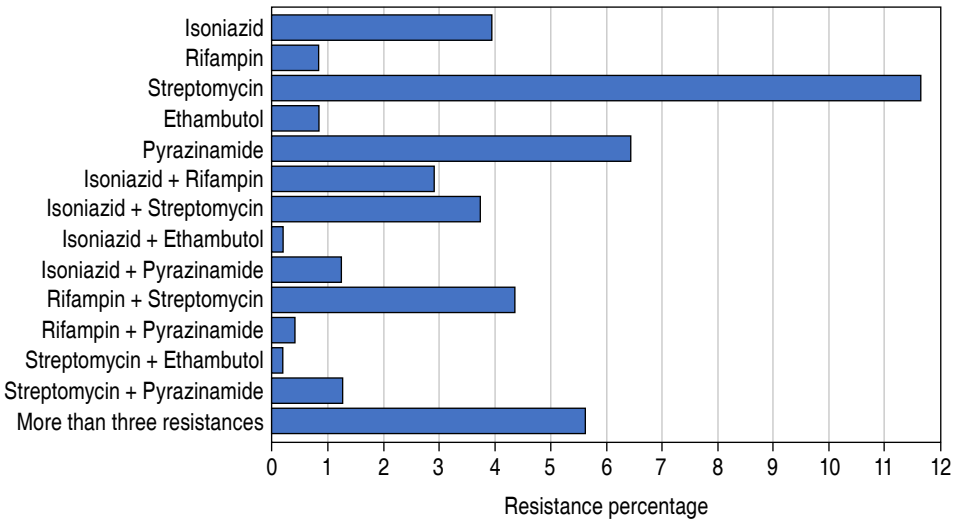

Figure 3:

Percentage distribution of resistance to anti-tuberculosis drugs and drug combinations in tuberculosis cases reported in Mexico during 2022. The figure shows the proportion of resistance to different anti-tuberculosis drugs and their combinations, each segment represents the percentage of resistance to a specific drug or drug combinations.

Prevalence of comorbidities

In this study, the frequency of various comorbidities in patients with TB resistant and sensitive to anti-tuberculosis drugs was evaluated. RR with 95%CI was calculated to compare the prevalence of each comorbidity between both groups as shown in *Table 2*. Most of the comorbidities evaluated were more frequent among cases of resistant TB compared to sensitive cases. In the case of HIV, it was observed that 2.86% of patients with drug-resistant TB also had this infection, compared to 1.86% of sensitive patients. The RR calculated for HIV was 1.553 (95% CI 0.453-4.509), suggesting that HIV infection is more common among patients with resistant TB, although the difference was not statistically significant. Diabetes was another common comorbidity in this study, present in 24.76% of drug-resistant patients and 18.59% of drug-sensitive patients. The RR for diabetes was 1.332 (95% CI 0.945-1.875), indicating that diabetes is common among patients with drug-resistant TB, although the difference was not significant. Regarding malnutrition, 7.14% of drug-resistant TB patients presented this comorbidity, compared with 7.06% of drug-sensitive patients. The RR of 1.015 (95% CI 0.533-1.925) suggests that malnutrition is equally common in both groups, with no notable difference in prevalence. Regarding neoplasia, only 0.48% of drug-resistant patients and 0.74% of drug-sensitive patients were diagnosed with this condition. The calculated RR was 0.642 (95% CI 0.084-4.875), indicating a lower prevalence of malignancies in patients with drug-resistant TB, although this difference was not statistically significant. Immunosuppression showed a more marked difference between the two groups. It was observed that 4.76% of patients with resistant TB also had some degree of immunosuppression, compared to only 1.49% of susceptible patients, with an RR of 3.214 (95% CI 1.083-9.581). This suggests that immunosuppressed patients are more than three times more likely to develop drug-resistant TB compared to those who are not immunosuppressed. This may imply that immunosuppression is a significant risk factor for TB resistance. Alcoholism was a relatively common comorbidity, present in 13.81% of resistant patients and 14.50% of susceptible patients. The calculated RR was 0.956 (95% CI 0.613-1.484), suggesting that alcoholism was equally prevalent in both groups. Smoking was observed in 15.24% of patients with DR-TB and 13.01% of patients with sensitive TB. The RR of 1.207 (95% CI 0.732-2.043) indicates a slightly higher prevalence of smoking among patients with resistant TB. Finally, the use of other drugs showed a significant difference between the groups; 6.67% of patients with drug-resistant TB also reported use of other drugs, compared to only 2.23% of sensitive patients. The RR of 3.000 (95% CI 1.213-7.449) suggests that the use of other drugs is considerably more common among patients with drug-resistant TB, which could indicate an additional risk factor for the development of resistance to anti-TB drugs. The analysis reveals comorbidities, such as immunosuppression and use of other drugs, are significantly more frequent in patients with drug-resistant TB, which could have important implications for the clinical management and treatment strategies of these patients. As shown in *Table 2*, comorbidity analysis revealed that immunosuppression and use of other drugs are significantly associated with an increased risk of drug-resistant TB, with a RR of 3.214 (95% CI 1.083-9.581, $p = 0.05$) and 3.00 (95% CI 1.213-7.449, $p = 0.0203$), respectively. These associations suggest that immunosuppressed patients and those who use drugs should be considered at high risk for developing resistance to anti-tuberculosis treatment.

DISCUSSION

The disruption of public health services caused by the COVID-19 pandemic reversed the gradual progress made globally in reducing TB mortality and incidence, causing havoc that has yet to be fully determined. According to results reported by the Instituto Nacional de Salud Pública, Mexico saw a 23% decrease in diagnoses in 2022 compared to the average of the previous five years, and a 42% decrease in mortality, suggesting an underestimation of actual cases.[6] Other determinants, such as timely treatment, have been disrupted, as suggested in the WHO's global tuberculosis report. This document reported that treatment coverage in 2022 was only 58%, compared to 70% in 2019, triggering the spread of the disease and thus facilitating the development of antibiotic resistance.[1] In the present study, we found that 43.75% of the cases diagnosed during 2022 at the UIBMZ-IMSS showed resistance to a first-line drug. It is important to highlight that this value is well above that observed with the national average, which is around 3% of total diagnoses. This arrival bias could be due to the fact that the data collected belong to a laboratory specialized in the evaluation of the susceptibility profile, highlighting the need to implement this strategy nationally, since the lack of specific methodologies and knowledge of this service would provide an overview of the drug resistance situation in Mexico.[6]

It is important to note that the overrepresentation observed in Nuevo León is significant, given that Monterrey, being an urban center with a more developed healthcare system, may have better diagnostic capabilities and greater access to healthcare services, which could explain the higher representation of cases in this region.[7] In contrast, other states with high TB rates, such as Sinaloa and Baja California, may face significant challenges in TB identification and treatment. Populations in these states often face barriers to accessing healthcare services, such as lack of documentation, language, fear of arrest, mistrust, and/or access to the healthcare system.[8]

Table 2: Distribution of comorbidities according to resistance or sensitivity to anti-tuberculosis treatments.

	Resistant N = 210 n (%)	Sensitive N = 270 n (%)	RR (95% CI)	p
HIV				
Yes	6 (2.86)	6 (2.22)	1.54	0.469
No	204 (97.14)	264 (97.7)	(0.453-4.509)	
Diabetes				
Yes	52 (24.76)	51 (18.88)	1.33	0.115
No	158 (75.24)	219 (81.11)	(0.945-1.875)	
Malnutrition				
Yes	15 (7.14)	19 (7.06)	1.015	> 0.999
No	195 (92.86)	251 (93.31)	(0.533-1.925)	
Neoplasms				
Yes	1 (0.48)	2 (0.74)	0.6429	> 0.999
No	209 (99.52)	268 (99.63)	(0.084-4.875)	
Immunosuppression				
Yes	10 (4.76)	4 (1.49)	3.214	0.050
No	200 (95.24)	266 (98.88)	(1.083-9.581)	
Alcoholism				
Yes	29 (13.80)	39 (14.50)	0.9560	0.895
No	181 (86.20)	231 (85.87)	(0.613-1.484)	
Smoking				
Yes	32 (15.24)	35 (13.01)	1.207	0.508
No	178 (84.76)	235 (87.36)	(0.732-2.043)	
Other drugs				
Yes	14 (6.67)	6 (2.23)	3.000	0.020
No	196 (93.33)	264 (98.14)	(1.213-7.449)	

RR = relative risk. 95%CI = 95% confidence interval.
p values ≤ 0.05 are considered statistically significant.

These factors may result in underdiagnosis of the disease, since the diagnostic service is aimed exclusively at IMSS beneficiaries, and the study population is limited to this population.

It is essential to consider the influence of associated factors in the development of resistant TB, including comorbidities, socioeconomic and cultural factors.[9]

In perspective, it is necessary to improve the diagnosis and epidemiological surveillance of DR-TB in at-risk populations, adapting treatments to local resistance patterns. The need to focus on vulnerable populations, such as immunosuppressed individuals or those with drug addiction, with specialized care programs is emphasized. Furthermore, it is proposed to strengthen public policies to prioritize TB after the impact of the pandemic. It is also proposed to expand research into the genetic and environmental factors that influence drug resistance, in order to optimize control and treatment strategies.

CONCLUSION

The present study described that the relative risk of developing drug-resistant tuberculosis was mainly associated with the presence of immunosuppression resulting from the use of biological agents and recreational drug use.

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Open access protocol and classification of scientific literature on spirometry

Protocolo de acceso abierto y clasificación de la literatura científica sobre espirometría

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ABSTRACT. Health personnel who perform lung function tests must be well informed about specialized literature to use the equipment, interpret the results, and establish a diagnosis for monitoring lung diseases. Spirometry is the most widely used lung function test, which is why it is essencial to train technical and health personnel for its correct performance. The objective of this research is to create a protocol to organize and classify the technical and research literature on spirometry, allowing fast and efficient processing for both humans and machines. To achieve our objective, semantic annotations were made in 96 specialized documents on spirometry, with 99 tags categorized into seven key variables analyzed: type of document, access, topic, tests associated with spirometry, stage involved in performing spirometry, functional patterns and diseases studied through. These annotations are available online, are open access, semantic and interoperable, and can be processed by both humans and computers on a user-friendly platform (https://web.hypothes.is/). Due to the characteristics of the annotations, physicians and technicians who perform spirometry can interact with them and other users, thus promoting the analysis of key health information in an open and social manner, which can be useful for practice, research and teaching of pulmonology.

Keywords: data, hypothes.is, semantic web, spirometry.

RESUMEN. El personal de salud que realiza pruebas de función respiratoria debe estar informado sobre la literatura especializada para utilizar el equipo, interpretar los resultados y establecer un diagnóstico para el seguimiento de las enfermedades pulmonares. Dentro de estas pruebas, la espirometría es la que tiene una mayor difusión, por lo que es indispensable la capacitación del personal de salud para su correcta realización. El objetivo de esta investigación es crear un protocolo para organizar la literatura técnica y de investigación sobre espirometría, permitiendo un procesamiento rápido y eficiente, tanto para humanos como para máquinas. Se realizaron anotaciones semánticas en 96 documentos especializados sobre espirometría, con 99 etiquetas categorizadas en siete variables clave analizadas: tipo de documento, acceso, tema, pruebas asociadas a la espirometría, etapa implicada en la realización de la espirometría, patrones funcionales y enfermedades estudiadas. Estas anotaciones están disponibles en línea, son de acceso abierto, semánticas e interoperables, y pueden ser procesadas tanto por humanos, como por computadoras en una plataforma amigable (https://web.hypothes.is/). Por las características de las anotaciones, médicos y técnicos que realizan espirometrías pueden interactuar con ellas y otros usuarios, con lo que se fomenta el análisis de información clave en salud de manera abierta y social, lo que es de utilidad para la práctica, investigación y enseñanza de la neumología.

Palabras clave: datos, hypothes.is, web semántica, espirometría.

Abbreviations:

DLCO = Diffusing capacity of the lungs for carbon monoxide
RFT = Respiratory function tests

INTRODUCTION

Respiratory function tests (RFTs) are fundamental in the diagnosis and monitoring of diseases that affect the lungs,

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as they allow us to know the mechanical, ventilatory and gas exchange properties, as well as other markers of inflammation that are related to disease control.

Spirometry is one of the most far-reaching tests, with a history of more than 175 years.[1] This tool has been used to assess the health status and quality of life of individuals over time. Despite advances in technology and tools, automating these tests is impossible.Therefore, the training of technical and health personnel is essential for its correct implementation. Although the technical and interpretation standards are frequently updated and publicly available,[2,3] there are drawbacks in terms of training and updating information among the personnel who perform it, requiring continuous training programs to achieve an impact on the application of the test,[4] so exploring new ways of transmitting knowledge related to this test could be an option to promote the dissemination of spirometry.

Conventionally, the term spirometry is used to designate a type of RFT in which a forced maneuver is performed. Additionally, there is the term slow vital capacity, in both the lungs are completely filled from total lung capacity (TLC), but in the latter the expiration until emptying the lungs is at a slower rate. For the purposes of our study, we designated the term spirometry as a synonym for forced spirometry.

The report of a spirometry must contain the following elements: 1) anthropometric and patient identification data; 2) equation used for interpretation; 3) values obtained in the maneuvers, the best maneuver and its relationship with the prediction equation (with the lower limit of normal [LLN], z-score or percentage of that predicted); 4) graphs of the maneuvers performed; 5) quality of the maneuver; and 6) in case of performing a maneuver after the administration of a bronchodilator medication, the same data mentioned for the post-bronchodilator maneuver.[5]

Digital health research consists of collecting, organizing, annotating and analyzing digital information, mainly data and specialized literature. In this process, computer tools are used to perform specific functions, generate interoperability and automate processes. Among the most common tools are databases designed to structure and retrieve information;[6] bibliographic managers, which facilitate the task of managing references and citations;[7] alerts and feeds, which allow you to face the immediacy and overload of information by receiving news about updates;[8] and text mining tools,[9] big data, network analysis,[10] scientometrics and artificial intelligence, which enhance the analysis of information, both in natural language and in machine language.[11]

In addition, there are tools that work as bookmarks and annotations, allowing you to save the addresses of web pages and make notes in real time on them. In such a way that it is possible to put notes on all types of web pages with text, articles, books, images, videos, audios and data sets that are on the net.

When these annotations incorporate semantic web technology, they are called semantic annotators. The semantic web is a technology promoted by the World Wide Web Consortium (W3C),[12] that allows data of different types to be integrated, through the use of a standardized and interoperable format through links that are applied in the search for information, labeling and the design of knowledge maps.[13] The annotation facilitates the creation, exchange and analysis of the data generated from the contents of the pages, allowing their subsequent analysis, both quantitatively and qualitatively.[14]

Semantic annotation with open web applications such as hypothes.is has been implemented for projects of interest in biosciences such as the e-life journal,[15] *scibot*[16] and *sciscore*.[17] It has also been used in clinical[18] and pathological research,[19] with promising results.

Commonly, these topics of technological innovation are technical and complex, and little is published about them in Spanish. We are interested in disseminating and presenting them through attractive and interesting case studies, taking advantage of technologies accessible to all and open source tools.

The objective of this research is to generate a protocol to manage spirometry information in relation to four dimensions: equipment, procedure, results and disease. Through semantic annotations, we seek to gather and analyze key health information in an open, social, semantic and interoperable way, processable by both humans and computers. This approach will be valuable for research and teaching in our region.

MATERIAL AND METHODS

The literature handling procedure used in this RFT research (technique, interpretation and clinical utility) was divided into three stages. The first stage consisted of the retrieval of relevant literature. The second stage involved the annotation and curation of the scientific-technical literature. Finally, the third stage included the processing, analysis and visualization of the data obtained.

To locate the scientific-technical literature on spirometry, we consulted the official pages of bodies that certify the quality of RFT, such as the European Respiratory Society (ERS) and the American Thoracic Society (ATS). In addition, we are looking for manuals for equipment frequently marketed in Latin America.[20,21]

Key documents were selected as accurate and relevant examples from the bibliography, which served as a guide to identify other similar and related documents, an example is the following document:[2,3] https://hyp.is/go?url=https%2Ferj.ersjournals.com%2Fcontent%2F60%2F1%2F2101499&group=__world

Subsequently, the key terms used to design filters and specific queries that would facilitate the search for literature

Figure 1:

Example of an annotation generated in Hypothes.is for a document on spirometry.

in academic databases were identified. These terms included: «lung function test»[MeSH], «interpretation»[ti], «standard», «technical standard», «manual», «reference values». Five platforms were used to carry out the searches: Google Scholar, Europe PMC, Scielo, Lens and PubMed.

The inclusion criterion was based on the compilation of scientific-technical documents that explicitly address forced spirometry in humans,[22] which may be accompanied by other RFTs.[3] Five exclusion criteria were established for the documents: 1) those dealing with RFTs in animal models;[23] 2) those exploring experimental RFTs that were not standardized or performed in unusual environments;[24] 3) documents focused on mathematical models and equation calculations;[25] 4) documents that lacked variables necessary for analysis (see below); and 5) those documents that did not explicitly address RFTs, but focused only on related topics (such as principles of medical physiology, respiratory diseases, respiratory health, etc.), without addressing technical, theoretical, methodological or analytical aspects of the tests.[26-28]

Annotation and Healing

The second phase involved the exploration and annotation of the literature using Hypothes.is, a public platform and available at the link: https://hypothes.is/search?q=tag%3AAnotacionPFR+TipoDePrueba%2Fmesh%2FD002000%2FForcedSpirometry so that all the annotations of the documents were made in Hypothes.is,[29] a web resource annotator that facilitates the understanding of the information, the discussion and the generation of ideas. It is an open source tool that allows users to place text, underline, comment and add images or videos on the same web page, emulating the idea of «annotate on the edges of the pages of the book», with the advantage that the interactions made by the user can be shared in real time, being able to be analyzed by other users or processed by computers. In addition, the platform offers the option to report any annotation to moderators, who will review the reported annotation and determine if it violates community norms,[29] thus fostering a safe space for the dissemination of knowledge.

The annotation process

Annotation involves generating data associated with items to organize and classify them using labels *(Figure 1)*.

The variables studied covered aspects related to documents and RFT. Regarding the documents, variables such as the type of document, the type of access and the subject were considered. Regarding the RFT associated with spirometry, variables such as the type of test, the stage involved in its performance, the functional patterns and the diseases studied using spirometry were analyzed. The variables on the RFT were made consistent with four dimensions: equipment used to perform the test (spirometer), performance procedure, results displayed in the report and its relationship with the disease. Annotations

Table 1: Seven variables and 99 semantic tags used to analyzethe scientific-technical literature on spirometry on Hypothes.is.

Dimensions	Variables	Annotation
Equipment	Type of test (text)	Typeoftest/mesh/D002000/ForcedSpirometry Typeoftest/mesh/D008451/MaximalVoluntaryVentilation Typeoftest/mesh/D000089142/FractionalExhaledNitricOxideTesting Typeoftest/mesh/D010993/PlethysmographyWholeBody Typeoftest/mesh/D000072277/MaximalRespiratoryPressures Typeoftest/mesh/000070857/WalkTest Typeoftest/mesh/D011653/PulmonaryDiffusingCapacity Typeoftest/mesh/D000403/AirwayResistance Typeoftest/mesh/D001985/BronchialProvocationTests Typeoftest/mesh/D001784/BloodGasAnalysis
	Type of document (label)	spar/fabio/JournalArticle spar/fabio/ResearchPaper spar/fabio/Book spar/fabio/InstructionManual
	Type of access (label)	Open/access Closed/access
	Topic (text)	Topic/mesh/D012137/RespiratorySystem Topic/mesh/D058007/PhysiciansPrimaryCare Topic/mesh/D012890/Sleep Topic/mesh/D010372/Pediatrics Topic/mesh/D013909/Thorax Topic/mesh/D017216/Telemedicine Topic/mesh/D006666/HistoryOfMedicine Topic/mesh/D004389/DurableMedicalEquipment Topic/mesh/D001185/ArtificialIntelligence Topic/mesh/D012016/ReferenceValues Topic/mesh/D000086382/COVID19
Procedure	Test stage (text)	Teststage/Operational* Teststage/Standar* Teststage/Interpretation* Teststage/Clinic*
	Functional test pattern (Text)	FunctionalPattern/Obstruction* FunctionalPattern/PossibleRestriction* FunctionalPattern/MixedPossible* FunctionalPattern/Normal* FunctionalPattern/Bronchodilation* FunctionalPattern/NoBronchodilation* FunctionalPattern/SimpleRestriction* FunctionalPattern/ComplexRestriction* FunctionalPattern/MixedDisorder* FunctionalPattern/NormalVolumes* FunctionalPattern/Hyperinflation* FunctionalPattern/LargeLungs* FunctionalPattern/BloodFlowIncrease* FunctionalPattern/PulmonaryVascularAbnormality* FunctionalPattern/LostLocalizedVolume* FunctionalPattern/AlveolarCapillaryLoss* FunctionalPattern/NormalDiffusion* FunctionalPattern/NormalImpedance* FunctionalPattern/SmallAirwayObstruction* FunctionalPattern/TotalAirwayObstruction* FunctionalPattern/AlterationReactance*

Table 1 continues: Seven variables and 99 semantic tags used to analyzethe scientific-technical literature on spirometry on Hypothes.is.

Dimensions	Variables	Annotation
		FunctionalPattern/LowEosinophilicInflammation* FunctionalPattern/ModerateEosinophilicInflammation* FunctionalPattern/HighEosinophilicIn ammation* FunctionalPattern/NegativePCD* FunctionalPattern/PositivePCD* FunctionalPattern/MaximumNormalInspiration* FunctionalPattern/MaximumAlteredInspiration* FunctionalPattern/MaximumNormalExpiration* FunctionalPattern/MaximumAlteredExpiration* FunctionalPattern/PositiveBronchialChallenge* FunctionalPattern/NegativeBronchialChallenge* FunctionalPattern/Normoxemia* FunctionalPattern/Hypoxemia* FunctionalPattern/RespiratoryAcidosis* FunctionalPattern/MetabolicAcidosis* FunctionalPattern/RespiratoryAlkalosis* FunctionalPattern/MetabolicAlkalosis*
Disease	Disease (text)	Disease/mesh/D001249/Asthma Disease/mesh/D001987/Bronchiectasis Disease/mesh/D001991/Bronchitis Disease/mesh/D000086382/COVID19 Disease/mesh/D002925/PrimaryCiliaryDyskinesia Disease/mesh/D029424/ChronicObstructivePulmonaryDisease Disease/mesh/D017563/InterstitialLungDisease Disease/mesh/D003550/CysticFibrosis Disease/mesh/D001997/BronchopulmonaryDysplasia Disease/mesh/D009468/NeuromuscularDisease Disease/mesh/D017564/RadiationPneumonitis Disease/mesh/D011009/Pneumoconiosis Disease/mesh/D011649/PulmonaryAlveolarProteinosis Disease/mesh/D013121/SpinalCurvatures Disease/mesh/D012600/Scoliosis Disease/mesh/D054990/IdiopathicPulmonaryFibrosis Disease/mesh/D000081029/PulmonaryArterialHypertension Disease/mesh/D006469/Hemoptysis Disease/mesh/D011655/PulmonaryEmbolism Disease/mesh/D012891/SleepApneaSyndrome Disease/mesh/D008175/LungNeoplasm Disease/mesh/D011656/PulmonaryEmphysema Disease/mesh/D011014/Pneumonia Disease/mesh/D014376/Tuberculosis Disease/mesh/D019896/Alfa1AntitripsinDeficiency Disease/mesh/D011015/PneumoniaAspiration Disease/mesh/D015615/CysticAdenomatoidMalformationLung Disease/mesh/D000092122/BronchiolitisObliteransSyndrome Disease/mesh/D012130/RespiratoryHypersensitivity Disease/mesh/D012829/Silicosis

*Originally in Spanish.

were designed using the project tag and the name of the variables. To classify the type of document, the FaBiO ontology was used,[30] while, for variables related to the type of test, the subject and the disease, the MeSH thesaurus was used *(Table 1)*.[31]

Processing, analysis and visualization

The Hypothes.is annotations were extracted in JSON and CSV format using two digital tools designed by Jon Udell: https://jonudell.info/h/tools.html and https://jonudell.

info/h/facet Subsequently, the data were processed programmatically in Bash, the analyses were carried out and the corresponding graphs were made in R. For this purpose, the readr, dplyr, ggplot2, RColorBrewer and Viridis packages were used, which are available for the generation of graphs and the analysis of results.

In addition, a repository was created on GitHub https://github.com/lmichan/PFR with the details of this project and in which updates, data and the code used will be published. For images, we opted to use color palettes such as viridis_d32 to ensure accessibility for people with visual impairment (color blindness), and the rainbow color palette was reserved for cases where multiple variables were present.

RESULTS

96 documents were analyzed, retrieved and annotated, these were labeled with the name of the project «AnnotationRFT» and with the text «TypeOfTest/mesh/D002000/ForcedSpirometry», in relation to the data generated from the seven variables and the 99 labels. These labels were made in a manner consistent with the four dimensions analyzed *(Table 1)*. The complete collection can be consulted openly and under the Creative Commons license at the following link: https://hypothes.is/search?q=tag%3AAnotacionPFR+TipoDePrueba%2Fmesh%2FD002000%2FForcedSpirometry

Of the annotations made, 78 documents (81.25%) were found to offer open access, while 18 documents (18.75%) required a subscription, 84 were research articles, four books, two manuals, two data repositories, two websites, a catalogue and a standard one.

The topics addressed in the papers were 13 in total, this provides insight into the use of spirometry currently and the perspective of how information is generated *(Figure 2)*. Respiratory system (25 articles), quality control (19 articles) and reference values (14 articles) were observed to be the three most frequent topics. The remaining topics such as COVID-19, health education, medical equipment, history of medicine, artificial intelligence, first contact doctors, neuromuscular, pediatrics, telemedicine and chest were distributed among the other ten topics analyzed.

The results of this analysis include 96 articles exclusively related to spirometry, among which nine other RFTs are also mentioned *(Figure 3)*. Where plethysmography, with 26 documents and the diffusing capacity of the lungs for carbon monoxide test (DLCO), with 25 documents, are the most mentioned tests; the bronchial challenge test that sometimes requires a forced spirometry maneuver was

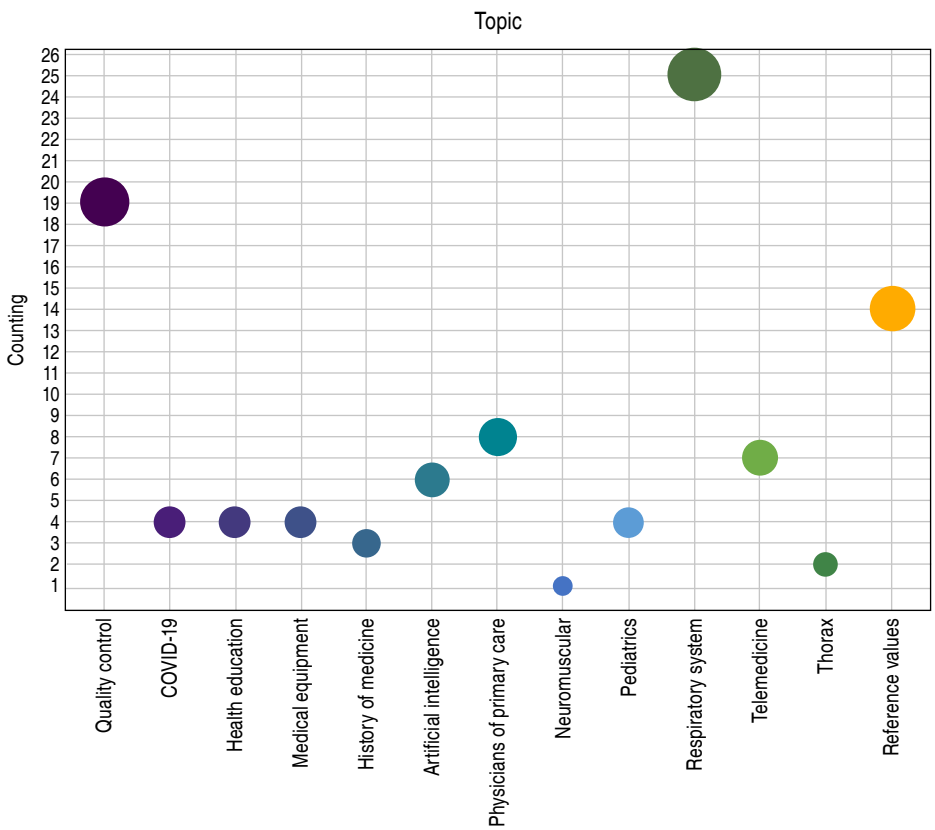

Figure 2:

Topics mentioned in the documents on spirometry.

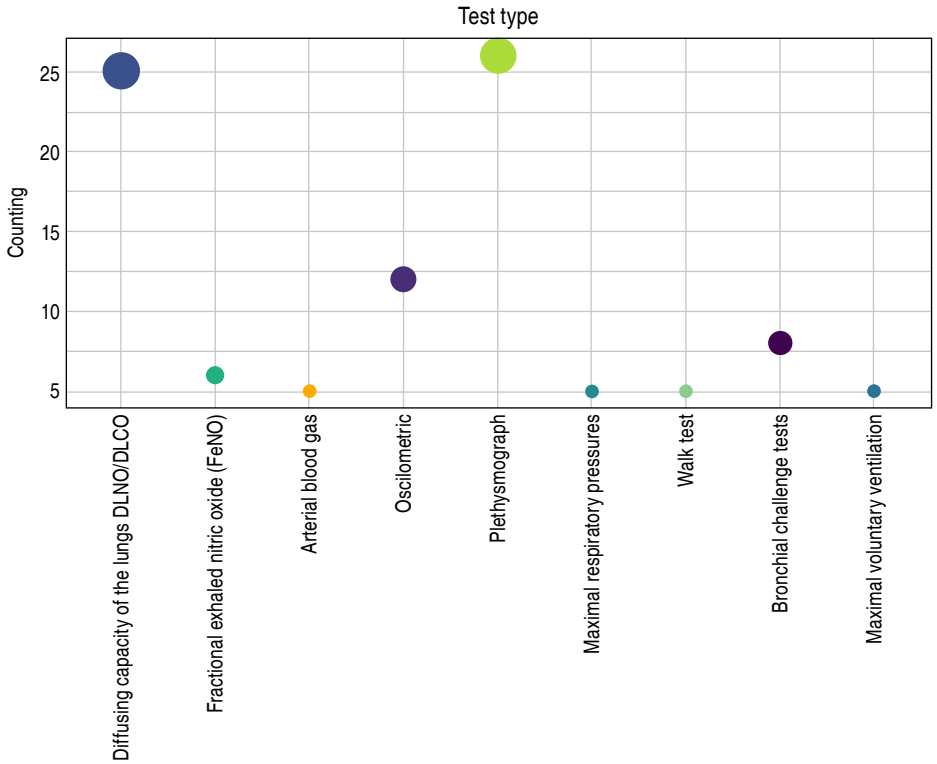

Figure 3:

Types of tests mentioned in spirometry documents.
DLCO = diffusing capacity of the lungs for carbon monoxide.
DLNO = diffusing capacity of the lungs for nitric oxide.

mentioned in eight documents. These results provide an overview of the most common and frequently mentioned respiratory function tests in the articles studied.

The functional patterns of spirometry were identified in 83 of the documents, in addition to other functional patterns of tests related to spirometry, coinciding plethysmography and DLCO patterns *(Figure 4)*.

To study what spirometry involves, we classified the documents according to the stage of the study, of which four were identified: 40 documents referring to interpretation, 19 that mention technical standards for performing the test, 19 in the operational stage that refers to technical and equipment aspects, and 14 in the clinical stage that were directly related to the use of the test in the disease.

The last variable evaluated for the documents was the relationship of spirometry with different diseases in the literature *(Figure 5)*. Asthma was the most common disease, mentioned in 41 papers, followed by chronic obstructive pulmonary disease (COPD), diffuse interstitial lung disease (IDPD), neuromuscular disease, cystic fibrosis, bronchitis, and spinal disorders.

DISCUSSION

In this research we created an annotation protocol to describe and analyze the scientific-technical documents on spirometry, this allowed us to integrate a large amount of information on 96 relevant texts, with 99 categorized labels to extract the information on four types of document, two types of access, 11 research topics, four stages involved in the performance of spirometry, 38 functional patterns and 30 associated diseases. All this data allowed us to know the structure and trends of this information, and from the label used for the project (AnnotationRFT), it is easy to locate it in a simple, accurate and efficient way so that it can be reused; thus avoiding information overload,[33] infodemia[34] and misinformation.[35]

The semantic annotations that are made in Hypothes. is allow you to take advantage of technology to interact with information, being able to extract the published data and process them by means of algorithms to generate new information.

This platform, which can be used in any area of knowledge, has previously been used in the area of health. In 2016, it worked for the registration of different research resources (reagents, materials and tools) used in scientific articles;[36,37] later Goller[38] and collaborators used it for the teaching of Goller metagenomics;[38] and recently Saleipour[39] and his team used it to annotate phenotypic variants and their genetic correlation in a rare disease of wide heterogeneity of presentation, Von Hippel-Lindau disease (VHL) Saleipour.[39]

The process of designing and structuring the annotations was detailed, long and meticulous, we had to carry out several tests to ensure consistency and define the correct protocol. In addition, annotations must be standardized

so that the retrieval of the generated data is relevant, consistent and processed correctly. To fulfill this purpose, we used systems of knowledge organization (SOC), a type of specification that facilitates the modeling of the structure of meaning implicit in an information domain, through the use of classes, labels, definitions, relationships and properties of concepts.[40-42] These tools were extremely useful in our research to annotate and structure data, they facilitated the search, interpretation, exchange and retrieval of digital content, in addition to facilitating the classification of the dimensions, categories and variables extracted from documents, as well as to visualize the scope, structure, hierarchy and semantic relationships of annotations, both manually and through algorithms. All this is summarized in *Table 1* and constitutes, together with the protocol, the most relevant methodological contribution of this article.

At present, access to scientific information and transparency in the knowledge generation process is very important, the accessibility and reproducibility of the results, both of the data and of the methods and results of a research must be openly available so that other researchers can access them, evaluate them and replicate the results.[43] Tools such as Hypothes.is encourage collaboration and the exchange of information between researchers, which promotes a faster and more effective advancement of scientific knowledge, the principles of open science also allow society in general to access information that is relevant and reliable.

As we are interested in practicing and promoting open science, we made sure that the information we generated was available to anyone, without the need to create an account. For this, all the annotations were made in the public group, in such a way that they can be seen by all interested parties and are reusable because they have an open license in the public domain.[44] We invite all specialists interested in spirometry and respiratory function tests to consult, reuse and make annotations to generate a greater set of information and knowledge on this important topic of pulmonology.

Limitations

The most important limitation of the protocol is that the analysis and selection of the documents was carried out only by a doctor with a high specialty in respiratory function; while the organization and processing of the data was in charge of specialists in the management of the information, this could limit the spectrum of the qualification of the articles and create a selection bias. However, we hope that, by making the invitation for cooperation with other specialists, better feedback can be generated from the selected documents, ideas can be shared, other documents

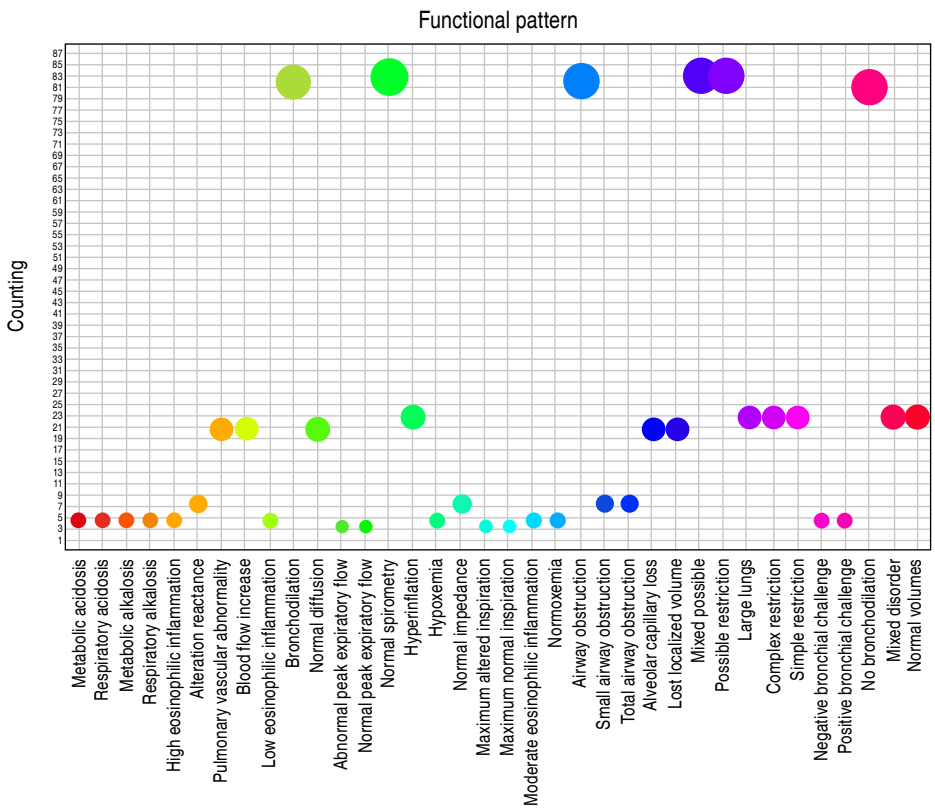

Figure 4:

Functional pattern mentioned in the documents on spirometry.

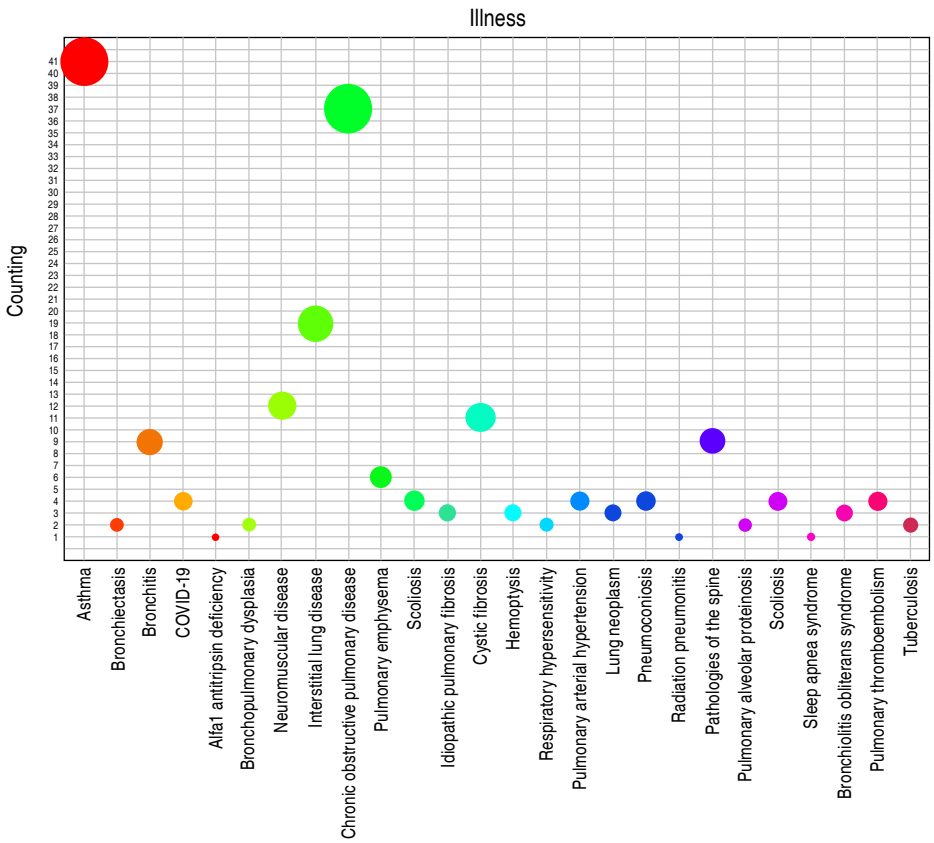

Figure 5:

Types of diseases mentioned in the documents on spirometry.

can be integrated into the compendium achieved to date, with the same approach for the realization, interpretation and teaching of the RFT.

Using the main tag, when in an open access format, anyone who has access to the Hypothes.is website can add information that, such as the translator's footnotes in a book, contribute more to the original text, with the advantage that this information can also be processed by computer systems, in order to promote not only research, but also the dissemination and teaching of this knowledge.

CONCLUSION

Semantic annotationson pages suchas Hypothes.is, allow the classification of documents focused on spirometry, so that other users can use them for educational and dissemination purposes of this respiratory function test.

Conflict of interests: the authors declare no conflict of interests.

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Empyema secondary to a septic embolus in a patient with septic cavernous sinus thrombosis: a case report and review of the literature

Empiema secundario a embolismo séptico en un paciente con trombosis del seno cavernoso: reporte de un caso y revisión de la literatura

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ABSTRACT. Septic cavernous sinus thrombosis is an unusual and fatal pathology that can develop as a result of infectious or non-infectious conditions. There are very few reports of septic pulmonary emboli secondary to septic cavernous sinus thrombosis. We describe a case of a 31-year-old female patient who was immunocompromised due to methylprednisolone intake, had chronic pansinusitis and developed fever, headache, facial pain, eyelid swelling and proptosis with ophthalmoplegia in the left eye, loss of visual acuity. Computed tomography revealed thrombosis of the cavernous sinus, blood, sinus and pleural cultures isolated *Streptococcus pneumoniae*. The computed axial tomography scan revealed a right multiloculated empyema and a cavitated nodule corresponding to an infectious process, highlighting the presence of multiple nodules scattered between both lungs, suggestive of septic pulmonary embolism. A multidisciplinary strategy was implemented and after discharge, the patient is under surveillance with adequate recovery. This peculiar case shows the importance of a multidisciplinary approach to the management of this rare entity. We have noted all kinds of scenarios and the basis for this is a timely diagnosis and avoidance of possible complications to prevent serious and permanent consequences.

Keywords: empyema, septic cavernous sinus thrombosis, septic embolism.

RESUMEN. La trombosis séptica del seno cavernoso es una patología inusual y mortal que puede desarrollarse como resultado de afecciones infecciosas o no infecciosas. Hay muy pocos informes de émbolos pulmonares sépticos secundarios a una trombosis séptica del seno cavernoso. Describimos el caso de una mujer de 31 años inmunocomprometida por la ingesta de metilprednisolona, contaba con pansinusitis crónica y desarrolló fiebre, cefalea, dolor facial, hinchazón de párpados y proptosis con oftalmoplejía en ojo izquierdo, pérdida de la agudeza visual. La tomografía axial computada reveló trombosis del seno cavernoso, en los cultivos de sangre, senos nasales y pleural se aisló *Streptococcus pneumoniae*. La tomografía axial computada reveló un empiema multiloculado derecho y un nódulo cavitado que corresponde a un proceso infeccioso, destacando la presencia de múltiples nódulos dispersos entre ambos pulmones, sugestivos de embolia pulmonar séptica. Se implementó una estrategia multidisciplinaria y luego del alta, la paciente se encuentra en vigilancia con adecuada recuperación. Este peculiar caso muestra la importancia del abordaje multidisciplinario para el manejo de esta rara entidad. Hemos notado todo tipo de escenarios y la base de ello es un diagnóstico oportuno y evitar posibles complicaciones para prevenir consecuencias graves y permanentes.

Palabras clave: empiema, trombosis del seno cavernoso, embolismo séptico.

Abbreviations:

CAT = computed axial tomography.
SCST = septic cavernous sinus thrombosis.

INTRODUCTION

Cavernous sinus septic thrombosis (SCST) is a rare and serious thrombophlebitic process arising from sinus infections and less common otogenic, odontogenic, and

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pharyngeal sources.[1] Fever, headache, periorbital edema, and ophthalmoplegia are some of the most common symptoms of SCST, and early identification is critical for a favorable outcome.[2]

The cornerstone is broad-spectrum parenteral antibiotic therapy, although surgery is reserved for intracranial processes and control of the underlying focus of infection.[3]

In this article we report a case of SCST complicated by pansinusitis and multiple pulmonary septic emboli in a 31-year-old woman leading to loculated empyema.

CASE PRESENTATION

A 31-year-old woman with a history of poorly controlled Graves-Basedow disease, schizophrenia, and chronic sinusitis. It is important to mention that the patient reports having been treated with methylprednisolone 500 mg three times a day for five days due to her Graves-Basedow treatment. Four days before admission to the emergency room, the patient began experiencing high fever, left-sided headache, facial pain, eyelid swelling, and proptosis with ophthalmoplegia in the left eye. She reports that the reason for admission was loss of visual acuity *(Figure 1)*.

Physical examination revealed vital signs within normal limits, and the patient exhibited no signs of pallor or jaundice. She was oriented to time, place, and person and spoke comprehensively. Ocular examination revealed marked swelling, redness, and ptosis of her right eyelid, accompanied by hemorrhagic conjunctival hyperemia and exophthalmos. She also reported blurred vision. She presented with limited extraocular movement due to pain on abduction and adduction, intraocular pressure of 13 mmHg, lagophthalmos of 5 mm, eyelid erythema, and telangiectasias. There were no signs of meningeal irritation or sepsis/septic shock. A review of the presenting symptoms leads to a series of differential diagnoses,

Figure 1: Case presentation photo.

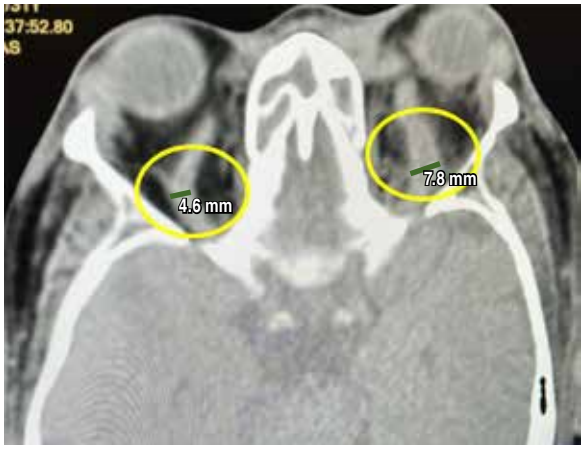

Figure 2: Computed tomography scan revealing bilateral superior ophthalmic vein thrombosis (yellow circles).

including, but not limited to, SCST, acute angle-closure glaucoma, subdural hematoma, subarachnoid hematoma, epidural and/or orbital infections. The most likely diagnosis was SCST due to the patient's history of chronic sinusitis and the immunodeficiency state secondary to the methylprednisolone overdose. It was also the most worrisome because of its higher probability of mortality and complications or disastrous outcomes.

A blood test showed a leukocytosis of 21.3 × 10^3/uL, with a slight shift to the left (92.5% neutrophils), elevated C-reactive protein of 27.8 mg/L, and D-dimer of 3.15 µg/mL. The platelet count and prothrombin time were within normal limits.

Orbital computed tomography (CT) showed chemosis, extraocular muscle thickening, ocular proptosis predominantly in the left eye, cellulitis and soft tissue edema. The right ophthalmic vein was enlarged to 4.6 mm and the left to 7.2 mm. The brain parenchyma was normal. A very marked pansinusitis was observed *(Figure 2)*.

Chest CT showed bilateral pulmonary nodules, multiloculated empyema was observed in the right hemithorax and a cavitated nodule in the left hemithorax, suggesting an infectious process *(Figure 3)*.

An MRI was ordered because it is the gold standard for diagnostic testing, but it was not performed for socioeconomic reasons. Two sets of blood cultures were performed and were positive for *Streptococcus pneumoniae*. Broad-spectrum antimicrobial treatment with ceftazidime and linezolid was initiated, along with low-molecular-weight heparin (LMWH), and was subsequently changed to enoxaparin. Transthoracic echocardiography showed no valvular involvement.

Due to marked pansinusitis, the patient was evaluated by the otorhinolaryngology service, endoscopic drainage of the ethmoid sinus was performed and cultures were taken, resulting in a positive result for *Streptococcus pneumoniae*.

The patient was also assessed by the thoracic surgery service for evacuation of multiloculated empyema, video-assisted thoracoscopic surgery transfusion (VATS), yielding 300 cm^3 of the locules and 2 mm visceral pleura. She maintained stable vital signs and did not develop complications, after 20 days in hospital she no longer had fever and the swelling in both eyes went down, she completed the antibiotic treatment, was discharged home and continues her follow-up as an outpatient *(Figure 4)*.

DISCUSSION

SCST is a rare, life-threatening thrombophlebitic process arising from sinus infections and less common otogenic, odontogenic, and pharyngeal sources. It can also result from severe injury or surgery, especially in the presence of thrombophilic disease.[3] In the pre-antibiotic era, it had a fatal prognosis, with a reported mortality rate of up to 80-100%; however, following the introduction of antibiotics and advances in diagnostic imaging, the incidence and morbidity and mortality rate have decreased to 30%.[3] Around 50% of patients have neurological sequelae, hence the importance of the disease and the need for early recognition, diagnosis and treatment.[4]

A variety of infectious organisms are capable of causing SCST, the vast majority of which are bacterial. *Staphylococcus aureus* is the most common pathogen (66%), followed by *Streptococcus species* (20%), oral anaerobic flora (10%), and gram-negative bacteria (5%). Fungal etiologies (*Aspergillus* and mucormycosis) of SCST are less common and usually arise in immunocompromised patients. Because SCST is so rare, statistics on its occurrence are scarce, so the incidence of SCST can be estimated at two to 13 cases per million per year, with a higher incidence in children.[1]

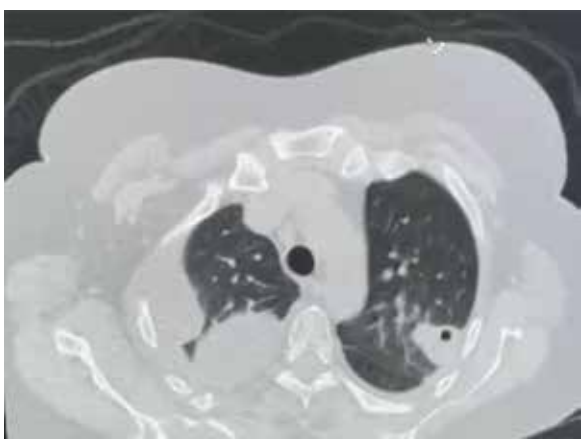

Figure 3: Chest scan demonstrating cavitary lung lesions and multiloculated empyema.

Figure 4: High photo.

Dural venous sinuses, blood can flow in either direction, allowing infectious agents to reach different parts of the brain and cause complications such as meningitis, dural empyema, or brain abscess. Most unilateral cavernous sinus infections eventually become bilateral due to communication between them via the intercavernous sinuses. Infection can also spread through the jugular vein to the pulmonary vasculature, resulting in septic emboli or abscesses, pneumonia, or empyema.[5] Most present with prominent acute features of sepsis, including tachycardia, vomiting, hypotension, confusion, and coma. Headache is present in 52-90% of cases.[3]

The ocular manifestations of SCST are the most universal features of this disease and result from obstruction of venous drainage from the orbit and dysfunction of the central nervous system traversing the cavernous sinuses, resulting in periorbital edema, ptosis, proptosis, chemosis, ophthalmoplegia, and vision loss.[3]

Chemosis, eyelid erythema, periorbital edema, and proptosis are most commonly seen (80-100% of cases), and symptoms present unilaterally at first, followed by bilateral progression within 24-48 hours of symptom onset.[3] Funduscopic examination reveals papilledema and/or retinal vein dilation in approximately two-thirds of patients; however, cloudy media may make visualization difficult in some cases with concurrent intraocular involvement.[3]

Thrombophlebitis associated with SCST may extend to the internal jugular vein, causing sore throat, neck mass/tenderness, anterior cervical lymphadenopathy, toothache or ear pain, dyspnea, hemoptysis, pleuritic chest pain, or trismus (Lemierre's syndrome).[3] Although ocular changes are the most common presenting symptoms and constitute a hallmark of this disease, other manifestations are common and will require appropriate treatment.

SCST can be complicated by intracranial processes such as meningitis, encephalitis, brain abscess, and subdural

empyema, as infection in the cavernous sinuses can spread through the valveless dural sinuses or the cerebral and emissary veins. In addition, infection can spread through the jugular vein to the pulmonary vasculature, causing lung abscesses, pneumonia, or empyema.[5]

Diagnosis is made on a clinical basis with appropriate radiologic imaging. Magnetic resonance imaging (MRI) is the most sensitive imaging modality (~95%) and has higher image resolution; however, contrast-enhanced CT may be preferable as it is easier to obtain, more cost-effective, and better able to identify the integrity of bony structures and/or the source of the underlying infection.[3]

There are no specific diagnostic laboratory tests for SCST; however, they may be useful in the evaluation of a patient with suspected SCST. The complete blood count is abnormal in most patients, and 90% demonstrate marked polymorphonuclear leukocytosis. Elevated levels of C-reactive protein, erythrocyte sedimentation rate, and D-dimer are also frequently observed.[3]

Due to the rarity of the disease, there are no randomized controlled trials (RCTs) to guide treatment.

Patient management, stabilization, acute resuscitation (including parenteral fluids and oxygen supplementation), and treatment of the underlying infection remain important first steps in all patients with suspected SCST.[5]

Parenteral antibiotics are the cornerstone of treatment and should be started immediately in all patients with SCST.

The initial empiric antibiotic regimen should include a third-generation cephalosporin, nafcillin, and metronidazole; however, if there is concern for methicillin-resistant *Staphylococcus aureus* (MRSA) or resistant strains of *Streptococcus pneumoniae*, then a regimen consisting of ceftriaxone, vancomycin, and metronidazole is preferred.[3]

Drainage of the cavernous sinus is rarely performed. Surgery, often performed endoscopically, is reserved for treatment of the primary site of infection; surgical procedures include sphenoidectomy, ethmoidectomy, maxillary antrostomy, mastoidectomy, craniotomy (for subdural empyema), orbital decompression, or ventricular shunt placement.[3]

The presence of a cavernous sinus thrombosis in our patient was an unexpected finding; this is the first time in the literature that a multiloculated empyema secondary to SCST has been reported in an immunocompromised patient. Morbidity and long-term sequelae remain high (50-75%) in patients who receive successful treatment for SCST, and the most common residual deficits observed in survivors include partial or complete vision loss (7-22%), cranial nerve palsy (predominantly III or VI), pituitary dysfunction, seizures, hemiparesis, facial disfigurement, and cortical vein thrombosis, with complete recovery achieved in less than 50% of cases.[3]

CONCLUSIONS

Cavernous sinus thrombosis remains a rare disease. Its rapid progression, high mortality rates, and potential for significant neurological disability in recovered patients require prompt diagnosis and treatment. This is the first case reported in the literature of multiloculated empyema secondary to SCST. We hope this case report can provide clinicians with insights into understanding SCST and, subsequently, lead to appropriate treatment of this disorder.

Conflict of interests: the authors declare no conflict of interests.

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