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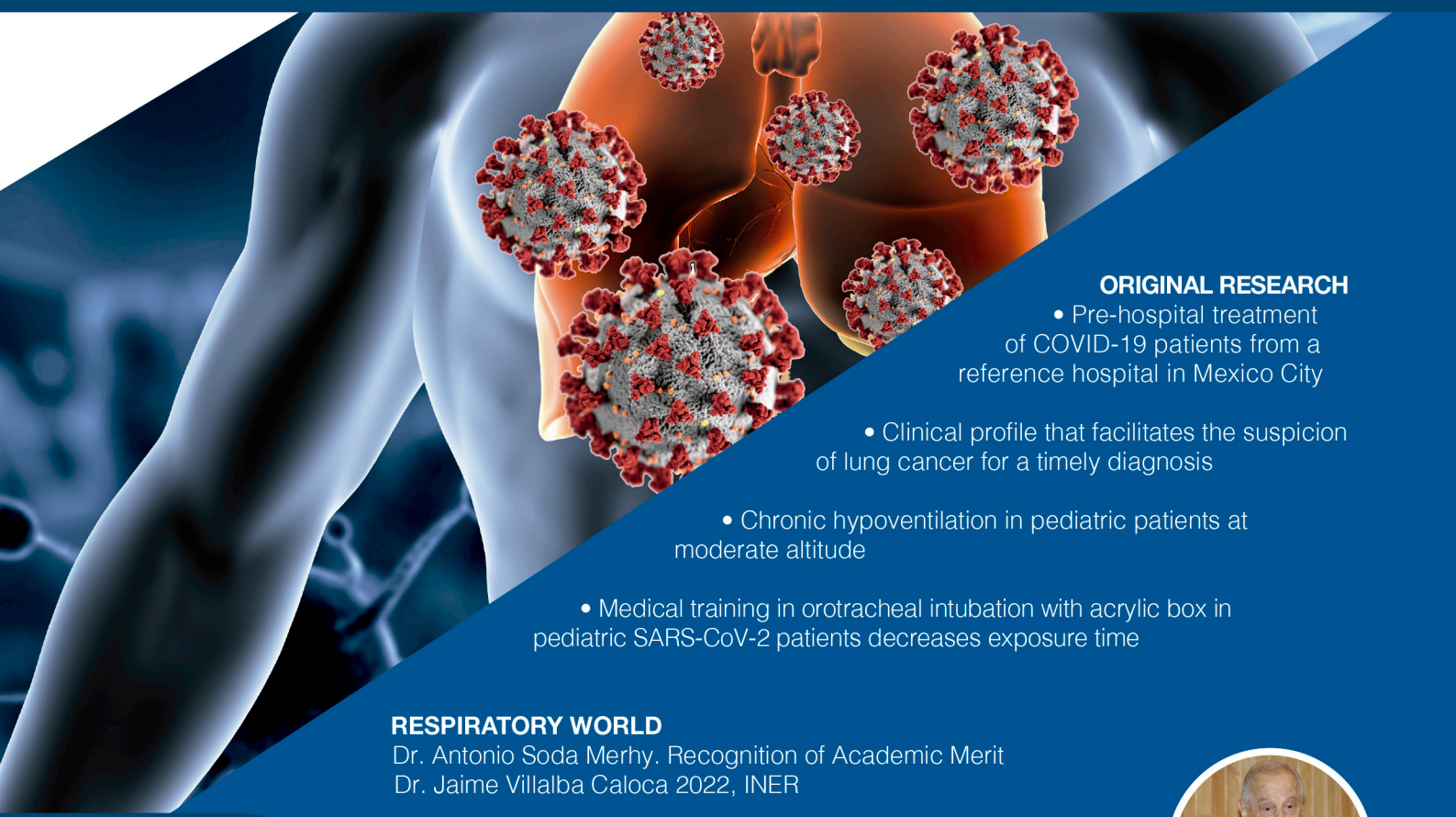
Outpatient treatment of COVID-19: a pending learning



ORIGINAL RESEARCH

- Pre-hospital treatment of COVID-19 patients from a reference hospital in Mexico City
- Clinical profile that facilitates the suspicion of lung cancer for a timely diagnosis
- Chronic hypoventilation in pediatric patients at moderate altitude
- Medical training in orotracheal intubation with acrylic box in pediatric SARS-CoV-2 patients decreases exposure time

RESPIRATORY WORLD

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Address correspondence to: Juan Carlos Vázquez García, Editor in Chief, Revista Neumología y Cirugía de Tórax, Oficina de Biblioteca y Editorial, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Calzada de Tlalpan 4502, Colonia Sección XVI. Mexico City, 14080, Telephone 55-5487-1700, ext. 5145.
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Contents

NCT
Neumología y Cirugía de Tórax

CONTENTS

Vol. 81 - No. 2 / April-June 2022

NCT
Neumología y Cirugía de Tórax

CONTENIDO

Vol. 81 - Núm. 2 / Abril-Junio 2022

Contents

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 2 / April-June 2022

Editorial
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Outpatient treatment of COVID-19: a pending learning

Tratamiento ambulatorio de COVID-19: un aprendizaje pendiente

Cristóbal Guadarrama-Pérez*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

The SARS-CoV-2 pandemic of 2020 made visible the great pending issues that are still pending in the Mexican Health System; without forgetting that Mexican specialized medicine has not stopped growing due to individual efforts or those of small groups housed in isolated institutions in the country such as medical centers, national health institutes and universities, achieving important contributions in some areas in an intermittent manner.

Today, we find a disjointed Health System, without clear guidelines in health policies. Preventive strategies are not a central governmental issue despite the costly and long pandemic suffered, we continue with lagging preventive programs without a clear definition of priorities. The first level health care centers have human resources with insufficient training, clinical laboratories with limited equipment, shortage of medicines and in most cases with high demand for care. During the COVID-19 health emergency, hospital units, both public and private, suffered the physical reconversion of areas; with health support personnel with little training for diagnosis, treatment and management of complications, the latter sometimes more serious than the infection itself due to the type of comorbidities of affected patients (elderly, obesity, diabetes, lung disease or chronic heart disease, etc.) that required intensive care units, which sometimes were not available or, in the best of cases, without the necessary equipment for their operation.

About 85 to 90% of those infected developed a mild to moderate disease; the vast majority were treated by physicians in private clinics or pharmacies, since most of them did not have social security and there was a great saturation of the public and private health system, otherwise, they could not have been treated. However, between 10 and 15% of those infected would develop a severe form of the disease, many of them not detected in time, with inadequate treatment, with a severe course of the disease and with complications (no less severe). Primary care physicians (private or pharmacy offices) did not have experience in the care of severe acute respiratory illnesses or treatment with very specialized drugs that required close monitoring during their use (such as anticoagulants, steroids, broad-spectrum antibiotics and handling of medical gases).

This issue publishes the article by Soriano-Hernández DC et al., *Tratamiento prehospitalario en COVID-19 atendidos en un hospital de referencia de la Ciudad de México*,[1] which describes that the most frequent comorbidities found in patients on admission were obesity (50.5%), followed by systemic arterial hypertension (36.6%) and diabetes mellitus (26.7%). Most cases received between four and five drugs as prehospital treatment; the most frequently prescribed drugs were corticosteroids and antibiotics. A mortality rate of 39% was reported due to some complication, while 55% of the patients were discharged due to improvement. In this context, patients arriving seriously ill to the emergency units had a history of being multitreated with long prescriptions (antibiotics, antivirals, steroids, NSAIDs, multivitamins) for several days. This sometimes affected the prognosis of patients due to the delay in hospital care, modifying the evolution of the disease and favoring co-infections by opportunistic germs (fungi, mycobacteria, etc.) and nosocomial infections once hospitalized (Pseudomonas, Acinetobacter and Stenotrophomonas), with an increase in days of hospitalization, mechanical ventilation and an impact on morbimortality and the cost of care.[2]

The therapeutic guidelines issued by the Ministry of Health in 2021 for the management of the pandemic in Mexico attempted to show clearer treatment guidelines based on the weight of scientific evidence levels up to

Correspondence:
Cristóbal Guadarrama-Pérez, MD
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas.
Mexico City, Mexico.
E-mail: cris.iner@gmail.com

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that time. In the world scientific literature there was too much information for and against several groups of drugs, leaving open the possibility of their use according to interpretation until better evidence was available.[3] The pandemic continues and others may emerge, so it is of utmost importance not to stop observing, analyzing and reflecting on how we can improve all the crucial points in the face of a health emergency of this size. It is important to continue strengthening our first level of care (community health centers, family medicine units and private clinics), in terms of their basic operating structure and with continuing medical education (dissemination of updated scientific knowledge). Likewise, it is necessary to improve the referral and counter-referral systems (rapprochement and coordination between levels of care) in order to avoid delaying the priority care of patients who require more specialized assessment and management. Finally, it is necessary to review the regulation and supervision of the operation of private clinics with records of patients treated in their communities.

The challenge continues and the reality is beyond us, so it is necessary to work together and organized at all levels of care and with all those who care for these patients.

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Original

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Pre-hospital treatment of COVID-19 patients from a reference hospital in Mexico City

Tratamiento prehospitalario en COVID-19 atendidos en un hospital de referencia de la Ciudad de México

Dulce Cinthia Soriano-Hernández,* Daniel Juárez-Carmona,* Yolanda González,* Laura Elena Carreto-Binaghi*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

D.C. Soriano-Hernández and D. Juárez-Carmona shared first author responsibilities.

ABSTRACT. Introduction and objective: more than a year after the emergence of COVID-19, many drug therapies have been considered, all based on a critical evaluation of the emerging literature. The main objective of our study was to know the pre-hospitalary treatment of patients with COVID-19. **Material and methods:** we reviewed 101 clinical records of hospitalized patients at the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas National (INER) diagnosed with COVID-19 during the second wave of the pandemic. A database was created, and descriptive statistics were performed using the software GraphPad Prism version 8. **Results:** the mean age of the patients was 52.3 (± 11.9) years. Patients received 4-5 medications as pre-hospital treatment; the most commonly prescribed medications were corticosteroids and antibiotics. **Conclusions:** COVID-19 patients received a large number of unnecessary medications during pre-hospital medical care; several of them were prescribed despite the lack of scientific evidence on their use and the national and international recommendations for treating the disease.

Keywords: COVID-19, SARS-CoV-2, pre-hospitalary treatment.

RESUMEN. Introducción y objetivo: a más de un año del surgimiento de la COVID-19, se han considerado muchas terapias farmacológicas, todas basadas en la evaluación crítica de la literatura emergente. El objetivo principal de nuestro estudio fue conocer el tratamiento prehospitalario de los pacientes con COVID-19. **Material y métodos:** se revisaron 101 expedientes clínicos de pacientes hospitalizados en el Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER) con diagnóstico de COVID-19 durante la segunda ola de la pandemia. Se conformó una base de datos y se realizó estadística descriptiva utilizando el programa GraphPad Prism versión 8. **Resultados:** el promedio de edad de los pacientes fue de 52.3 (± 11.9) años. Los pacientes recibieron de 4-5 medicamentos como tratamiento prehospitalario; los medicamentos que más se prescribieron fueron corticosteroides y antibióticos. **Conclusiones:** los pacientes con COVID-19 recibieron un gran número de medicamentos innecesarios durante la atención médica prehospitalaria; varios de ellos se prescribieron a pesar de la falta de evidencia científica sobre su uso y de las recomendaciones nacionales e internacionales para tratamiento de la enfermedad.

Palabras clave: COVID-19, SARS-CoV-2, tratamiento prehospitalario.

INTRODUCTION

SARS-CoV-2 disease (COVID-19) described in December 2019 resulted in a pandemic with a rapidly increasing incidence. More than two years after the emergence of COVID-19, many pharmacologic therapies have been considered for its treatment and it has been necessary to frequently update practices on their use based on a critical evaluation of the emerging literature. Practices related to the evaluation and treatment of COVID-19 during the first six months of the pandemic varied widely around the world. Depending on the severity of illness, supportive measures were adjusted: patients with mild disease usually recovered at home, with minimal care and isolation, while patients with moderate disease had to be monitored frequently, and sometimes hospitalized,[1] because they could progress to critical illness with hypoxemic respiratory failure and require prolonged ventilatory support.[2]

Initially, there was interest in the repositioning of drugs such as chloroquine and hydroxychloroquine,

Correspondence:
Laura Elena Carreto-Binaghi, MD
E-mail: lecarreto@iner.gob.mx

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sometimes accompanied by azithromycin, based on reports of randomized clinical trials with a small sample size.[3,4] Both drugs have been used in the treatment of autoimmune diseases due to their immunomodulatory effects and particularly for their action on proinflammatory cytokines, including interleukin-1 (IL-1) and IL-6.[5] Their use in COVID-19 was justified by the antiviral effects that these drugs exert in vitro against SARS-CoV-2 and, in association with azithromycin, it was suggested that they could reduce viral load.[3,4] In Mexico, on June 6, 2020, the «Recommendations for the treatment of infection by SARS-CoV-2, causative agent of COVID-19» were published, proposing the use of these drugs.[6] With the passage of time and the publication of international studies, it was observed that there was no beneficial effect of chloroquine or hydroxychloroquine in hospitalized patients with COVID-19.[7,8] The RECOVERY (Randomized Evaluation of COVID-19 Therapy) clinical trial showed that hydroxychloroquine did not decrease mortality in hospitalized patients compared to standard treatment (supportive care).[9] On December 23, 2020, the Infectious Diseases Society of America (IDSA) amended its guidelines to dismiss the use of hydroxychloroquine plus azithromycin as a strong recommendation, with evidence of moderate certainty.[10]

Glucocorticoids were also initially suggested due to concerns about the presence of a hyperinflammatory state that causes the severe manifestations of COVID-19, and other immunomodulatory therapies were also investigated. Several therapeutic interventions were proposed to mitigate the inflammatory organ injury in this viral pneumonia and the value of glucocorticoids was widely discussed.[11] A trial involving the use of a short course of methylprednisolone showed beneficial effect only in patients over 60 years of age with severe COVID-19; however, uncertainty remained about the use of glucocorticoids.[12] Later, the RECOVERY trial reported that dexamethasone reduced mortality among hospitalized patients with COVID-19, although the benefit was limited to patients receiving supplemental oxygen, being greatest among patients requiring mechanical ventilation.[13] In its September 2020 update, the IDSA added dexamethasone as a recommendation with moderate certainty evidence;[10] however, this drug did not improve the prognosis of patients who did not receive supplemental oxygen and could have undesirable effects; therefore, it is not recommended for the treatment of mild or moderate COVID-19.[1]

The use of ivermectin was evaluated empirically in uncontrolled studies for COVID-19,[14] and subsequently its use was not recommended outside the context of a clinical trial.[10] On March 31, 2021 the World Health Organization issued a warning on the inappropriate use of ivermectin for the treatment of COVID-19, considering the lack of scientific evidence about its efficacy and safety in the treatment of this disease.[15]

Antimicrobials have been overused during the COVID-19 pandemic. Some, such as doxycycline, because of the assumption that their intracellular effects could reduce viral replication, as well as prevent cell damage and expression of inflammatory molecules.[16] Others, such as macrolides, because of their potential immunomodulatory effect[17] that could counteract the exaggerated inflammatory process of COVID-19, have been used singly and in combination with other drugs.[4] Currently, antibiotics are only recommended when there is clinical and/or microbiological evidence of bacterial infection associated with SARS-CoV-2 pneumonia and short treatment regimens should be considered.[1]

Considering the clinical guidelines on the use of various drugs against COVID-19, the aim of this study was to describe the drugs that were indicated on an outpatient basis (prior to hospitalization) to patients seen at INER during the second upsurge of cases.

MATERIAL AND METHODS

The clinical records of 101 patients hospitalized at the *Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas* (INER) with a diagnosis of COVID-19 were reviewed, during the period from April to September 2021, when there was a spike in cases, according to information from the General Directorate of Epidemiology of Mexico. All patients who were admitted to INER, who signed the informed consent (patients or their relatives) and who had the complete file for review were included. Convenience sampling was performed.

Patient demographic data, pathologic history, days of evolution and symptoms of the disease and the outcome at hospital discharge were collected; a database was formed and descriptive statistics were performed using GraphPad Prism, version 8. The treatments that patients received on an outpatient basis (before hospitalization) were analyzed to determine whether there was an association with death or discharge due to patient improvement. Medications were separated by drug group and subsequently the Mann-Whitney U test (nonparametric) was performed to determine if there were differences between groups; a $p \leq 0.05$ was considered significant. The frequency of indication was also described, which refers to the number of times a drug was indicated, as some patients were prescribed the same drug on several different occasions during their evolution.

This project followed the ethical considerations mentioned in the declaration of Helsinki,[18] as last updated in Fortaleza, Brazil, and is part of protocol E08-20,

approved by the INER Ethics and Research Committee. The confidentiality of the patients' personal data was maintained.

RESULTS

Table 1 summarizes the demographic characteristics of the study population. Of the 101 patients studied, the mean age was 52.3 years (± 11.9); 55% of the patients were discharged due to improvement, while 39% died. Most patients had a history of obesity (50.5%), followed by systemic arterial hypertension (36.6%) and diabetes mellitus (26.7%). The average number of days spent in hospital was 10.9 days. Among the symptoms mainly reported by the patients or their relatives were fever (60.4%), myalgia (45.5%) and headache (40.6%). The respiratory symptom most frequently reported by patients or their relatives was dyspnea (83.2%); gastrointestinal symptoms were the least frequently reported, including diarrhea (9.9%), abdominal pain (3.0%) and vomiting (2.0%). On admission, patients had a mean oxygen saturation of 63% (± 18.4).

Table 2 shows the different drugs used for outpatient treatment of SARS-CoV-2 infection grouped according to the function of each type of drug, e.g., antibiotics, nonsteroidal anti-inflammatory drugs, etcetera. Some drugs were grouped under the name «airways», despite having different mechanisms of action, considering that their usefulness lies in improving the patient's ventilatory process. The table also shows the number of times each drug was prescribed and the number of patients in whom it was prescribed.

The patients received between four and five medications as prehospital treatment. The most frequently prescribed medications were corticosteroids and antibiotics. Dexamethasone was the most prescribed corticosteroid (47 patients); while, in the antibiotic group, azithromycin was found in first place (31 patients), followed by ceftriaxone (25 patients), levofloxacin (15 patients) and clarithromycin (11 patients).

Nonsteroidal anti-inflammatory drugs (NSAIDs) were the third most frequently prescribed group of drugs on an outpatient basis for the treatment of COVID-19; a total of 41 persons were prescribed paracetamol, while 20 were given ibuprofen. Antihistamines and anticoagulants were prescribed in a smaller proportion; enoxaparin was the anticoagulant with the highest frequency of indication (nine patients). The patients or their relatives also reported the prescription of bronchodilators, and four patients were also prescribed immunomodulators.

Table 1: Demographic characteristics of the population studied, N = 101.

	n (%)
Demographic characteristics	
Age*	52.3 ± 11.9
Body mass index (kg/m^2)	31.6 ± 6.1
Deaths	40 (39.6)
Discharges due to improvement	55 (54.5)
Transfer/voluntary discharges	1 (1.0)
Pathological history	
Obesity‡	51 (50.5)
Systemic arterial hypertension	37 (36.6)
Diabetes *mellitus*	27 (26.7)
Alcoholism	7 (6.9)
Pulmonary disease§	16 (15.8)
Heart disease¶	4 (4.0)
Kidney disease	2 (2.0)
Liver disease	1 (1.0)
Days of evolution*	10.9 ± 5
Symptoms	
Fever	61 (60.4)
Headache	41 (40.6)
Myalgias	46 (45.5)
Arthralgias	42 (41.6)
General condition attack	75 (74.3)
Dyspnea	83 (83.2)
Cough	52 (52.5)
Rhinorrhea	11 (10.9)
Odynophagia	31 (30.7)
Diarrhea	10 (9.9)
Abdominal pain	3 (3.0)
Hyporexia	16 (15.8)
Vomiting	2 (2.0)
Dysosmia	11 (10.9)
Oxygen saturation on admission*	63% (± 18.4)

* Mean ± standard deviation.
‡ Obesity was defined as body mass index > 30, according to the criteria established by the World Health Organization.
§ Four patients had chronic cough, four had chronic obstructive pulmonary disease, two had nonspecific interstitial pneumonia, two had interstitial disease, one had pulmonary fibrosis and one had asthma.
¶ All four patients had chronic heart failure.

DISCUSSION

The COVID-19 pandemic has generated difficulties in patient care, initially due to the lack of knowledge of the virus and the disease itself, as well as the sudden increase of cases in all countries, which sometimes exceeded the capacities of the different health systems in the world. Over time, treatment guidelines emerged based on recommendations from the countries that handled the first cases of this disease. Initially, these recommendations included drugs used in various viral infections and anti-inflammatory drugs in general, and later key points observed in severe patients, such as systemic inflammation and coagulation alterations, were considered.

Table 2: Medications indicated in the study population for outpatient management of SARS-CoV-2 infection, N = 101.

Drug	Frequency of indication	Number of patients, (%)
Antibiotics		
Azithromycin	31	31 (30.7)
Ceftriaxone	25	25 (24.7)
Levofloxacin	15	15 (14.9)
Clarithromycin	11	11 (10.9)
Amikacin, amoxicillin	4	7 (6.9)
Cefixime, cephalexin, moxifloxacin, penicillin, cefotaxime	2	10 (9.9)
Erythromycin, lincomycin, ciprofloxacin, nitrofurantoin, benzylpenicillin, ampicillin, ertapenem, clindamycin, norfloxacin, cefuroxime, cephalothin	1	8 (7.9)
NSAIDS		
Paracetamol	41	41 (40.6)
Ibuprofen	20	20 (19.8)
Aspirin	12	12 (11.9)
Metamizole	10	10 (9.9)
Naproxen	3	3 (2.9)
Meloxicam	2	2 (1.9)
Nimesulide, lysine clonixinate, serratiopeptidase, diclofenac	1	4 (3.9)
Airways		
Ambroxol	12	12 (11.9)
Acetylcysteine	5	5 (4.9)
Ipratropium bromide + salbutamol	4	4 (3.9)
Salbutamol	6	6 (5.9)
Doxofylline, bromhexine, dextromethorphan, levodropropizine, theophylline, benzonatate	1	6 (5.9)
Corticosteroids		
Dexamethasone	47	47 (46.5)
Prednisone	14	14 (13.8)
Budesonide/formoterol, budesonide/ipratropium bromide	4	8 (7.9)
Beclomethasone, betamethasone	3	7 (6.9)
Methylprednisolone	2	2 (1.9)
Deflazacort/salmeterol/fluticasone propionate, dexamethasone + ipratropium bromide/ salbutamol, fluticasone	1	3 (2.9)
Antihistamines		
Loratadine	3	3 (2.9)
Chlorphenamine	2	2 (1.9)
Anticoagulants		
Enoxaparin	9	9 (8.9)
Rivaroxaban	4	4 (3.9)
Apixaban	4	4 (3.9)
Heparin	3	3 (2.9)
Dabigatran	1	1 (0.9)
Clopidogrel	1	1 (0.9)
Antivirals		
Oseltamivir	18	18 (17.8)
Lopinavir/ritonavir	2	2 (1.9)
Amantadine, acyclovir, elvitegravir/cobicistat/emtricitabine/tenofovir	1	3 (2.9)
Immunomodulators		
Interferon beta, gamma globulin, pidotimod, tocilizumab	1	4 (3.9)

NSAIDs = non-steroidal anti-inflammatory drugs.

By the beginning of the second wave of the COVID-19 pandemic, sufficient information was already available regarding the effectiveness of some of the repositioning drugs for emergency use in the treatment of patients with COVID-19. Based on clinical studies, clinical practice guidelines were modified, ruling out the effectiveness of the use of chloroquine or hydroxychloroquine, the combination of hydroxychloroquine with azithromycin, and ivermectin.[10] Although the use of dexamethasone was found to reduce mortality in hospitalized patients with COVID-19, its usefulness was restricted only for patients requiring supplemental oxygen and/or mechanical ventilation.[13]

In this review, we evaluated the follow-up of recommendations in guidelines for the treatment of COVID-19, with a focus on prehospital primary care, and assessed whether there was a correlation with the outcome of patients seen at INER. It was observed that despite existing recommendations for the treatment of patients with COVID-19, dexamethasone and prednisone were prescribed in half of the patients during the primary care they received prior to admission to INER. Prescription of antibiotics without evidence of bacterial infection was also observed, with azithromycin being the most commonly used.

No differences in outcome were observed in patients who were prescribed steroids prior to hospitalization compared to those who were not. These results are consistent with Annane's review, where glucocorticoid use was not associated with an increased risk of bacterial infection or delayed viral clearance.[19]

An interesting fact we found in this study is that all types of medications were applied in patients who initially had a mild symptom picture and apparently did not prevent patients from developing a severe picture requiring hospitalization, considering that all of them were admitted to INER for medical care. However, one of the limitations of the study is the difficulty of analyzing the effect of prehospital treatment on hospital treatment and the outcome of the patients, considering that we found a large number of variables related to the amount and type of drugs used, as well as the variables of the individuals themselves, such as age, sex and presence of comorbidities, which together may contribute to the evolution of the disease.

CONCLUSIONS

Given the lack of a specific treatment against SARS-CoV-2 virus, and the variety of clinical manifestations, including the severity of the clinical picture, it is important to follow the recommendations of national and international health authorities, which are based on the most recently generated scientific evidence, and which consider different population groups for their development. The use of repositioning drugs has been a commonly used option in clinical practice. However, the lack of knowledge of the pathophysiology of the disease and the inability to predict the outcome of each patient should not be a reason to abuse unnecessary drugs, such as antibiotics, which involves other important problems in global public health, such as bacterial resistance. It is not advisable to exceed the use of other drugs that have proven useful in a specific group of patients, such as steroids, since their indiscriminate use could have unfavorable consequences on clinical outcome. Furthermore, the adverse effects of all drugs should be considered, especially when they are used in combination; their use should be prudent in patients with a disease that is still being studied worldwide.

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Clinical profile that facilitates the suspicion of lung cancer for a timely diagnosis

Perfil clínico que facilita la sospecha de cáncer de pulmón para un diagnóstico oportuno

Renata Báez-Saldaña,*‡ Alberto Vargas-Rojas,*‡ D. Yair Chavarría-Castro,*‡ Uriel Rumbo-Nava,* Belinda Contreras-Garza,*‡ Paulina Guinto-Ramírez,*‡ Óscar Arrieta§

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico; ‡Facultad de Medicina, Universidad Nacional Autónoma de México. Mexico City, Mexico; §Instituto Nacional de Cancerología. Mexico City, Mexico.

ABSTRACT. Introduction: lung cancer (LC) is usually diagnosed late. Understanding how patients present at the time of their diagnosis it is useful for early identification of the disease. **Objective:** to identify the clinical profile of patients with lung cancer, allowing to suspect the diagnosis and to propose an algorithm for early referral. **Material and methods:** prospective case series of lung cancer. The general characteristics, smoking, exposure to wood smoke, time from symptom onset to diagnosis and the type and frequency of symptoms were studied and their association with pleural effusion was analyzed. **Results:** the median age was 65 years, 55% were men. History of smoking 50.2%, exposure to wood smoke 43.9%. The median time from symptom onset to diagnosis was 120 days and in 94% it was more than 3 weeks. The most frequent symptoms were cough 88%, cough for 3 weeks or more 94.6%, dyspnea 75.2%, chest pain 50%, weight loss 70%, and hemoptysis 22%. Malignant pleural effusion 44.9%. Dyspnea, chest pain and oxygen saturation < 88% simultaneously were associated with pleural effusion OR (95% CI) 7.54 (3.28-17.34). **Conclusions:** adult patients who report cough for 3 weeks or more and/or any of the following symptoms: dyspnea, chest pain, weight loss, hemoptysis, or fatigue that are not explained by established diagnosis, should be evaluated by chest x-ray for early referral to a specialized unit.

Keywords: lung cancer, symptoms, diagnosis, pleural effusion, early diagnosis lung cancer.

RESUMEN. Introducción: el cáncer de pulmón (CP) por lo general se diagnostica tardíamente. El entendimiento de cómo se presentan los pacientes al momento de su diagnóstico es útil para la identificación temprana de la enfermedad. **Objetivo:** identificar el perfil clínico de pacientes con cáncer de pulmón que permita sospechar el diagnóstico y proponer un algoritmo para su referencia temprana. **Material y métodos:** serie de casos prospectiva de cáncer de pulmón. Se estudiaron las características generales, tabaquismo, exposición a humo de leña, tiempo desde el inicio de síntomas al diagnóstico, y el tipo y frecuencia de los síntomas y se analizó su asociación con derrame pleural. **Resultados:** la mediana de la edad fue 65 años, 55% fueron hombres. Antecedente de tabaquismo 50.2%, exposición a humo de leña 43.9%. La mediana del tiempo desde el inicio de síntomas al diagnóstico fue de 120 días y en 94% éste fue de más de tres semanas. Los síntomas más frecuentes fueron tos 88%, tos por tres semanas o más 94.6%, disnea 75.2%, dolor torácico 50%, pérdida de peso 70%, hemoptisis 22%, derrame pleural neoplásico 44.9%. La presencia simultánea de disnea, dolor torácico y saturación de oxígeno < 88% se asociaron a derrame pleural OR (IC 95%) 7.54 (3.28-17.34). **Conclusiones:** en pacientes adultos que refieran tos por tres semanas o más y/o cualquiera de los siguientes síntomas: disnea, dolor torácico, pérdida de peso, hemoptisis o fatiga que no se expliquen con base en un diagnóstico deberán evaluarse mediante una radiografía de tórax para su referencia temprana a una unidad especializada.

Palabras clave: cáncer de pulmón, síntomas, diagnóstico, derrame pleural, diagnóstico temprano del cáncer de pulmón.

Correspondence:
Renata Báez-Saldaña, MD
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas.
Mexico City, Mexico.
E-mail: baezrd@unam.mx

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INTRODUCTION

Lung cancer in Mexico is one of the 10 leading causes of cancer incidence and mortality. Its age-standardized incidence and mortality rates are similar, 5.3 and 4.9 per 100,000 inhabitants.[1] This similarity is attributed to the fact that in the context of the natural history of lung cancer, it is usually diagnosed late, which is associated with a very low survival rate.[2] The low yield for early diagnosis is due on the one hand to the peculiarities of the lung anatomy such as the absence of nerve terminals for pain, thus, a malignant

lesion can grow and even metastasize outside the thorax before it causes symptoms. Another large part of the delay in diagnosis is attributed to both the patient and the physician. In the United Kingdom patients took a median of 12 months between the onset of symptoms and the first visit to the general practitioner.[3] In another study of Swedish patients the average was 43 days with a maximum minimum interval of zero to 256 days[4] and even when the patient presents to the general practitioner with symptoms suggestive of lung cancer, the latter may not consider the diagnosis because the symptoms are nonspecific and in general practice it is an infrequent pathology. Lung cancer can present with a wide range of symptoms, the most common being cough, dyspnea, chest pain, weight loss, dysphonia, anorexia and fatigue among others.[5,6] And it has been termed a silent disease, as it lacks unique core symptoms or signs that can function as early indicators, hemoptysis can be considered an exception, as it is strongly associated with lung cancer, although it is quite rare as a silent first symptom.[7]

Chest X-ray is the first laboratory study that should be performed in patients with respiratory symptoms that could be due to lung cancer; ideally, it should be performed within 14 days to favor timely diagnosis;[8] however, this was achieved in 35% of patients with suspected lung cancer according to the results of a recent study carried out in England, which also showed that the time between the first visit with the general practitioner and the performance of the chest X-ray was 49 days, with an interquartile range of five to 172 days.[9] The delay in diagnosis could be reduced by screening asymptomatic subjects with risk factors and by better identification of the symptomatic patient who already has the disease. Although screening reduces the mortality incidence rate (IRR) between 0.85 [95% CI, 0.75-0.96] and 0.75 [95% CI, 0.61-0.90][10] in Mexico there is no active public screening program for lung cancer. In the present study we are going to refer to the clinical diagnosis of lung cancer in the symptomatic patient, because the information available to support the first contact physician in distinguishing between patients who may have lung cancer from those who have nonspecific symptoms associated with a benign respiratory disease is scarce. The relative importance of the clinical features of these cases has not been previously described in our population. Understanding how patients with lung cancer present at the time of diagnosis will be useful for early referral to a specialist, as well as for timely diagnosis of the disease. Our objective was to identify the symptom-based clinical profile of patients with lung cancer, which allows us to suspect the diagnosis and propose an algorithm for early referral.

MATERIAL AND METHODS

The study was approved by the institutional research and research ethics committees. The design is a prospective case series that was developed from 2013 to 2019 in a referral hospital for respiratory diseases in Mexico City. Incident cases of any type of lung cancer confirmed by histopathological study were included. Incident cases of any type of lung cancer confirmed by histopathological study were included. Lung cancer was defined as primary cancer of any histological type derived from the lung, trachea or bronchi. In all cases, frontal chest X-ray, computed tomography of the chest and skull and bone scintigraphy were performed. Imaging studies such as PET-CT or cranial MRI were performed in selected cases according to the individual case. The biopsy procedures performed to reach the histopathologic diagnosis varied according to the most appropriate individual case. Among the most frequent procedures were fibrobronchoscopy, closed pleural biopsy and tomography-guided biopsy. Procedures such as thoracoscopy, thoracotomy or mediastinoscopy were performed when diagnosis was not obtained by the first mentioned methods. All patients received oncological and pneumological treatment according to the clinical stage and histological type.

Sampling was by convenience, and cases were included consecutively as they met the inclusion criteria.

Using a standardized format for the study, the general characteristics of the patients (age, sex, schooling, place of birth, place of residence), history of lung cancer in first-degree relatives, comorbidities, history of exposure to smoking, exposure to asbestos at work and in the home were collected. Smoking history included previous and current smoking and passive smoking. Symptoms, time of current illness, cough for more than three weeks, pleural effusion, number of physicians the patient visited before referral or arrival at the hospital, histological type of lung cancer, functional status according to the Eastern Cooperative Oncology Group (ECOG) and Karnofsky scale, clinical stage of disease according to the eighth TNM classification for lung cancer, and serum carcinoembryonic antigen levels in those cases where this variable was available were recorded.

Finally, a diagnostic and referral algorithm was proposed for patients with suspected lung cancer, based on symptoms and frontal chest X-ray findings.

Statistical analysis

Statistical analysis was performed using the STATA statistical package, version 17 (StataCorp LP, College Station, TX, USA).

Descriptive statistics were performed on the clinical characteristics of the sample studied, using median and interquartile range 25-75 (IQI) for the continuous scale variables, and nominal variables were summarized as frequency and percentage. Bivariate logistic regression

was used to analyze the association between the type of symptom by admission service (emergency versus outpatient) and by the presence or absence of pleural effusion. A significant p value < 0.05 was considered significant.

RESULTS

A total of 508 cases were studied, whose median (IIC) age was 65 (55-73) years, 280 (55.1%) were men, 179 (35.2%) cases reported a history of any type of cancer in a direct relative and 37 (7.28%) lung cancer.

The frequency of exposure history was as follows: active or past smoking 255 (50.2%) cases, with a median (IIC) smoking index of 20 (five to 47) pack-years; wood smoke 223 (43.9%) cases with a median (IIC) wood smoke exposure index of 99 (36-192) hours per year; exposure to asbestos in the home 129 (25.4%) cases.

Regarding comorbidities, 255 (50.2%) cases of the sample presented some comorbidity, of which the most frequent were arterial hypertension with 156 (30.7%) cases and diabetes with 94 (18.5%) cases *(Table 1)*.

The median (interquartile range IQI) time from symptom onset to diagnosis was 120 (60-210) days, 30% of the cases reported a duration of current illness between 30 and 60 days and 459/488 (94.06%) cases reported a duration of current illness > 3 weeks. The most frequent symptom was cough with 448 (88%) cases, with a median (IIC) cough duration of 120 (60-216) days, followed by dyspnea 382 (75.2%) cases and weight loss 357 (70.3%). Pleural effusion was observed in 228 (44.9%) cases *(Table 2)*.

Regarding clinical laboratory findings, the frequency of leukocytosis, lymphopenia, neutrophilia, anemia and hypoalbuminemia were variable, ranging from 16.8 to 18.8% for thrombocytosis and lymphopenia, respectively, to 37% for hypoalbuminemia. Carcinoembryonic antigen was elevated in 176/190 (60.7%) cases.

Adenocarcinoma represented 76% of the total histological types of lung cancer, followed by squamous cell carcinoma with 11% and small cell carcinoma in 9.7% of the cases. The most frequent stages at diagnosis were III and IV, with 494 (97.2%) cases. The most frequent extrathoracic metastases were to bone with 117 (23%) cases and to the central nervous system with 55 (10.8%) cases. The functional

Table 1: Clinical characteristics of 508 patients with lung cancer.

Variables	n (%)
Age*	65 (55-73)
Male Female	280 (55.1) 228 (44.9)
History of cancer in a family member History of lung cancer in a relative	179 (35.2) 37 (7.28)
Smoking Smoking rate‡ Smoking rate > 30 Passive smoking Wood smoke Wood smoke index Exposure to asbestos in the home	255 (50.2) 20 (5-47) 108 (42.4) 72 (14.2) 223 (43.9) 99 (36-192) 129 (25.4)
Any comorbidity Arterial hypertension Diabetes Obesity Overweight COPD Heart disease Malnutrition Other*	255 (50.2) 156 (30.7) 94 (18.5) 77 (15.2) 117 (23.0) 42 (8.27) 35 (6.9) 24 (4.7) 19 (3.74)

* Median (interquartile range 25-75).

Table 2: Signs and symptoms of lung cancer patients.

Symptoms and signs, n = 508	Total n (%)
Time from symptom onset to diagnosis (days)*	120 (60-210)
Time from symptom onset to diagnosis > 3 weeks	459/488 (94.06)
Number of physicians before diagnosis* (n = 339)	2 (1-3)
Cough	448 (88.2)
Cough > 3 weeks	406/429 (94.6)
Expectoration	323 (63.6)
Dyspnea	382 (75.2)
Hemoptysis	113 (22.2)
Chest pain	254 (50.0)
Fatigue	100 (19.7)
Weight loss	357 (70.3)
Kilograms of weight lost*	7 (5-11)
Anorexia	45 (8.9)
Fever	78 (15.4)
Chills	22 (4.3)
Dysphonia	27 (5.3)
Dysphagia	21 (4.1)
Nausea	13 (2.6)
SpO_2 < 88%	168 (33.0)
Pleural effusion	228 (44.9)

* Median (interquartile range 25-75).

status measured by the Eastern Cooperative Oncology Group (ECOG) scale, 153/360 (42.5%) cases were in the 0 and 1 classification, and with the Karnofsky scale the score between 70 and 80 was the most frequent with 168 (47%) cases. Median (IIC) survival was 117 (28-299) days.

The symptoms and signs that were associated with a patient's arrival to the emergency department were: dyspnea, fever, pleural effusion and an oxygen saturation < 88%. The remaining symptoms both respiratory and constitutional showed no association *Table 3*.

Dyspnea, chest pain and oxygen saturation < 88% were analyzed together, because they were the symptoms that presented the strongest association with pleural effusion when performing the bivariate analysis, and a positive trend was demonstrated when having one to three symptoms, for the latter the association was OR (95% CI) 7.54 (3.28-17.34) *(Table 4)*.

The algorithm proposed for the diagnosis and referral of patients with suspected lung cancer was based on symptoms and frontal chest X-ray findings *(Figure 1)*.

DISCUSSION

The present study demonstrated the clinical profile of patients who arrived at the hospital with lung cancer at the time of diagnosis. Of these, 96% showed respiratory symptoms for more than three weeks without an explanatory diagnosis. Half of the cases had exposure to smoking and 43.9% to wood smoke. The main symptoms with a frequency greater than or equal to 50% in decreasing order were cough, dyspnea, weight loss and chest pain, similar to what has been reported in other studies;[5,6] 60% had elevated carcinoembryonic antigen biomarker. Of the patients, 57.3% were admitted to the emergency department for dyspnea and fever associated with oxygen saturation < 88% and pleural effusion, the latter present at a high frequency in 44.9% of cases. Therefore, we evaluated the symptoms associated with pleural effusion, which were dyspnea, chest pain and oxygen saturation < 88%. When the three variables were presented simultaneously, a positive association OR (95% CI) 7.54 (3.28-17-34) was observed. Cough is the most frequent symptom of lung cancer and the results of the present study confirm this. According to a meta-analysis on the value of symptoms for the diagnosis of lung cancer, those with the highest value measured by diagnostic odds ratio (OR) were hemoptysis 6.39 (3.32-12.28), followed by dyspnea 2.73 (1. 54-4.85), cough 2.64 (1.24-5.64) and chest pain 2.02 (0.88-4.60).[11] Hemoptysis is the only symptom that has demonstrated association with lung cancer and the one with the highest predictive value compared to other respiratory symptoms.[12] However, this occurs in only 21.6% of cases,[13] whose frequency was similar in our study 22.2% and which compared to cough, dyspnea and chest pain is quite minor, so its absence does not rule out at all the possibility of lung cancer in the patient with other respiratory symptoms.

Most of these patients first consult a general practitioner or an internist for one or more of these symptoms. In the first level of care or in a general practice, cough is very frequent, and given the unspecificity of this symptom, on most occasions the diagnosis of lung cancer, or at least suspecting it, is a challenge for the physician, since

Table 3: Association between selected clinical variables and the clinical department through which the cases initially arrived at the institution.

Symptoms	Emergencies N = 291 n (%)	Outpatient consultation N= 217 n (%)	OR (95% CI)	p
Cough	254 (87.3)	194 (89.4)	0.81 (0.47-1.41)	0.465
Dyspnea	233 (80.1)	149 (68.7)	1.83 (1.22-2.75)	0.003
Hemoptysis	67 (23.0)	46 (21.2)	1.11 (0.73-1.70)	0.625
Chest pain	150 (51.6)	104 (47.9)	1.11 (0.73-1.70)	0.420
Fever	54 (18.6)	24 (11.0)	1.83 (1.1-3.00)	0.022
Fatigue	56 (19.2)	44 (20.3)	0.94 (0.6-1.46)	0.772
Weight loss	197 (67.7)	160 (73.7)	0.75 (0.50-1.1)	0.142
Dysphonia	14 (4.8)	13 (6.0)	0.79 (0.36-1.72)	0.558
Dysphagia	13 (4.5)	8 (3.7)	1.22 (0.50-3)	0.662
Vena cava syndrome	3 (1.03)	1 (0.46)	2.25 (0.23-21.78)	0.484
Pleural effusion	163 (56.0)	65 (30.0)	2.98 (2.05-4.32)	0.000
Oxygen saturation < 88%	115 (39.5)	53 (24.4)	2.02 (1.37-2.98)	0.000

Table 4: Symptoms associated with pleural effusion in patients with lung cancer.

Symptoms	With pleural effusion N = 228 n (%)	Without pleural effusion N= 280 n (%)	OR (95% CI)	p
Cough	200 (87.7)	248 (88.6)	0.92 (0.54-1.58)	0.767
Dyspnea	192 (84.2)	190 (67.9)	2.53 (1.63-3.90)	0.000
Hemoptysis	37 (16.2)	76 (27.1)	0.52 (0.33-0.81)	0.004
Chest pain	135 (59.2)	119 (42.5)	1.96 (1.38-2.80)	0.000
Fever	37 (16.2)	41 (14.6)	1.13 (0.70-1.83)	0.622
Fatigue	54 (23.7)	46 (16.4)	1.58 (1.01-2.4)	0.042
Weight loss	162 (71)	195 (69.6)	1.07 (0.73-1.57)	0.730
Dysphonia	15 (6.6)	12 (4.3)	1.57 (0.72-3.43)	0.255
Dysphagia	8 (3.51)	13 (4.6)	0.75 (0.30-1.83)	0.524
Oxygen saturation < 88%	88 (38.6)	80 (28.6)	1.57 (1.08-2.28)	0.017
Dyspnea, chest pain and oxygen saturation < 88% combined				
None of the 3	13 (5.7)	36 (12.9)	Referencia	
At least 1 of the 3	64 (28.1)	117 (41.8)	1.5 (0.75-3.06)	0.247
At least 2 of the 3	102 (47.7)	109 (38.9)	2.59 (1.30-5.16)	0.007
3 of the 3	49 (21.5)	18 (6.4)	7.54 (3.28-17.34)	0.000

in general practice only 0.2% of patients presenting with cough for more than three weeks have lung cancer.[14] In the United Kingdom the time between first consultation and referral for lung cancer is a median of 14 days, with longer intervals of between 60 and 90 days documented in 17.9% of cases.[15] In our study, the median time between the onset of symptoms and referral to our institution was 120 days, which we consider to be a very long time, which could partly explain why 97% of the cases arrived at an advanced stage of the disease, again highlighting the priority of recognizing symptoms for faster referral, as there is evidence to suggest that when patients have faster access to the study, their survival is better.[16] Also, there is evidence that several consultations prior to diagnosis occur during this time interval.[17] Specifically, one-third of patients diagnosed with lung cancer have received medical attention by a general practitioner for symptoms attributable to cancer three or more times prior to diagnosis.[18] We did not measure the number of times they consulted a physician, but the number of physicians the patient consulted prior to referral to the institute, the median was two physicians with a minimum-maximum range of zero to 10 physicians.

Early detection programs that include social marketing interventions may increase the likelihood that patients will see a primary care physician when they first present with symptoms, who in turn increases the level of suspicion that leads to a chest x-ray and an increase in diagnosis rates by referral of these cases.[19] However, there is concern about overburdening the health system due to the evaluation of patients with symptoms not due to lung cancer.[20] Therefore, it is suggested that programs could preferentially target those at high risk of lung cancer such as people with a history of smoking, and in the case of Mexico also those with a history of exposure to wood smoke and occupational exposure. It is important to note that in the cases included in this study, smoking was reported in 50.2% of the cases, so that in Mexico the possibility of lung cancer must be considered whether or not this risk factor is present. In general, one out of every seven cases of lung cancer occurs in people who have never smoked.[21] In our population this proportion was higher, almost one to one, 49.8% are non-smokers; however, the population has other types of exposures that are risk factors for lung cancer and that must be considered, such as exposure to wood smoke, which was present in 43.9%, and although it is considered a probable carcinogen,[22] it is associated with high rates of lung cancer.[23]

The route of entry of patients to the referral center, whether by scheduled consultation or emergency department, suggests the severity of the disease and the difficulty patients have in being referred from the onset of their symptoms. One third of lung cancer cases are diagnosed in the emergency room;[24] in the setting of our cases, 57.28% of them presented to the emergency department where the approach was initiated, this constitutes a much higher frequency than that referred elsewhere and reflects once again the delay in diagnosis, which contributes to cases arriving at such advanced stages of the disease. Of the cases admitted to the emergency department, 56% had pleural effusion, which in a patient with lung cancer classifies it as an advanced stage.

Unlike tissue biomarkers in lung cancer, serum biomarkers are not widely used; in fact, diagnostic and treatment guidelines for lung cancer do not recommend them, giving priority to respiratory and constitutional

symptoms and signs as the initial criteria for requesting a chest X-ray and referral within a period of no more than two weeks.[8,25]

Of the multiple biomarkers for lung cancer, one of the most studied and the one we have available at our institution is carcinoembryonic antigen (CEA), which we use as a diagnostic support to evaluate response to treatment and prognosis. In our population, we documented that 60% had elevated this biomarker, so it could be useful to guide the diagnosis and referral for suspected lung cancer when a patient presents with respiratory symptoms without a diagnosis that explains it.

Strengths and limitations

The results are valid, as they were derived from a prospective design with a large n. The clinical profile we describe includes symptoms that occurred with a frequency of 50% or more, except for hemoptysis, which had a frequency of 22.2%, a respiratory symptom that has the highest predictive value and diagnostic value. The group of symptoms that we describe independently of exposure to risk factors, are the same that have demonstrated the highest diagnostic value associated with lung cancer and, taking into account previous evidence on the subject, offer a possible benefit for the diagnosis of lung cancer based on symptoms in the patient seeking medical attention at a first level of care. The proposed algorithm pathway is based partly on patient symptom findings and mainly on the experience of the investigators *(Figure 1)*.

The results of this study are derived from hospital-based research at one center, so they may not be generalizable. Also, due to its purely descriptive design and the fact that only lung cancer cases were included, it is not possible to obtain estimators of the diagnostic value of the symptoms or of the clinical profile described. In addition, although we described the time between the onset of symptoms and the time it took for referral to the tertiary care unit, we did not investigate the period between the onset of symptoms and the first visit to the physician, which of course affects the time from the actual condition to the time of diagnosis.

CONCLUSIONS

Adult patients of any age, with or without risk factors for lung cancer, who report cough for three weeks or more without an explanatory diagnosis and/or any of the following symptoms: dyspnea, chest pain, weight loss, hemoptysis or

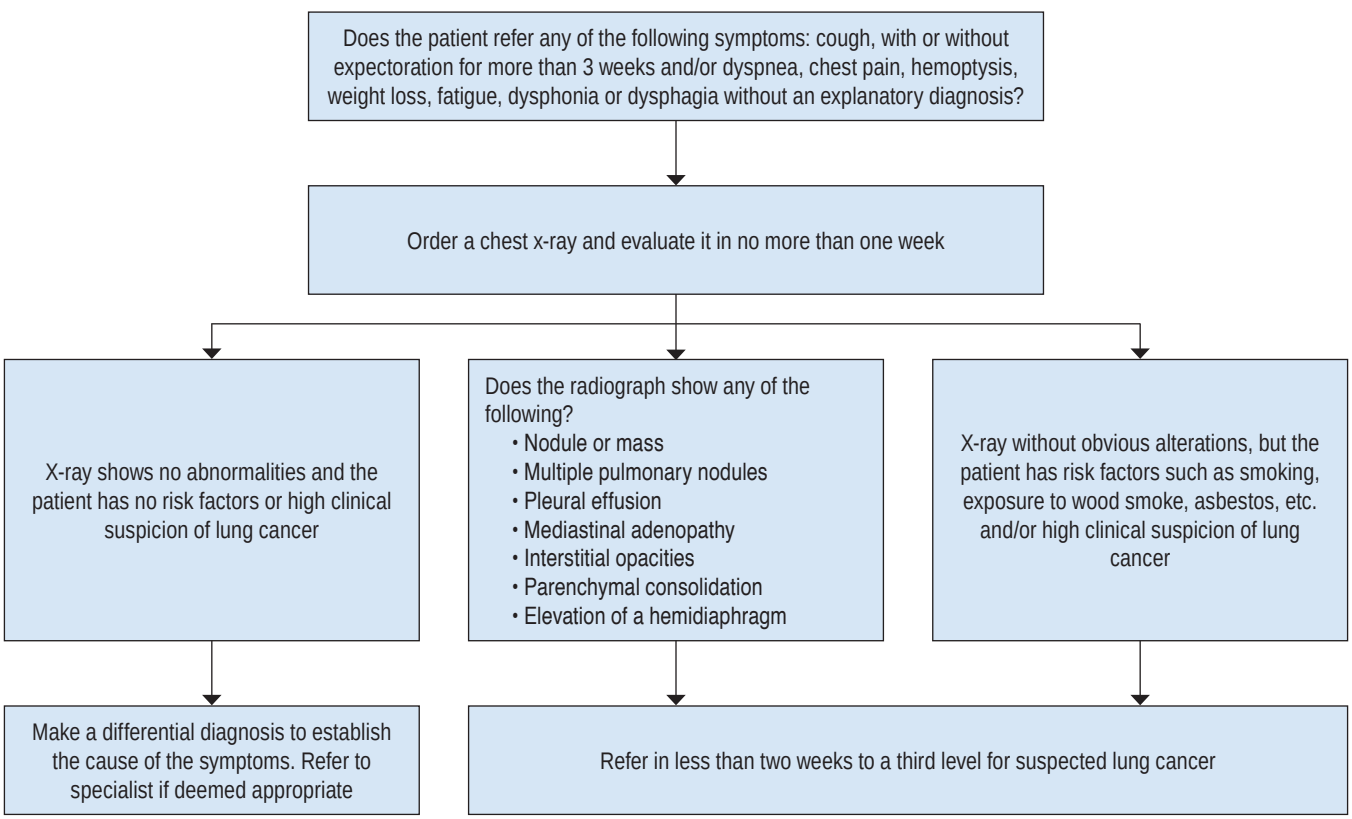

Figure 1: Proposed algorithm for diagnosis and referral of patients with clinical suspicion of lung cancer.

fatigue, should be evaluated clinically and at least with a chest X-ray, and referred to a specialized unit for suspicion of lung cancer. In cases with these characteristics we suggest performing CEA measurement.

Cases with simultaneous dyspnea, chest pain and oxygen saturation < 88% are 7.5 times more likely to have pleural effusion associated with lung cancer.

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Chronic hypoventilation in pediatric patients at moderate altitude

Hipoventilación alveolar crónica en pacientes pediátricos a altitud moderada

Ángela Andrea Pesántez-Abril,* Adriana del Carmen Alva-Chaire,* Francisco Javier Cuevas-Schacht*

*Instituto Nacional de Pediatría. Mexico City, Mexico.

ABSTRACT. Introduction: chronic alveolar hypoventilation is defined as the clinical condition by increased $PaCO_2$ with normal pH figures; at sea level ≥ 45 mmHg and in Mexico City (2200 masl) ≥ 38 mmHg, the latter due to a decrease in the partial and alveolar pressure of oxygen due to a drop in barometric pressure. Altitude generates increased work of breathing, increased volume/minute to maintain adequate PO_2, eliminating CO_2, negatively impacting ventilatory control in patients with chronic lung diseases. **Objective:** to describe the main characteristics of pediatric patients with chronic alveolar hypoventilation at moderate altitude. **Material and methods:** observational, descriptive, cross-sectional, retrospective study, in patients from zero to 18 years of age in the period 2007 to 2020 treated at the National Institute of Pediatrics, Mexico City. **Results:** 17 patients with chronic alveolar hypoventilation were found, with a median age of 6 years, in 58.82% of cases the etiology was peripheral; the most frequent daytime symptoms were tiredness and irritability (41.2%) and among the nocturnal symptoms were snoring (41.2%) and respiratory pauses (29.4%). In 41.2% some type of non-invasive ventilation device (NIV) was used; decrease in complications and symptoms was observed after one year of follow-up in both the groups with and without NIV; although without statistical significance. **Conclusions:** it was established that the main causes are peripheral, although NIV showed benefits, its use was recorded in less than half of the cases

Keywords: chronic alveolar hypoventilation, clinical manifestations, non-invasive ventilation, evolution, complications.

RESUMEN. Introducción: la hipoventilación alveolar crónica se define como la condición clínica por aumento de la $PaCO_2$ con cifras de pH normal, a nivel del mar ≥ 45 mmHg y en Ciudad de México (2,200 msnm) ≥ 38 mmHg, esto último debido a la disminución de la presión parcial y alveolar de oxígeno por descenso de la presión barométrica. La altitud genera aumento del trabajo respiratorio, incremento del volumen/minuto para mantener una PO_2 adecuada, eliminando CO_2, lo que impacta negativamente el control ventilatorio en pacientes con enfermedades pulmonares crónicas. **Objetivo:** describir las principales características de los pacientes pediátricos con hipoventilación alveolar crónica a altitud moderada. **Material y métodos:** estudio observacional, descriptivo, transversal, retrospectivo en pacientes de cero a 18 años de edad en el período de 2007 a 2020 atendidos en el Instituto Nacional de Pediatría, Ciudad de México. **Resultados:** se encontraron 17 pacientes con hipoventilación alveolar crónica con una mediana de edad de seis años, en 58.82% de los casos la etiología fue periférica; los síntomas diurnos más frecuentes fueron cansancio e irritabilidad (41.2%) y entre los síntomas nocturnos el ronquido (41.2%) y pausas respiratorias (29.4%). En 41.2% se utilizó algún tipo de dispositivo de ventilación no invasiva (VNI); se observó disminución de complicaciones y sintomatología al año de seguimiento tanto en los grupos con y sin VNI, aunque sin significancia estadística. **Conclusiones:** se estableció que las principales causas son las periféricas; a pesar de que la VNI demostró beneficios, su utilización se registró en menos de la mitad de los casos.

Palabras clave: hipoventilación alveolar crónica, manifestaciones clínicas, ventilación no invasiva, evolución, complicaciones.

INTRODUCTION

Chronic alveolar hypoventilation is defined as a clinical condition characterized by a decrease in ventilation/minute with elevation of arterial partial pressure of carbon dioxide ($PaCO_2$) greater than 45 mmHg above sea level and 38 mmHg in Mexico City due to the altitude (2,200 meters above sea level), this is due to the decrease in barometric pressure and therefore, the partial and alveolar pressure of oxygen triggers the adaptation process of the human organism with an increase in respiratory work due to the need to increase the volume/minute to maintain

Correspondence:
Adriana del Carmen Alva-Chaire, MD
Instituto Nacional de Pediatría. Mexico City, Mexico.
E-mail: a.alva.ch@gmail.com

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an adequate partial pressure of oxygen (PO_2), eliminating carbon dioxide (CO_2), that is, increasing alveolar ventilation.[1] The increase in CO_2 levels is accompanied by normal pH levels due to metabolic compensation and increased bicarbonate values.[2]

Alveolar hypoventilation disorders can be classified as central or peripheral depending on the underlying pathology;[3] in central disorders there is a low or absent sensitivity of the respiratory center to CO_2, they can derive from a variety of congenital or acquired conditions.[4-6] In peripheral hypoventilation disorders there is an alteration in the mechanics of breathing that prevents an adequate response to ventilatory needs as in neuromuscular diseases (NMDs), chest deformities,[3,7] also in underlying lung parenchymal diseases[8] and hypoventilation obesity syndrome (HOS).

The most common clinical manifestations of hypoventilation do not occur in isolation, but within the spectrum of signs and symptoms generated by the wide variety of underlying diseases, these will be more evident during sleep, although daytime symptomatology will also be present and its severity is directly related to the magnitude of nocturnal hypoventilation.[1,7,9,10]

Diagnosis is based on clinical data and different invasive and non-invasive techniques for measuring the CO_2 level, one of the most commonly used techniques being arterial or capillary blood gases; however, blood collection during the night interrupts patients' sleep, so daytime samples that reflect the ventilation status throughout the night are chosen.[11]

Management initially focuses on any causal factor, but sometimes these measures will not be sufficient, so the treatment of patients with chronic hypoventilation is support with noninvasive ventilation with bilevel positive pressure, demonstrating short and long term benefits.[12-14]

Early identification of manifestations associated with hypoventilation and complications such as infectious processes together with cardiovascular deterioration, explained by the vasoconstrictor response in the pulmonary bed, will be important. The increase in pulmonary vascular resistance results in an increase in the work of the right ventricle and hypertrophy and eventual heart failure.[9]

In adults in Mexico, hypoventilation was detected in up to 68% of patients with obesity and in 69% with NME;[15] and the prevalence in children is not underestimated, so in the absence of local data, this study was undertaken.

MATERIAL AND METHODS

The aim of this research is to describe the main characteristics of patients with chronic alveolar hypoventilation in the National Institute of Pediatrics (INP), for this purpose an observational, descriptive, cross-sectional, retrospective study was carried out in patients from zero to 18 years of age, diagnosed with chronic alveolar hypoventilation in the pulmonology and thoracic surgery service from January 1, 2007 to December 31, 2020. Patients of both genders with at least one year of follow-up and a control in the first quarter after diagnosis were included. Patients with additional diseases with dyspnea were excluded. Data were collected by searching clinical records in both physical and electronic format after filling out the database and analysis using the SPSS v.21 statistical package. The statistical evaluation was carried out descriptively through univariate analysis with frequencies and percentages for qualitative variables and measures of central tendency and dispersion for quantitative variables. Finally, the results were presented in the form of tables.

RESULTS

Forty-one outpatient records with a diagnosis of alveolar hypoventilation were reviewed; only 17 met all the criteria necessary to be included in the study. Of these, 88.24% were female, with ages between 4 months and 16 years and a median of 6 years. The lowest median age of diagnosis was in patients with MND, while the latest was in chest wall and spine deformities *(Table 1)*. The most frequent causes were peripheral with 58.82%, among them chest wall and spine deformity with 35.29% (scoliosis n = 5, bone dysplasia n = 1) followed by ENM (Duchenne dystrophy n = 1 and spinal cord atrophy n = 1) and obesity (n = 2) each with 11.7%; with respect to central causes, they were present in 35.29% of the subjects.

Among the most frequent diurnal symptoms, tiredness and irritability stand out with 41.2% each; similar pattern of presentation in central and peripheral disorders. As for nocturnal symptoms, snoring stood out with 41.2% with an average of four days/week, respiratory pauses with 29.4% with an average of seven days/week *(Table 2)*. Facial dysmorphias were observed in 52.4%, evidenced in half of the subjects with central causes.

In patients with peripheral causes, the group with scoliosis presented a Cobb angle measurement classified as moderate and severe, of this group, four cases underwent respiratory function tests (RFT), specifically spirometry, all of them showed a reduction in both forced expiratory volume in the first second (FEV1) with a mean of 34.5% of the predicted value (PV) and in forced vital capacity (FVC) values with a result of 39.8% of the PV. It should be noted that only two patients underwent respiratory function tests prior to the diagnosis of alveolar hypoventilation.

The nutritional status of the patients was eutrophic in 35.3%, mainly in the group of peripheral causes (66.6%) and malnutrition in 29.4%, especially in patients with central causes and ENM. As for the gasometric data, at the time

Table 1: Distribution of patients according to etiology, sex and age at diagnosis in patients with chronic alveolar hypoventilation at the National Pediatric Institute. 2007-2020.

Characteristics	Total (N = 17)	Centrals (N = 6)	Peripherals (N = 10)			
			Deformity of the thoracic cage and spine (N = 6)	Neuromuscular diseases (N = 2)	Obesity (N = 2)	Mixed (N = 1)
Age (median) years	6	4.5	13.5	3	6.5	6
Interquartile range	11.5	9	8.2	–	–	–
Maximum-minimum value	4 meses-16 años	–	–	–	–	–
Sex, n (%)						
Female	15 (88.24)	6 (100)	6 (100)	2 (100)	1 (50)	–
Male	2 (11.76)	–	–	–	1 (50)	1 (100)

Table 2: Daytime and nocturnal symptomatology at diagnosis.

Characteristics	Total (N = 17) n (%)	Centrals (N = 6) n (%)	Peripherals (N = 10)			Mixed (N = 1) n (%)
			Deformity of the thoracic cage and spine (N = 6) n (%)	Neuromuscular diseases (N = 2) n (%)	Obesity (N = 2) n (%)	
Daytime symptomatology						
Excessive daytime sleepiness	6 (35.3)	4 (66.7)	2 (33.3)	–	–	–
Morning headache	3 (17.6)	1 (16.7)	2 (33.3)	–	–	–
Exercise intolerance	4 (23.5)	1 (16.7)	3 (50)	–	–	–
Dyspnea	6 (35.3)	1 (16.7)	3 (50)	–	2 (100)	–
Fatigue	7 (41.2)	2 (33.3)	3 (50)	–	1 (50)	1 (100)
Irritability	7 (41.2)	4 (66.7)	2 (33.3)	–	–	1 (100)
Morning sickness	2 (11.8)	1 (16.7)	1 (16.7)	–	–	–
Supine thoracoabdominal dissociation	2 (11.8)	1 (16.7)	–	–	1 (50)	–
Use of accessory muscles of respiration	1 (5.9)	–	–	–	1 (50)	–
Learning and memory problems	3 (17.6)	1 (16.7)	2 (33.3)	–	–	–
Nocturnal symptomatology						
Restless sleep	3 (17.6)	3 (50)	–	–	–	–
Nocturnal awakenings	2 (11.8)	2 (33.3)	–	–	–	–
Parasomnias	–	–	–	–	–	–
Snoring	7 (41.2)	4 (66.7)	2 (33.3)	–	1 (50)	–
Mean (range) days/week	4 (1-7)	–	–	–	–	–
Breathing pauses	5 (29.4)	2 (33.3)	–	–	2 (100)	1 (100)
Mean days/week	7	–	–	–	–	–
Choking sensation at night	3 (17.6)	1 (16.7)	–	–	2 (100)	–
Mouth breathing	3 (17.6)	3 (50)	–	–	–	–
Thoracoabdominal dissociation during sleep	2 (11.8)	1 (16.7)	–	–	1 (50)	–

of diagnosis, hypoxemia was reported in 64.7%, being frequent in central causes with 83.3% and in all patients with ENM and obese *(Table 3)*.

Regarding complications, they were present in all groups, with a lower occurrence in patients with mixed disorder; the most frequent were pneumonias, which were present in 47% with a mean of 1.6 events/year, and were common in the subgroups of peripheral causes; followed by pulmonary artery hypertension (PAH) in 41.2% and respiratory failure with 35.3%, both described in all obese and ENM patients.

As part of the treatment, NIV was used in 41.2%, of which one patient used a continuous positive airway pressure device (CPAP), a patient corresponding to the obese group; in the other groups, bilevel pressure devices in ST mode were used; it was not possible to determine the parameters used due to incomplete information in the

records. The mean daily use was 14.4 hours, highlighting that patients with central causes and ENM required day/night ventilation, while the rest used nocturnal ventilation. Meanwhile, the device titration method was performed in sleep laboratories and hospital with similar frequency (42.86%); it should be clarified that titration in the hospital was in patients who were referred to the pulmonology service because of difficulty in weaning from oxygen or withdrawal of mechanical ventilation, even without an established diagnosis of alveolar hypoventilation. With respect to the interface, the most commonly used was nasal (57.14%) and only one case of complications related to skin lesions due to its use was reported *(Table 4)*.

Regarding the evolution of the patients who used NIV, in the short term the symptomatology was very similar to that manifested at the time of diagnosis; however, in the long term it was completely reduced, except for the snoring that was maintained in one of the patients, who belonged to the mixed disease group, with poor adherence to NIV treatment. In all the variables studied, the p-value was not significant, probably due to the small sample size *(Table 5)*.

In addition, at one year follow-up, a decrease in the frequency of complications was observed in the groups with and without NIV. Both patients with Cor pulmonale and the vast majority of PAH cases evolved favorably, except for one patient (5.9%) with restrictive thorax secondary to severe scoliosis who did not use NIV, and no new respiratory failure events were recorded. Specifically in patients with NIV device use, long-term improvement was demonstrated with the exception of two cases that required hospitalization: central cause (n = 1) and thoracic deformity (n = 1); in the latter, an event of pneumonia was also reported; although complications were reduced compared to baseline findings, there was no significant difference in general and with each of the groups *(Table 6)*.

DISCUSSION

The increase in $PaCO_2$ can be secondary to a variety of pathologic processes,[16] the most frequent being peripheral disorders, similar to the study by Castro et al. in 622 children with alveolar hypoventilation who used NIV, who found 83% peripheral causes, among the most frequent: obesity and Down syndrome; and only 17% reported a central cause. These authors also report a median age at diagnosis of 7.8 years,[17] something similar to that observed in the present investigation. The ages were younger in patients with MND; in contrast, Katz and Fauroux report later ages (mean 11.7 years);[18,19] while the latter authors mention that diagnosis in the group with rib cage and spine deformities was more common in the school year 18 versus what was found in this study, which was in adolescence.

In the spectrum of symptomatology, the present study showed a greater frequency of daytime symptoms such as tiredness and irritability followed by excessive daytime sleepiness and dyspnea; in the work of Casas

Table 3: Nutritional status and gasometric data.

Characteristics	Total (N = 17) n (%)	Centrals (N = 6) n (%)	Peripherals (N = 10)			Mixed (N = 1) n (%)
			Deformity of the thoracic cage and spine (N = 6) n (%)	Neuromuscular diseases (N = 2) n (%)	Obesity (N = 2) n (%)	
Nutritional status						
Malnutrition	5 (29.4)	3 (50)	1 (16.7)	1 (50)	–	–
Eutrophic	6 (35.3)	1 (16.7)	4 (66.6)	1 (50)	–	–
Overweight	2 (11.8)	1 (16.7)	–	–	–	1 (100)
Obesity	4 (23.5)	1 (16.7)	1 (16.7)	–	2 (100)	–
Gasometric data						
Hypoxemia	11 (64.7)	5 (83.3)	2 (33.3)	2 (100)	2 (100)	–
$PaCO_2$ mmHg X	52.7 (45-72)*	48.4	54.9	54.1	56.7	54.7
HCO_3 mmol/L X	28.0 (22-44)*	25.5	28.8	31.5	25.5	36.3
Complications						
Pneumonias‡	8 (47.0)	2 (33.3)	3 (50.0)	2 (100)	1 (50)	–
Respiratory failure	6 (35.3)	1 (16.7)	1 (16.7)	2 (100)	2 (100)	–
Pulmonary arterial hypertension	7 (41.2)	1 (16.7)	2 (33.3)	1 (50)	2 (100)	1 (100)
Cor pulmonale	4 (23.5)	1 (16.7)	2 (33.3)	1 (50)	–	–

* Range. ‡ Medium pneumonias: 1.6 events (1-3).

Table 4: Characteristics of use of noninvasive ventilation with bilevel positive pressure.

Characteristics	Total (N = 17)	Centrals (N = 6)	Deformity of the thoracic cage and spine (N = 6)	Neuromuscular diseases (N = 2)	Obesity (N = 2)	Mixed (N = 1)
Use of non-invasive ventilation, n (%)	7 (41.2)	1 (16.7)	2 (33.3)	2 (100)	1 (50)	1 (100)
Hours of use of ventilation, average (range)	14.4 (8-24)	19	11	22	8	8
Time from diagnosis to onset of ventilation (months) mean (range) 7 (3-24)						
	n (%)					
Interface types	N = 7					
Nasal	4 (57.14)					
Buconasal	1 (14.29)					
Tracheostomy ventilation	2 (28.57)					
Device titration method						
Sleep laboratory (polysomnography)	3 (42.86)					
Hospital	3 (42.86)					
Home	1 (14.29)					
Origin of the devices						
Own	1 (14.29)					
Institutional	1 (14.29)					
Donation	4 (57.14)					
Rented	1 (14.29)					
Presence of complications from the use of devices						
Yes	1 (14.3)					
No	6 (85.7)					
Need for tracheostomy						
Yes	2 (28.6)					
No	5 (71.4)					
Time elapsed between diagnosis and tracheostomy (months), mean	18					

they were mostly dyspnea and asthenia followed by daytime hypersomnolence 77%;[9] in relation to dyspnea was a cardinal symptom in OHS, similarly, Espínola et al. made a comparison with obese patients with obstructive sleep apnea/hypopnea syndrome (OSAHS) without hypoventilation, demonstrating a greater degree of dyspnea ($p = 0.04$) in the OHS group;[20] this event was reproduced in our population and in the patient with mixed disease. Regarding nocturnal symptomatology, snoring and respiratory pauses were mainly detected, results similar to other studies.[21,22]

Adenotonsillar hypertrophy produces upper airway narrowing, and when superimposed with other factors results in clinically significant dynamic airway obstruction during sleep, resulting in hypoventilation.[23,24] Rosen et al. found adenotonsillar hypertrophy in 2/3 of the children studied,[22] while in the present work it was recorded in 1/3 of the cases. Another variant is facial dysmorphia, closely related to genetic variants such as the expansion mutation in PHOX2B;[25] those found in this work were related to central etiology and half of them were syndromic, and in the rest, despite genetic evaluation, they were not integrated into a definitive diagnosis; in none of the cases was it congenital.

Part of the study of patients with hypoventilation includes RFT, FVC and FEV1 values lower than 50% of PV, which usually announce the onset of ventilatory failure by increasing $PaCO_2$. Despite its importance, not all patients manage to perform them for different reasons,[26] Fauroux records the performance of RFT in 56% of his sample[27] compared to the current work in which it was documented in only 23.6%.

Another point to discuss is the nutritional status, Rosen reports that obesity was present in more than a quarter of the study population and the rest were eutrophic,[22] in the current study 1/3 of children were eutrophic, although it would be expected that most patients would be eutrophic except for patients with obesity hypoventilation syndrome; the presence of malnutrition was noteworthy with a not insignificant percentage and constituting half of the cases with central etiologies and neuromuscular diseases.

In the diagnosis of alveolar hypoventilation, the mean $PaCO_2$ was higher in children with obesity (56.7 mmHg) and lower in central causes (48.4 mmHg); meanwhile Poh Tan pointed out high figures in patients with pulmonary parenchymal disease (58 mmHg) followed by OHSS (56 mmHg); in addition the author indicated hypoxemia in 32% of the cases, especially in parenchymal disease.[21] In this study, hypoxemia was observed in 64% of cases, mainly in central causes, and it is emphasized that half of these patients also presented clinical symptoms and images suggestive of aspiration pneumopathy, leading to lung parenchymal damage and increased hypoxemia.

Regarding complications, they are frequently related to infectious processes together with cardiovascular deterioration.[28] In the study, the main complications described were pneumonia and in 1/3 the presence of respiratory failure. Marik found pneumonia in 20% and respiratory failure in 63%, and also found heart failure in up to 39% of cases[29] versus 23.5% determined in this study. Other complications such as PAH, according to Held's study, were observed in 10% of cases.[30]

NIV with bilevel positive pressure has demonstrated benefits in chronic alveolar hypoventilation,[12] usually used initially during sleep by means of a nasal interface or mask, and in cases in which continuous ventilation is required, tracheostomy is the preferred option.[31] The use of NIV stands out in this study in only 41.2% of the cases, in contrast to what occurs in other centers in developed countries, where there is greater accessibility to the devices, exceeding 90% of the cases[21] and as previously mentioned, most of the NIV devices were donations due to the difficulty in acquiring the equipment in our environment, especially life support equipment due to its high cost, and often the start-up times for ventilation are prolonged until the equipment is obtained, with lapses of up to 24 months.

In relation to the use of ventilation, the literature shows a slightly greater survival advantage with use of more than four hours/day, exposing the clinical benefit of NIV over other forms of treatment. As for pediatric populations, it depends on age and in general terms it is recommended that at least 50% of hours should be used during sleep.[32]

In relation to the evolution of patients in the short and long term, although the objective of this study was not

Table 5: Evolution of daytime/nighttime symptomatology at diagnosis, three months and one year with and without use of noninvasive bilevel positive pressure ventilation.

Characteristics (N = 7)	With NIV, n (%)			Without NIV, n (%)		
	Basal	3 months	1 year	Basal	3 months	1 year
Daytime symptomatology						
Excessive daytime sleepiness	1 (14.3)	1 (14.3)	0 (0.0)	5 (50)	3 (30)	5 (50)
Morning headache	2 (28.6)	2 (28.6)	0 (0.0)	1 (10)	3 (30)	1 (10)
Exercise intolerance	3 (42.9)	4 (57.1)	0 (0.0)	2 (20)	2 (20)	3 (30)
Dyspnea	3 (42.9)	2 (28.6)	0 (0.0)	4 (40)	3 (30)	3 (30)
Fatigue	3 (42.9)	2 (28.6)	0 (0.0)	3 (30)	4 (40)	3 (30)
Irritability	1 (14.3)	0 (0.0)	0 (0.0)	5 (50)	3 (30)	2 (20)
Morning sickness	1 (14.3)	1 (14.3)	0 (0.0)	1 (10)	0 (0)	0 (0)
Supine thoracoabdominal dissociation	0 (0.0)	0 (0.0)	0 (0.0)	2 (20)	1 (10)	0 (0)
Use of accessory muscles of respiration	0 (0.0)	1 (14.3)	0 (0.0)	1 (10)	0 (0)	0 (0)
Learning and memory problems	1 (14.3)	0 (0.0)	0 (0.0)	2 (20)	2 (20)	2 (20)
Nocturnal symptomatology						
Restless sleep	0 (0.0)	0 (0.0)	0 (0.0)	3 (30)	2 (20)	3 (30)
Nocturnal awakenings	0 (0.0)	0 (0.0)	0 (0.0)	2 (20)	2 (20)	2 (20)
Parasomnias	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)	0 (0)
Snoring	2 (28.6)	2 (28.6)	1 (14.3)	6 (60)	4 (40)	5 (50)
Breathing pauses	1 (14.3)	0 (0.0)	0 (0.0)	3 (30)	1 (10)	4 (40)
Nocturnal choking sensation	1 (14.3)	0 (0.0)	0 (0.0)	2 (20)	3 (30)	1 (10)
Mouth breathing	1 (14.3)	1 (14.3)	0 (0.0)	3 (30)	5 (50)	3 (30)
Thoracoabdominal dissociation during sleep	0 (0.0)	0 (0.0)	0 (0.0)	2 (20)	1 (10)	0 (0)

NIV = noninvasive ventilation.

Table 6: Need for hospitalization, complications and death one year after diagnosis in patients with chronic alveolar hypoventilation with/without use of noninvasive ventilation.

	Basal, n (%)			1 year, n (%)					
Characteristics	Total (N = 17)	Ventilation (N = 7)	No ventilation (N = 10)	Total (N = 17)	p	Ventilation (N = 7)	p	No ventilation (N = 10)	p
Hospitalizations	7 (41.2)	4 (57.1)	3 (30)	3 (17.64)	0.13	2 (28.6)	1.00	1 (10)	0.24
Pneumonias*	8 (47.0)	4 (57.1)	4 (40)	2 (11.76)	1.00	1 (14.3)	0.24	1 (10)	0.24
Respiratory insufficiency	6 (35.3)	3 (42.9)	3 (30)	–	–	–	–	–	–
Pulmonary hypertension	7 (41.2)	4 (57.1)	3 (30)	1 (5.9)	–	–	–	1 (10)	0.47
Cor pulmonale	4 (23.6)	2 (28.6)	4 (40)	–	–	–	–	–	–
Deceased	–	–	–	0	–	–	–	–	–

* Mean number of pneumonia events: 1.

specifically to establish cause-effect of the use of NIV, nevertheless with the data described, a marked reduction in both daytime and nocturnal symptomatology was observed in ventilation users, especially in the long term versus those who did not use it, although the statistical probability was not significant due to the small size of the sample.

Authors such as Annane in a systematic review of studies with nocturnal NIV in chronic hypoventilation in patients with ENM and chest wall concluded that the short-term evolution (one to three months) of the patients improved symptomatology with a significant difference, as well as diurnal hypercapnia and nocturnal oxygen saturation (13). Casas evaluated the evolution of patients after one year of NIV use in patients with motor neuron disorders, showing a decrease in dyspnea and disappearance of asthenia, hypersomnolence, headache, lower limb edema and memory loss; there was also an improvement in gas exchange: PaO_2/FiO_2 and $PaCO_2$.[9] Young also demonstrated significant reduction in daytime somnolence and headache after the use of NIV in children with MND[33] analogous to this article.

On the basis of the above considerations, it is expected that pneumonia, respiratory failure and cardiovascular repercussions[30] will improve in patients using bilevel positive pressure NIV compared to those who do not. On the contrary, in this study a reduction in complications was observed in both groups, although without statistical significance; surely this is due to the establishment of other therapeutic alternatives such as amygdalectomy, improvement of nutritional status, optimization of respiratory physiotherapy, orthopedic correction of spinal deformities, etc. Although gasometric controls are ideal after the establishment of therapeutic measures for patient monitoring, not all patients had control gasometry, and this limited the long-term assessment of hypoxemia and CO_2 levels.

CONCLUSIONS

The present work is one of the first investigations of chronic alveolar hypoventilation in pediatric population at moderate altitude, knowing that higher altitude has a negative impact on ventilatory control in patients with chronic diseases that are associated with an inherent impairment in alveolar ventilation. Altitude implies an increase in volume/minute proportional to the decrease in partial pressure of oxygen and therefore an increase in work of breathing that may incur disproportionate increases in these patients.

It should be noted that most patients at the time of diagnosis presented both daytime and nocturnal symptoms, the main causes of hypoventilation were of peripheral origin; and despite the benefit of NIV as an effective measure in reducing symptoms and complications, it was not widely used as would be expected due to the high cost of equipment acquisition.

Finally, the main limitations of this work were the small size of the population studied and limited information in the records. In addition, the patients who met the criteria to be part of this study did not correspond to the exact number of alveolar hypoventilation cases in the pulmonology service due to underreporting in the hospital's computer system. As a recommendation for future research, we emphasize the need for further studies with a greater number of patients with complete information recorded in their records, as well as close follow-up of patients with NIV use.

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Medical training in orotracheal intubation with acrylic box in pediatric SARS-CoV-2 patients decreases exposure time

El entrenamiento médico en la intubación orotraqueal con caja de acrílico en pacientes pediátricos con SARS-CoV-2 disminuye el tiempo de exposición

Adriana del Carmen Luna-Castañeda,* Carlos Juárez-Ortiz,‡ Abril Arellano-Llamas,‡ María Viridiana Figueroa-Gómez,* Blanca Estela Martínez-Martínez,* Laura Patricia Thomé-Ortiz,* Ingrid Basemat Guerrero-Macías,* Areli Pichardo-Estrada,* Carlos Ramos-Verástica,* Ricardo Flores-Galindo§

*Centro Médico Nacional Siglo XXI. Unidad Médica de Alta Especialidad (UMAE) Hospital de Pediatría «Dr. Silvestre Frenk Freund», IMSS; ‡Centro Médico Nacional «La Raza». Unidad Médica de Alta Especialidad (UMAE) Hospital «Dr. Gaudencio Garza González». Instituto Mexicano del Seguro Social (IMSS); §Centro de Simulación para la Excelencia Clínica y Quirúrgica, Instituto Mexicano del Seguro Social (IMSS).

ABSTRACT. Introduction: in the SARS-CoV-2 pandemic, the modification of the intubation technique using the aerosol box, in order to reduce exposure to aerosols generates anxiety in Health Workers (HCWs), by increasing the degree of difficulty and time of endotracheal intubation (IT). Simulated intubation environments allow to measured IT and also increase intubation ability and decrease IT. **Objective:** to measure IT pre (without box without training -SS-, with box without training -CS-, with box with training -CC-) and post educational maneuver. **Material and methods:** retrospective, comparative, before and after; with physicians trained in a simulated environment. **Results:** n = 82, age 29 years (27 to 31 years), clinicians 69.5%, residents 82.9%. IT: SS 35 s (27-47.25 s), CS 39.5 s (28-56.5 s) and CC 22 seconds (17.5-30 s), p = 0.0001. Higher IT of clinical vs surgical physicians SS 39 s (30-52 s) versus 32 s (24-34 s), p = 0.004; CS 42 s (33-59 s) versus 28 s (21-43 s), p = 0.016; CC 25 s (20-35 s) versus 19 s (16-21 s) p = 0.018. Higher TI novice vs experienced SS 68 s (39-135 s) versus 34 s (27-46 s), p = 0.058; CS 144 s (84-210 s) versus 38 (28-54 s), p = 0.001, CC 46 s (30-55 s) versus 22 s (17-30 s), p = 0.030. Using the device without training increased IT, but post-training IT decreased in all groups -16 s (-26 to -7 s), which was more noticeable among novices -98 s (-163 to -45.5 s) and the clinical

RESUMEN. Introducción: en la pandemia por SARS-CoV-2, la modificación de la técnica de intubación utilizando dispositivos de barrera (aerosol box) para disminuir la exposición a aerosoles generó ansiedad en los trabajadores de la salud (TS), al incrementar el grado de dificultad y el tiempo de intubación endotraqueal (TI). Los ambientes simulados de intubación incrementan la habilidad para la intubación y disminuye el TI. **Objetivo:** medir el TI pre y posmaniobra educativa (sin caja sin entrenamiento -SS-, con caja sin entrenamiento -CS-, con caja con entrenamiento -CC-). **Material y métodos:** retrospectivo, comparativo, con médicos capacitados en el ambiente simulado. **Resultados:** n = 82, clínicos 69.5%, residentes 82.9%. TI: SS 35 s (27-47.25 s), CS 39.5 s (28-56.5 s) y CC 22 s (17.5-30 s), p = 0.0001. Mayores TI de clínicos versus quirúrgicos SS 39 s (30-52 s) versus 32 s (24-34 s), p = 0.004; CS 42 s (33-59 s) versus 28 s (21-43 s), p = 0.016; CC 25 s (20-35 s) versus 19 s (16-21 s), p = 0.018. Mayor TI novatos versus experimentados SS 68 s (39-135 s) versus 34 s (27-46 s), p = 0.058; CS 144 s (84-210 s) versus 38 s (28-54 s), p = 0.001; CC 46 s (30-55 s) versus 22 s (17-30 s), p = 0.030. El uso del dispositivo sin entrenamiento aumentó el TI, pero en todos los grupos hubo disminución del TI posterior a la capacitación -16 s (-26 a -7 s), más notoria entre los novatos -98 s (-163 a -45.5 s) y el grupo

Correspondence:
Adriana del Carmen Luna-Castañeda, MD
Centro Médico Nacional Siglo XXI. UMAE Hospital de Pediatría «Dr. Silvestre Frenk Freund», IMSS. Mexico City, Mexico.
E-mail: lunac.neumoped@gmail.com

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group -18.5 s (-32 to -7 s). **Conclusion:** the use of devices with training can be efficient in terms of IT, regardless the degree of experience and type of medical specialty.

Keywords: aerosol box, clinical simulation, simulated learning, acrylic box .

clínico -18.5 s (-32 a -7 s). **Conclusión:** el uso de dispositivos puede ser eficiente en términos de TI con un entrenamiento independientemente de la experiencia y especialidad médica.

Palabras clave: aerosol box, simulación clínica, aprendizaje simulado, caja de acrílico.

INTRODUCTION

The transmission pathway of SARS-CoV-2 is airborne, via droplets or aerosols. Procedures that generate aerosols (droplets less than 5 microns), such as endotracheal intubation, expose health care workers (HW) to risk. At the beginning of the pandemic, it was considered that a transparent acrylic intubation box or aerosol box that partially isolate the patient can increase the protection of the HW, specially in places with little access to personal protective equipment (PPE) or videolaryngoscopes.[1-5]

The intubation box (IB) is an acrylic box that does not have a standardized design, it consist of an acrylic device of 6 mm thick, the dimensions of the original design (40 cm high in the distal wall, 50 cm wide and 40 cm deep, the front face is divided into two walls one at 90º of 25 cm high, on which is the second with an angle of 70º of 21 cm for a total of 46 cm, the ceiling of the box measures 25 cm deep. The anterior face has two circular holes of 12.5 cm in diameter placed at 12.5 cm from the base) were modified from the original proposal by Hsien-Yung and reproduced by Canelli, because of the smaller dimensions of the pediatric patient.[6,7] The intubation was then more difficult, which generated distress in the HW. There are observations that the use of the intubation box by expert anesthesiologists lengthens the intubation time in simulated environments, but that it has no clinical significance.[8-10] Even though the current guidelines for airway management in the patient with COVID-19 recommend the use of the videolaryngoscope, since it confers a lower degree of difficulty and decrease in intubation time (although in the last systematic review of Cochrane there were no significant differences between the intubation time with both equipment), it is an equipment that may not be accessible in all the health centers.[3,4,11,12]

The use of the aerosol box is suggested as an additional element or in certain moments when there is a deficit of personal protection elements, that is, the box must be used without ignoring the other recommended protective elements.[13] Several studies have evaluated the risks of using the aerosol box during intubation with greater risk of exposure to aerosolized particles, as well as obstruction of the procedure, with variable results.[9,10,12]

The simulated education spaces are educational tools that facilitate the knowledge and skill acquisition for health care[14-16] and during the beginning of the pandemic it was crucial to prepare the HW in simulated environments that would give them the security to perform procedures in optimal times with the personal protection tools available, reducing anxiety and increasing the skills of the clinicians, translating into real life reduction of the risk of exposure to aerosols.[17]

A clinical simulated environment for the pediatric endotracheal intubation dexterity was design in the unit that includes the development of sedation, relaxation and endotracheal intubation skills in a pediatric manikin, with the addition of the acrylic aerosol box, with the described characteristics and depicted in *Figure 1*.

Our objective was to measure the effect of education in a simulated environment on effective intubation time (IT), with and without the use of the acrylic box as personal protective material before and after training, and to compare according to the level of experience of the HW, the type of speciality and the type of hiring with in the hospital.

MATERIAL AND METHODS

A retrospective, comparative study was carried out before and after an educational maneuver in a simulated environment in a third level pediatric hospital in Mexico City.

Doctors of several pediatric specialities were included, who were classified into clinical and surgical specialities,

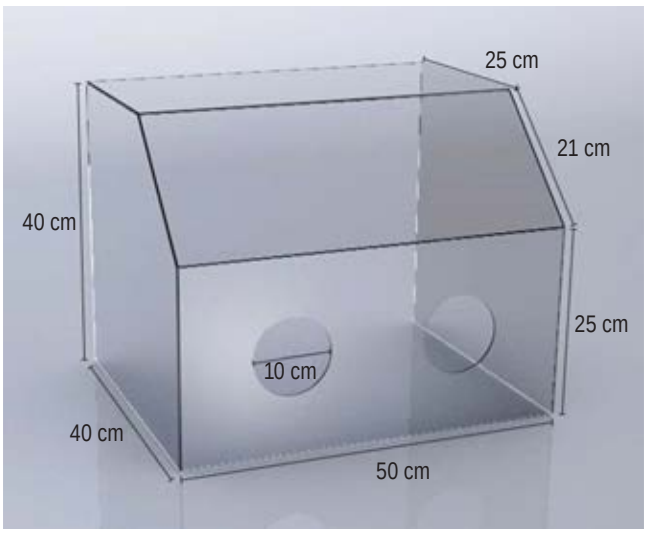

Figure 1: Acrylic box designed for this study.

and by the type of work they perform in the hospital as residents in training or seconded personnel. In addition, physicians were classified according to their intubation experience, those with no experience in endotracheal intubation (novice) and those who had experience were called experienced.

The educational maneuver consisted of training for pediatric endotracheal intubation with a pediatric manikin by adding an acrylic box between the doctor and the manikin. The educational maneuver was developed in workstations, where the doctors were instructed in teams of two resuscitators.

Each stations consisted of two tables, the first with audiovisual equipment, the second with simulation equipment (Laerdal brand neonatal intubation head, Kawe brand laryngoscope, with Miller blade number 0, intubation equipment, acrylic box designed by the biomedical team of the hospital). Trained doctors used in the simulated environment only gloves as personal protective equipment.

The training was divided into three phases:

1. Audiovisual explanation of 10 minutes, where the generalities of the technique of intubation, team roles and rapid sequence of intubation were explained, as well as the modified technique for intubation with the acrylic box.
2. The team's instructors made a demonstration of the intubation procedure, by simulation, with the pediatric manikin *(Figure 1)*.
3. The last phase was divided into the following sections:
   a. The intubation time without the acrylic box was timed with the technique that doctors routinely use (it was called time WITHOUT box and WITHOUT training -WW-). The IT was measured with chronometer from the moment the laryngoscope was taken until the tube position check was done when inflating with self-inflating bag.
   b. The intubation was timed using the acrylic box (it was called time with BOX, WITHOUT training -BW-) The IT was timed with chronometer starting with the arms out of the box and finished until the position of the endotracheal tube was checked.
   c. Five intubation exercises without chronometer were performed with the instructor on a personalized basis, where feedback and detailed correction of the technique were performed.
   d. Once again, the intubation time was timed with acrylic box after training (it was named with BOX, with TRAINING -BT-). IT was timed with chronometer starting with the arms out of the box and finished until the position of the endotracheal tube was checked.

Table 1: Characteristics of the population and intubation times.

	Total sample n (%)
Male sex	24 (29.3)
Age [years]*	29 [27-31]
Speciality type	
Clinicians	57 (69.5)
Surgical	25 (30.5)
Experience	
Novice	4 (4.9)
Experienced	78 (95.1)
Type of hiring	
Residents	68 (82.9)
Seconded	14 (17.1)
Time WW s,*	35 [27-47.25]
Time BW s,*	39.5 [28-56.5]
Time BT s,*	22 [17.5-30]

WW = without box without training. BW = with box without training. BT = with box with training. s = seconds.
* Data expressed in median [interquartile range].

Intubation times without box and without training -WW-, with box and without training -BW- and with box and with training -BT- were compared. The times were compared with the Wilcoxon test, the variables with medians and interquartile range are described. The statistical analysis was done with the SPSS program.

RESULTS

82 doctors were included in this study. The characteristics of the sample are found in *Table 1*, where it is highlighted that the majority were female (71%), the median age was 29 years old (27 to 31), most of the clinical group (69.5%) and residents in training (82.9%), there were four people who had no experience in intubating (4.9%).

Regarding the degree of training: three (3.6%) were general practitioners hired for the COVID area, 32 (39%) second and third year pediatric residents, 22 (26.8%) qualified pediatricians and sub specialists and 25 (30.48%) from the surgical area.

The WW intubation times for all the population were 35 seconds (27-47.25 s), BW of 39.5 seconds (28-56.5s) and BT of 22 seconds (17.5-30.0 s), resulting in a significant difference generated from training (p= 0.0001).

There were no differences for intubation times between the sexes in any of the three timed phases (WW p = 0.808, BW p = 0.808, BT p = 0.321), nor between the type of in-hospital hiring (residents versus seconded personnel WW p = 0.769, BW p = 0.379, BT p = 0.951). No correlation was observed between

intubation times and the age of who intubates (WW rho = -0.173, p = 0.302; BW rho = -0.035, p = 0.379; BT rho = -0.065, p = 0.282).

A significant difference in intubation time was observed in the three timed phases between clinical and surgical doctors, having shorter times the doctors of surgical speciality systematically: clinical WW 39 s (30-52 s) versus surgical 32 s (24-34 s), p = 0.004; clinical BW 42 s (33-59 s), surgical 28 s (21-43 s), p = 0.016; and clinical BT 25 s (20-35 s) and surgical 19 s (16-21 s), p = 0.018.

Regarding intubation experience it was also observed a significant difference in the three intubation times between novices and experienced: novices WW 68 s (39-135 s), experienced 34 s (27-46 s), p = 0.058; novices BW 144 s (84-210 s) and experimented 38 s (28-54 s), p = 0.001; and novices BT 46 s (30-55 s) and experimented 22 s (17-30 s), p = 0.030.

For all the groups there was a significant decrease in intubation times, BT versus BW *(Table 2)*. It stands out that in the group of clinicians the best decrease in the intubation time after training was noticed.

DISCUSSION

The number of COVID-19 patients requiring endotracheal intubation can increase to until 40%.[18-20]

According to the Begley results *et al.*, intubation with acrylic box increases the execution time, however, the learning based on simulation can address those challenges.[10] We have observed that the group that systematically takes the longest to achieve intubation is that of clinician, and that with training in simulated environments it is the most benefited in reducing intubation time with the use of aerosol box. In this sense, the clinicians are given two safety measures for their clinical practice: the first, the use of a barrier that decrease exposure to aerosol and, the second, the dexterity of achieving intubation in less time.

In this study it was not possible due to limitation of personal protection resources to carry out the training with this equipment, which can influence the IT in real life. The debate persists as to whether this procedure can lengthen IT by introducing a new device. Álvarez *et al.* observed that when using aerosol box and personal protective equipment in a simulated scenario hinders intubation maneuver and may prolong execution time; in inexperienced personnel, the aerosol box has been shown to increase IT. A study carried out in anesthesiology residents found that despite previous training in simulated environments, IT with acrylic box increased significantly compared to IT without box; however, the sample of this study was limited.[21] For Fong *et al.* there were no significant differences between IT with box and without box, with a difference of seconds in simulated scenarios with normal airway, only during difficult scenarios where not only was IT increased, but also more intubation attempts were required; although several studies have found that the use of the aerosol box slows down the procedure even in experimented airway specialists, due to greater difficulty in handling the devices, reduction of arm movements inside the box, increase in cognitive load by having to systematize a new process and lack of experience. Some other authors conclude that the aerosol box is clinically irrelevant as long as the operator is experienced in handling the airway, this under normal conditions.[9,10,12,22-28]

Starting from the original box, several modifications have been made that have decreased the limitations originally published, recently Kim *et al.* evaluated IT with different aerosol box designs in manikins with normal and difficult airway, finding that a modification in the box reduce IT, without finding significant differences in IT without aerosol box versus modified aerosol box for both normal and difficult airway, which gives protective benefit without delaying the intubation time.[29]

In our study, training in simulated environments improved the intubation time, even compared to intubation without box, similar to what was reported by Lima *et al.*, who found the IT improved after five intubation maneuver for each participant with box and without aerosol box, with similar times to what was reported in our study.[30] This again opens up the need for continuing education in essential skills, as it shows that clinicians are required to have ongoing training in simulated environments to improve their performance under stressful conditions and increased cognitive load. The simulation, in addition to being a controlled learning environment, provides information to modify or improve the systematization of processes. Colman *et al.*, with biomedical engineering help, manage to adapt the acrylic box based on the information of each participant after use it in simulated environments.

Table 2: Intubation time with acrylic box after training.

	Reduction of intubation time with use of box after maneuver, seconds	p
Total of population	-16 (-26 a -7)	
Residents	-14 (-25 a -7)	0.188
Seconded	-19 (-57 a -11)	
Clinicians	-18.5 (-32 a -7)	0.096
Surgical	-12 (-21 a -7)	
Novices	-98 (-163 a -45.5)	0.001
Experienced	-15 (-24 a -7)	

It is required that doctors have ongoing access to training to prevent skills from being lost over time. Young generations perform better in learning in simulated environments compared to the seconded group, making it an area of opportunity for health personnel training centers.

The particular box used in this study was a modification to the original model, since the adults dimensions differ from the pediatric population. In this project, the ability to limit the generation of aerosols or avoid exposure was not assessed, nor was the time with complete PPE evaluated, since these were reserved for the clinical care of patients, the issue of the removal of the device was not explored to ensure that the staff did not suffer further exposure. These are open lines of research and it is not the intention of this observation to give an opinion on these aspects.

CONCLUSION

Training in the endotracheal intubation procedure in a simulated intubation environment with the use of acrylic box, in times of COVID-19 pandemic, in a pediatric hospital, decreased the exposition in time to aerosols timed by the procedure time. The simulated environment significantly favors endotracheal intubation skills in stressful TS situation, thereby improving rapid and effective action in a state of severe airway compromise.

This study has several limitations. In first place, was not possible to carry out the training with the entire PPE given the scarcity that existed at the beginning of the pandemic. In second place, we only evaluate intubation time after training in manikins with normal airway, so our results are limited.

The main objective of this work was to measure the impact of the educational maneuver after the training of the use of aerosols in a simulated environment, we consider that given the significant reduction of IT and better performance of the TS after the educational maneuver, the aerosol exposition time can be reduced, so all hospitals should consider these educational resources in the continuing training of their personnel.

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Review
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Eicosanoids as regulators of inflammation and immune processes during pulmonary tuberculosis

Los eicosanoides como reguladores de procesos inflamatorios e inmunológicos en la tuberculosis pulmonar

Ana Luisa Escalona-Sarabia,* Esmeralda Juárez‡

*Universidad Nacional Autónoma de México, Mexico City, Mexico; ‡Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico.

ABSTRACT. Human tuberculosis (TB) is a public health problem. Although it is a curable disease, the actual treatment protocol is long and difficult to maintain. Because of the limit progress of new therapies during the latest years, host-directed therapies have taken more interest, being one of the proposals the intervention on the eicosanoids' metabolic route. Eicosanoids are local chemical mediators that promote or limit inflammation progress. During TB, hyperinflammation generates damage to the pulmonary parenchyma with the subsequent deterioration of respiratory function. Despite the importance of this circuit, reports about the utility in tuberculosis sometimes are controversial or not conclusive. With the aim of knowing and integrating the information published, in this review we search and analyze different studies that look forward to defining the eicosanoids' role on *M. tuberculosis* infection. For this, we review the role of eicosanoids post-infection *in vivo* or *in vitro*, and the modification of their metabolic route before or after infection. We also propose an algorithm to optimize the future investigations of eicosanoids and their utility as therapeutic targets during TB.

Keywords: tuberculosis, eicosanoids, host-directed therapies.

RESUMEN. La tuberculosis (TB) humana es un problema de salud pública. Aunque es una enfermedad curable, el protocolo de tratamiento actual es largo y difícil de mantener. Debido al limitado avance de nuevos tratamientos en los últimos años, las terapias dirigidas al hospedero han tomado un mayor interés, siendo una de las propuestas la intervención en la ruta metabólica de los eicosanoides, los cuales son mediadores químicos locales que favorecen o limitan la inflamación. Durante la TB, un estado de hiperinflamación genera daño al parénquima deteriorando la función respiratoria. A pesar de la importancia de este circuito, los reportes sobre su utilidad en tuberculosis en ocasiones son controversiales y no concluyentes. Con el objetivo de conocer e integrar la información publicada, en este trabajo se analizaron diversos estudios que buscan definir el papel de los eicosanoides en la infección por *M. tuberculosis*. Para ello, analizamos el papel de los eicosanoides posinfección *in vivo* o *in vitro*, y las intervenciones terapéuticas en su ruta metabólica *in vivo* pre- o posinfección. Además, proponemos un algoritmo que permita para optimizar futuras investigaciones sobre eicosanoides y su utilización como blancos terapéuticos de la TB.

Palabras clave: tuberculosis, eicosanoides, terapias dirigidas al hospedero.

INTRODUCTION

Human tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is one of the 10 leading death causes in the world.[1] In Mexico, more the 20,000 new cases are reported each year, mostly in the pulmonary form.[2,3] Chronic inflammation in the lungs can cause damage to the parenchyma and deterioration of the respiratory function,[4,5] making the inflammatory circuit a therapeutic target to preserve pulmonary function. Consequently, host-directed therapies such as cytokines modulators (IFN-γ and TNF-α), anti-fibrotic, or molecules that activate macrophages are ideal because of their ability to modulate the immune system and limit post-infection tissue damage.[6,7]

Intervening the metabolic pathway of eicosanoids is a therapeutic option to prevent inflammation and preserve pulmonary function. Eicosanoids are lipids derived from polyunsaturated fatty acids (PUFA) that are obtained from the intake of omega-6 or ω-6 fatty acids (arachidonic acid [AA]) and omega-3 or ω-3 (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]). These lipids are synthesized enzymatically by lipoxygenases (LOX) and/or cyclooxygenases (COX) in leukocytes, endothelial cells

Correspondence:
Esmeralda Juárez, MD
Instituto Nacional de Enfermedades Respiratorias
Ismael Cosío Villegas, Mexico City, Mexico.
E-mail: ejuarez@iner.gob.mx

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and platelets.[7] There are two main families of PUFA with antagonistic activities, pro-inflammatory and pro-resolution.

The pro-inflammatory eicosanoids include thromboxanes, prostaglandins and prostacyclins synthesized by COX-2, and leukotrienes, synthesized by 5 and 15-LOX from AA. Pro-inflammatory eicosanoids are chemoattractant of neutrophils, activate phagocytosis in alveolar macrophages,[8] mediate the cells trafficking,[9] and induce necrosis, edema, increase blood flow and production of pro-inflammatory cytokines. Pro-resolution eicosanoids, or specialized pro-resolution lipid mediators (SPMs), are synthesized by 5 and 15-LOX and include lipoxins, resolvins, protectins and maresins.[10] These lipids limit the flow of neutrophils, block the production of reactive oxygen species, induce apoptosis and increase the macrophage phagocytic activity favoring the return of homeostasis and cell regeneration.[11,12]

As important as this circuit is for the respiratory infection, its contribution in the inflammatory regulation in TB needs to be reviewed in terms of published experimental models. In this revision, we will consider the molecular mechanisms of eicosanoids involved in the regulation of inflammation during TB in animal models; we will observe that some phenomena observed in animal models cannot be replicated in humans and vice versa; and we will analyze the validity of using host-directed therapies based on the molecular mechanisms that eicosanoids regulate.

Experimental models used to study the role of eicosanoids in tuberculosis

To define the role that eicosanoids play in *M. tuberculosis* infection we established three experimental designs: 1) post-infection eicosanoid quantification; 2) therapeutic intervention *in vivo* with polyunsaturated fatty acids (PUFA) before infection; and 3) therapeutic intervention with PUFA post-infection.

Post-infection eicosanoid quantification. Animal models infected *in vivo* with virulent strains of *M. tuberculosis* (H37Rv, Erdman or HN878), as well as samples of patients, reveal changes in eicosanoids levels during and after TB infection that correlate with the severity of the disease.[13,14] The most studied eicosanoids are derived from AA: PGE2, lipoxin A4 (LXA4) and LTB4. The presence of LXA4 and LTB4 is associated with necrosis and tissue damage,[12] while the presence of PGE2, or its receptor EP2, have opposite effects and are associated with infection resistance.[12-14] Increase of LXA4 is associated with a greater susceptibility to disease and PGE2 with a protective response. In the pulmonary tissue of patients with pulmonary TB, the presence of AA and leukotriene A4 hydrolase (LTA4H) are observed in necrotic centers and presence of cyclooxygenases at the periphery of the lesions are observed.[15] Patients with pulmonary TB, multidrug-resistent (MDR) TB or latent TB have higher circulating amounts of PGE2, LTB4 and LXA4 than a healthy person.[16-18]

Although other eicosanoids were measured in some studies, such as maresin (Mar1, Mar2), resolvins RvD (RvD1-6) and RvE (RvE1-4); prostaglandins (PGF2, PGD2), protectins (PD1) and eicosanoid precursors 12-HETE or 15-HETE,[19-21] none of these are relevant for TB individually. Rather, the effects of eicosanoids depend on their relative contribution.[22] For example, an increase in serum LTB4/Mar1 ratio distinguishes patients from healthy individuals,[19] the LTB4/LXA4 ratio decreases post-treatment,[13] the connections between SPM and pro-inflammatory lipids are higher in TB-DM patients compared to TB-only patients,[20] and PGE2 levels depend on the LTB4/LXA4 ratio.[23]

The relationship between PGE2 and LXA4 is antagonistic in macrophage cultures, LXA4 induces necrosis and PGE2 induces apoptosis for cell protection against infection.[24-26] As in *in vivo* determinations, increased LXA4 is associated with increased susceptibility to infection, increased inflammation and bacillary burden. In addition, *M. tuberculosis* infection increases the release of AA in macrophages and its transformation into LXA4 mediated by 5-LOX.[24] Inhibition of LXA4 synthesis protects against necrosis,[12] and therefore its induction seems to be a survival strategy of the mycobacterium. Regarding SPM, RvD1 and Mar1, they induce anti-inflammatory mechanisms and restore the synthesis of antimicrobial peptides in human macrophages infected with the virulent strain *M. tuberculosis* H37Rv.[25] The lack of measurement of other eicosanoids prevents us from knowing the real impact of the inflammation-resolution circuit during *M. tuberculosis* infection.

Therapeutic interventions performed *in vivo* prior to infection. Research in which eicosanoids are administered or therapeutics that modify their metabolic pathways are applied prior to infection can explain the mechanisms involved during the disease process. The most common interventions are the use of diets enriched with omega-3 and omega-6 fatty acids, diets deficient in these fatty acids, and drugs that inhibit eicosanoid synthesis.

Mice treated with ω-6 supplemented diets[26,27] and guinea pigs fed with ω-3 supplements[28] show increased bacterial load, but BALB/c and C3HeB/FeJ mice fed omega-3 enriched diets show reduced bacterial load and reduced amounts of pro-inflammatory cytokines released into the local environment.[26,29,30] In humans, a longitudinal-prospective study revealed that there was a higher risk of developing TB at higher cholesterol intake and a lower risk of developing TB at higher intakes of ω-3 and ω-6 of marine origin.[31] However, due to their antagonistic biological effects, it is difficult to reach a conclusion when consumption is varied and occurs prior to infection.

Drug intervention includes 5-LOX or COX-2 inhibitors to manipulate the metabolic pathway. Inhibiting 5-LOX

has negative effects because it increases susceptibility to infection by decreasing the number of leukocytes and increasing bacterial load.[32-34] The molecular mechanism involved is uncertain, since 5-LOX participates in the synthesis of LTB4 and LXA4 from AA, both with antagonistic effects, and also in the production of resolvins from DHA and EPA, which are pro-resolution. In cases where 5-LOX inhibitor was administered, the absence of resolvins, and not LTB4, could be the reason for the lack of infection control.

COX-2 inhibition has benefits such as a decrease in bacterial load, the size and presence of granulomas and mortality.[19,32-35] COX-2 inhibition involves blocking prostaglandins, prostacyclins and thromboxanes, whose biological effects on TB have not been explored. This strategy has prophylactic potential for people exposed by close contact with patients. However, in most of these trials, treatments were administered before infection and continued during infection, so it is difficult to know whether the result is due to activation of pre-infection mechanisms or to their post-infection maintenance.

Therapeutic interventions performed post-infection. Post-infection interventions include direct supplementation of eicosanoids *(Table 1)* or pharmacological inhibition of their synthesis *(Table 2)*. Schemes using dietary changes

Table 1: Effect of eicosanoid supplementation during *M. tuberculosis* H37Rv infection.

Mouse strain/model	Eicosanoid administered	Treatment	Main effects	Ref.
SV129 and deficient in 5-LOX	LTB4 single treatment	*In vivo*	LTB4 induces IFN-γ, decreasesTNF-α, promotes necrosis and increases pathogenicity and mortality. IncreasesTNF-α in 5-LOX deficient mice	19
C57BL/6	PGE2 single treatment	*In vivo*	PGE2 reduces excess of IFN-γ, necrosis and pulmonary damage and does not interfere with the action of antibiotics	37
C3HeB/FeJ	Iron-enriched diet + AIN-93G (EPA/DHA supplement)	*In vivo*	EPA/DHA + iron causes decreased IL-1, TNF-α and IFN-γ and increased bacterial load. Supplements alone decrease inflammation and anemia. EPA/DHA decreases bacterial load, increases SPM and T-cell recruitment	64
C3HeB/FeJ	Enriched EPA/DHA diet + rifafour + RIF (rifampicin)-INH (isoniazid)	*In vivo*	EPA/DHA-enriched diet reduces the production of pro-inflammatory cytokines (IFN-γ IL-1β, IL-6, IL-1α). The EPA/DHA diet elevates SPM, reduces pro-inflammatory lipids, and decreases pulmonary damage	74
Monocytes from TB patients and healthy individuals treated with ibuprofen	PGE2	*Ex vivo/in vitro*	PPGE2 reduces IFN-γ and TNF-α, expression of surface receptors (SLAMF1, CD31, CD46, CD80, CD86, MHC1) necessary for T cell activation and receptors (SLAMF1, PD-L1) in neutrophils. PGE2 protects the host from excessive inflammation and promotes autophagy	69
MDM from healthy donors	PGE2, EP2 or EP4 receptor blockers or agonists	*In vitro*	Treatment with EP2 agonists results in lower cell necrosis. Treatment with EP4 antagonists results in COX-2 inhibition	67
Monocytes from healthy donors	AA Analogs	*In vitro*	AA analogs induce cell death by both apoptosis and necrosis. Necrosis induced by AA derivatives in monocytes requires calcium mobilization, production of reactive oxygen species, calcium modulating enzymes, PLA2 and calpains	53
Blood mononuclear cells from donors of unknown status	Short-chain fatty acids (AG) (C4)	*In vitro*	Short-chain AGs do not affect COX-2 expression, but decrease IL-10 and Th17 proliferation	54
MDM from healthy donors	RvD1, RvD2, PDX, LXA4 or Mar1 without conventional treatment	*In vitro*	RvD1, LXA4 and Mar1 reduce TNF-α production. RvD1 and Mar1 induce anti-inflammatory and antimicrobial mechanisms and NFκB translocation. RvD1 and PDX increase phagocytosis	25

All experiments carried out with different bacterial loads. All treatments administered in different post-infection regimens. Rifafour (150 mg rifampicin + 75 mg isoniazid + 400 mg pyrazinamide + 275 mg ethambutol).

Table 2: Effect of pharmacological inhibition of eicosanoid synthesis on *M. tuberculosis* infection.

Experimental model	Drug	Drug function	Main effects	Ref.
Mice C57BL/6 infected with *M. tuberculosis* H37Rv	Zileuton + conventional treatment	5-LOX inhibitor	It increases the amount of PGE2 without interfering with conventional antibiotics	37
Mice C3HeB/FeJ infected with *M. tuberculosis* Erdman	T863	Triglycerides synthesis inhibitor	It increases 5-LOX products and decreases the production of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, IFN-β), prostanoids, bacillary load and neutrophil infiltration	43
Mice C57BL/6J infected with *M. tuberculosis* H37Rv	SC-26196	Inhibits FADS-2, ω-3 formation	Chronic infection induces the synthesis of new PUFA to generate eicosanoids (mainly AA). Inhibiting PUFA synthesis has no effect on bacterial growth in the liver or lung	44
Mice BALB/c infected with *M. tuberculosis* H37Rv	SBG or SBG + NA + conventional treatment	SBG is TGF-β inhibitor, NA is COX-2 inhibitor	Increased pneumonia in mice with blockers (SBG or NA), but less pulmonary fibrosis. Blocking agents enhance the activity of antibiotics	45
Mice BALB/c infected with *M. tuberculosis* H37Rv	NA	COX-2 inhibitor	Blocking COX-2 at the onset of infection causes increased interstitial and perivascular inflammation, pneumonic areas, and bacterial load. Advanced phase blockade of infection causes increased area of granuloma, IFN-γ, TNF-α, and iNOS with decreased pneumonic area and bacterial load	46
Mice C3HeB/FeJ infected with *M. tuberculosis* H37Rv	Ibuprofen + conventional treatment	Ibuprofeno is COX-2 inhibitor	Ibuprofen reduces the production of pro-inflammatory cytokines (IFN-γ, IL-1β, IL-6, IL-1α)	74
Swiss albino mice infected with *M. tuberculosis* H37Rv	Diclofenac + STR (streptomycin)	Diclofenac is COX-2 inhibitor	Diclofenac decreases inflammatory cytokines (IL-2, TNF-α, IFN-γ), induces antimicrobial activity, enhances antibiotic activity of STR and increases survival	47
Mice C3HeB/FeJ and CB6F1 infected with *M. tuberculosis* H37Rv and Erdman	Celecoxib or ibuprofen	Both are COX-2 inhibitors	Celecoxib impairs the immune response of CD4+ T cells. The effect of both COX-2 inhibitors depends on the initial bacterial load of the infection, when the bacterial load and inflammation are very high, a benefit is seen when using COX-2 inhibitors	75
Mice C3HeB/FeJ infected with *M. tuberculosis* H37Rv	Aspirin + rifafour	Aspirin is COX-2 inhibitor	Aspirin reduces IL-1α, increases TNF-α, IL-17, IL-1β and IL-6 and reduces pulmonary damage	42
Mice BALB/C infected with *M. tuberculosis* H37Rv	Aspirin or ibuprofen + INH	Aspirin and ibuprofen are COX-2 inhibitors	Aspirin inhibits the antibiotic activity of INH but ibuprofen does not. None of the COX-2 inhibitors alone have effects on bacterial load	38
Mice BALB/C infected with *M. tuberculosis* H37Rv	Aspirin or ibuprofen + PZA (pyrazinamide)	Aspirin and ibuprofen are COX-2 inhibitors	Reduction of inflammation with ibuprofen or aspirin. Combination of aspirin or ibuprofen with PZA increases the antibacterial effect by reducing the bacterial load on the liver and lung	76
Mice C3HeB/FeJ infected with *M. tuberculosis* H37Rv	Ibuprofen	COX-2 inhibitor	Ibuprofen decreases the severity of necrotic lesions, reduces bacterial load and increases survival	50
BMDM of mice C57/6BL infected with *M. tuberculosis* H37Rv	siRNA for COX-2 + PG	COX-2 inhibitor	COX-2 inhibition causes increased bacterial load associated with inhibition of autophagy in infected macrophages	77
BMDM of mice C57BL/6 infected with *M. tuberculosis* Erdman	IFN-γ + T863	Triglycerides synthesis inhibitor	IFN-γ promotes the formation of lipid droplets during infection. T863 prevents the formation of these droplets and decreases the amount of prostaglandins and LXA4	78

Continue toTable 2: Effect of pharmacological inhibition of eicosanoid synthesis on *M. tuberculosis* infection.

Experimental model	Drug	Drug function	Main effects	Ref.
BMDM of mice C57BL/6J infected with *M. tuberculosis* H37Rv	SC-26196	FADS-2 inhibitor	Reduction of inflammation gene transcription (TNF-α, IL-1β, IL-6) and production of reactive oxygen species. Induction of synthesis of new PUFAs for generation of PGE2, PGD2, TXB2, LXA4 and as a nutrient for mycobacteria	44
Plasma of TB patients	Ibuprofeno + conventional treatment	COX-2 inhibitor	Lower amount of PGE2 in patients with ibuprofen. Patients with more PGE2 had reduced radiological lesions, T-cell proliferative response, and secretion of IFN-γ and TNF-α	48
Patients with pulmonary TB	Etoricoxib + conventional treatment	Etoricoxib is COX-2 inhibitor	COX-2 inhibition causes decreased frequency of myeloid-derived suppressor cells (M-MDSCs), necrosis, and disease severity	49
Patients with pulmonary and extra-pulmonary TB	Celecoxib + conventional treatment	Celecoxib is COX-2 inhibitor	Inhibiting COX-2 reduces inflammation by activation of the 5-LOX pathway with reduction of pro-inflammatory cytokines and production of LXA4. Patients with cavities had higher concentrations of LXA4	52
Whole blood form healthy donors infected *in vitro* with *M. tuberculosis* H37Rv	Celecoxib + RIF or PZA	Celecoxib is COX-2 inhibitor	COX inhibition decreases T-cell response. Celecoxib alone has no antibacterial effects and its use does not potentiate the effect of antibiotics	79
Blood mononuclear cells of healthy donors and patients with TB infected *in vitro* with *M. tuberculosis* H37Ra	HQL79 or NS398	HQL79 is PGD2 inhibitor and NS398 of COX-2	Decreased PGE2 decreases the number of regulatory T cells, but does not affect the production of IL-10 and TNF-α	80

All experiments carried out with different bacterial loads. If not specified, no antibacterial agent was included in the therapeutic scheme. Rifafour (150 mg rifampicin + 75 mg isoniazid + 400 mg pyrazinamide + 275 mg ethambutol).

or agonists of PGE2, LTB4 or other eicosanoids post-infection are scarce. In general, direct supplementation with eicosanoids reduces the production of pro-inflammatory cytokines, influences pathogenicity[19] or confers protection.[36,37] Paradoxically, PGE2 is a pro-inflammatory with immunosuppressive effects.[12] In addition, RvD1 and Mar1 have anti-inflammatory effects without detriment to antimicrobial mechanisms.[25]

On the other hand, eicosanoids of both types are produced during infection,[38-40] and diets supplemented with DHA/EPA have anti-inflammatory effects,[41,42] but the relationship between the two phenomena is unknown. Further research is needed to know the true potential of DHA/EPA supplementation during TB in humans.

Pharmacological inhibition of eicosanoid synthesis during *M. tuberculosis* infection *(Table 2)* relies mainly on the *in vivo*, *in vitro* and *ex vivo* use of COX-2 inhibitors (niflumic acid [NA], aspirin, celecoxib, etoricoxib or ibuprofen). This inhibition generally causes reduced inflammation by decreasing cytokine production, reduced tissue damage, and increased survival. Controversially, inhibiting COX-2 may increase the bacterial load when treatment is applied in early stages of infection,[43] probably due to the immunosuppressive effects of PGE2,[12] whereas the late use of these inhibitors allows a better resolution of the disease, with reduction of bacterial load and inflammation, which protects against tissue damage.[33,44-47] COX-2 inhibition needs to be taken with caution, as its immunosuppressive effects may affect the patient during the early stages of the disease and further studies are required to determine its efficacy in TB.

Molecular mechanisms associated to metabolism of eicosanoids in *M. tuberculosis* infection

During the first hours of infection, AA of nuclear and plasma membrane is processed by COX-1 and COX-2 into PGH2, which it is converted to PGE2 by cPGES, mPGES-1 or PGES-2.[48] In infected macrophages, PGE2 production correlates with decreased phagocytosis, nitric oxide production, prevention of necrosis, increased pro-inflammatory cytokines and induction of apoptosis, protecting the mitochondrial membrane, promoting plasma membrane repair and enhancing the control of innate immunity to mycobacterial infection.[14,18,49] PGE2 also activates autophagy by enhancing bacterial elimination in autophagolysosomes.

Autophagy, in turn, controls inflammation by regulating innate immune signaling, modulating the secretion of immune mediators and eliminating endogenous agonists from the inflammasome.[50]

After the first 24 hours post-infection, there is an increased production of LXA4[37] in macrophages, which causes a change in AA metabolism mediated by 5-LOX.[24] Increased LXA4 levels are associated with reduced necrosis, bacillary burden, pro-inflammatory cytokines, vascular permeability, polymorphonuclear leukocyte (PMN) entry to the sites of inflammation and Th1-type protective response.[14,15,18]

The effect of 5-LOX on AA also causes an increase in LTB4. During the early stages of inflammation, only mesothelial cells and macrophages are able to release LTB4 into the pleural space in response to an initial inflammatory stimulus. Once the inflammatory process is established, other cells, such as neutrophils, produce LTB4 amplifying the inflammatory process.[51] LTB4, in turn, induces necrosis, increased nitric oxide production and chemotaxis *(Figure 1)*.

On the other hand, AA is also metabolized in thromboxanes and prostacyclins,[19,52] but these have not been associated with TB. Other membrane PUFA that are metabolized during inflammation and cellular stress are DHA and EPA. The conversion of omega-6 and omega-3 precursors into PUFA is controlled by fatty acid desaturase enzymes (FADS) 1 and 2.[36] Subsequently, these are transformed by 5-LOX into maresin, protectins and resolvins. Although they have been reported during TB,[35,53,54] the involvement of these eicosanoids in the disease process is unknown, with the exception of resolvin D1 (RvD1) and maresin 1 (Mar1) which contribute to the control of *M. tuberculosis* infection *in vitro* by increasing bactericidal permeability-increasing protein (BPI) and cell regeneration.[25]

Scope of interventional therapies of the eicosanoid metabolic pathway

Post-infection interventions have allowed us to understand the scope of these host-directed therapies *(Figure 2)*. Currently, three metabolic pathways involved in eicosanoid synthesis have been inhibited: COX-2, 5-LOX and triglyceride synthesis. COX-2 inhibitors decrease PGE2 production causing different effects depending on the time at which they are administered;[43] at the onset of the disease, they induce an increase in necrotic areas, a greater amount of inflammatory cytokines and T cells;[37] on the other hand,

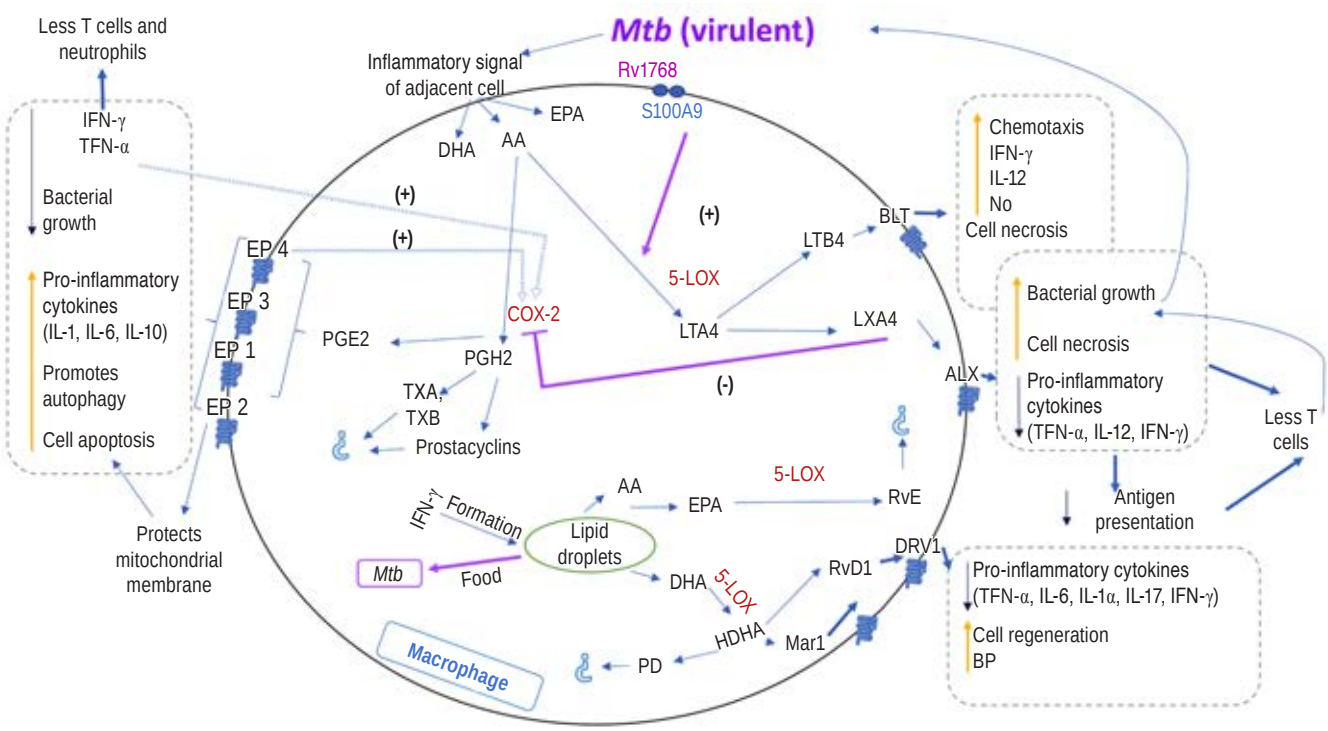

Figure 1: Molecular mechanisms involved in eicosanoid metabolism during *M. tuberculosis* infection. Infection with the virulent strain of *M. tuberculosis* activates the metabolic pathway of LTA4 for the production of LTB4 and LXA4, whose cellular effects are antagonistic. At the same time, a blockage occurs in COX-2-associated signals, paradoxically inducing additional pro-inflammatory mechanisms. Eicosanoid receptors and precursors taken from: Esser-von Bieren J[9] and Duvall MG, et al.[80]

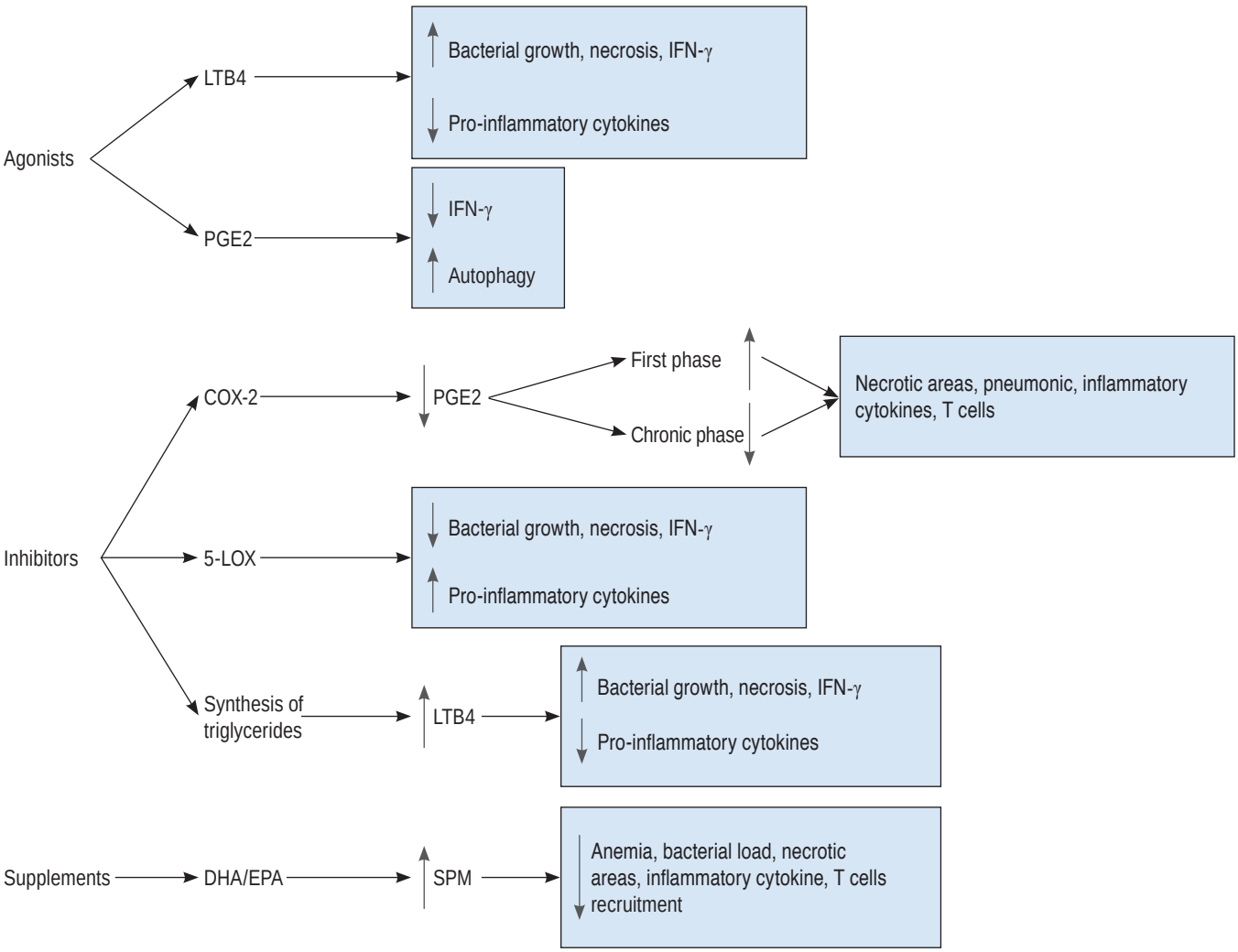

Figure 2: Scope of interventions on the metabolic pathways of eicosanoids post-infection with *M. tuberculosis.* The main therapeutic interventions reported are the use of agonists or inhibitors of the components of the metabolic pathway of eicosanoids and the modification of the diet with precursors. Downward arrows indicate decrease and upward arrows increase in the production of the metabolite or in the magnitude of the biological phenomenon described as a result of the intervention.

COX-2 inhibition in chronic stages decreases lesions and disease severity.[36] In general, no interference with the use of conventional antibiotics was found.

Inhibition of 5-LOX reduces bacterial growth and necrosis, but increases pro-inflammatory cytokines;[23] it is unknown whether this effect is due to increased LXA4 or reduced LTB4. Triglyceride synthesis up-regulates 5-LOX, but inhibition of triglycerides reduces bacterial load, possibly because it represents nutrient depletion.[38,40] With the use of DHA/EPA dietary supplements, animal models reveal a reduction in anemia, inflammation and bacterial load and increased SPM synthesis.[54] The impact this intervention would have in humans is unknown; however, SPM derived of DHA/EPA, MAR1 and RvD1 in *in vitro* cultures of human cells are known to have cell regeneration and inflammation-lowering effects.[25] However, studies on genetic polymorphisms report an increased susceptibility to disease in populations with variations in 5-LOX,[8] LTA4H[55] or EP2[56] genes; while others report no associations between these same genes and disease severity.[57-59]

Although animal models offer a variety of resources for the study of tuberculosis, some limitations of currently used experimental models prevent critical analysis and implementation of therapeutic interventions in humans. For example, not all mouse strains experience a predominantly inflammatory response, whereas immunocompetent humans experience exacerbation of inflammation.[35] The variety of mouse strains used influences the outcome; in

many cases it was necessary to modify some gene to allow the study of the metabolic pathway of interest.[60] C3HeB/FeJ and Sv129 mice are extremely susceptible to *M. tuberculosis* infection, and C57BL/6J and BALB/c mice are resistant.[61-63] In mice, the biological action of PGE2 is mediated by four prostanoid receptor-linked proteins EP1, EP2, EP3 and EP4. These receptors are also expressed in human macrophages.[14] However, in infected murine macrophages there is a higher amount of EP4 compared to EP2, which does not occur in human macrophages.[64]

In humans, the most frequent form is pulmonary tuberculosis; however, in research, mainly plasma and blood cells from donors are studied, which do not reflect what occurs in the alveolar space. Currently, different types of CT scans have been used to monitor the natural history of the disease, but it is difficult to carry out experimental studies in humans.[65]

Other animal models have been used. For example, rabbits infected with *M. tuberculosis* HN878 produce lesions similar to those found in humans. The distribution patterns of AA within the granuloma are similar in humans and rabbits,[15] which would make the rabbit a better model; however, in rabbits *M. bovis* strains are normally used for the study of tuberculosis,[65] rabbits are more expensive to maintain and their high susceptibility to stress demands strict control of environmental factors. In addition, the different biological responses between breeds and the positions of the various animal advocacy associations preclude further information.[66]

Regarding supplementation with ω-3 (omega-3), the experimental models are very diverse and do not predict the expected result in humans. Even the experimental doses used do not realistically represent the dietary intake in humans;[67] the Food and Agriculture Organization of the United Nations (FAO) recommends a daily intake of 250 mg of EPA + DHA.[68] In recent years, the demand for supplements has been increasing, but the necessary amount of consumption of each of them separately is unknown, since each one has a different metabolism.[69] In Mexico, the average consumption of DHA/EPA is also unknown; however, following the COVID-19 pandemic, the consumption of fish (main source of these fatty acids) was reduced in households by 27-43%.[70] For laboratory animals, the latest National Research Council (NRC) nutritional requirement tables published in 1995 do not specify the amounts of PUFA needed in the diet,[71] but it is known that their administration is important to avoid a fatty acid deficiency that causes signs such as dermatitis, fatty liver, weight loss and reproductive problems.[72] Dietary recommendations are changing according to new discoveries in the nutritional area.[68,69]

Finally, *ex vivo/in vitro* studies do not fully reflect the complexity of lung structure and pathogen-host interactions.[73] *Ex vivo* whole blood studies have the advantage over *in vitro* cultures in that they allow us to evaluate the integration of the effects of antimycobacterial therapies through the host immune response[37] and allow

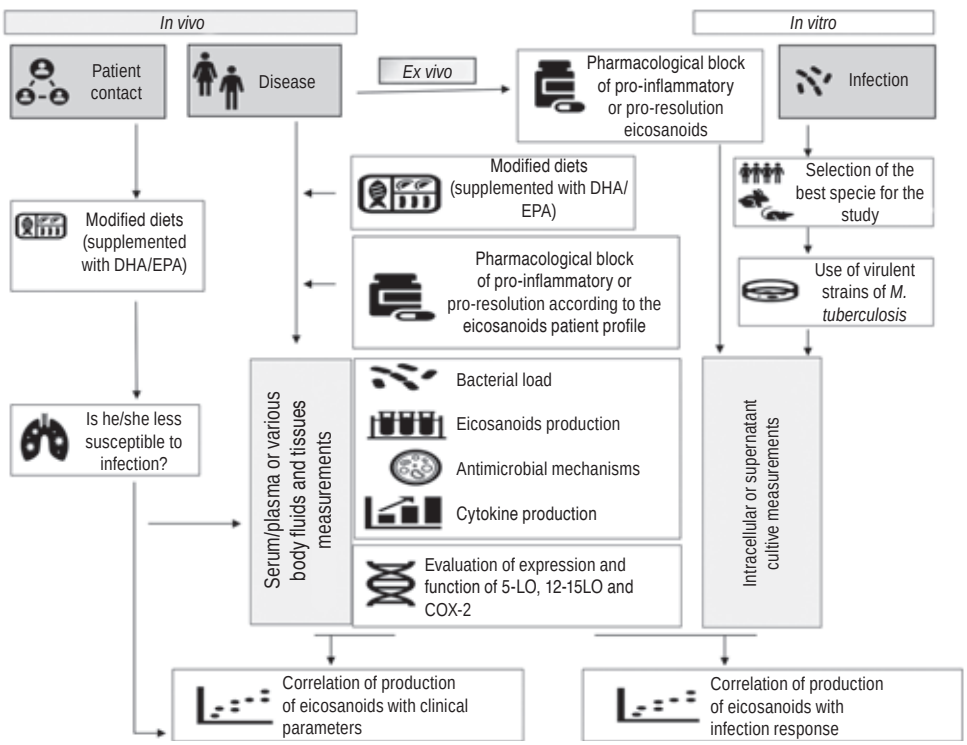

Figure 3:

Experimental optimization for the study of eicosanoids and their use as therapeutic targets. Critical factors to be taken into account for the search for host-directed therapies based on the intervention in the metabolic pathway of eicosanoids.

us to get closer and closer to understanding the molecular mechanisms involved in TB.

Requirements for future experimental designs

Interventions in the metabolic pathway of eicosanoids offer different therapeutic targets for TB that allow reducing pulmonary inflammation to preserve lung functionality without loss of antimicrobial immunity. For future research to better understand the mechanism of action of eicosanoids and to propose effective therapeutic schemes in TB, experimental strategies need to be optimized *(Figure 3)*. Whether *in vivo, in vitro* and *ex vivo* investigations, the use of virulent TB strains will be important to better understand host-parasite metabolic interactions. In addition, it is necessary to prioritize research in humans, *in vitro* and *ex vivo*, both TB patients and their contacts. To know the real scope of interventions in the eicosanoid pathway, it will be necessary to measure bacterial load, cytokine production and cellular antimicrobial activity, as well as to define the complete profile of eicosanoid production with a view to personalized medicine, taking into account the previous profile and the phase of the disease in which the patient is.

CONCLUSIONS

Because eicosanoids offer therapeutic targets of interest for TB, it is important to optimize experimental models and their impact on the generation of these targets. Diets with DHA/EPA supplementation and pharmacological blockade of either pro-inflammatory or pro-resolution eicosanoids could be beneficial to both the patient and the patient contact. Eicosanoids not only have roles in the inflammatory response, but also act as mediators of the pathogenesis process, so further research is needed to better understand the potential of eicosanoids as future host-directed therapies.

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Review
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Pathophysiological effects of the E-cigarettes: a public health issue

Efectos fisiopatológicos del cigarro electrónico: un problema de salud pública

Marnix Valdemar Martínez-Larenas,* Ángel Antonio Montañez-Aguirre,* César Antonio González-Valdelamar,* Mariana Fraga-Duarte,* Gabriela Cossío-Rodea,* Juan Carlos Vera-López*

*Universidad La Salle, Mexico City, Mexico.

ABSTRACT. Nowadays electronic nicotine delivery systems (ENDS) have become very popular among the general population, specifically among adolescents; however, the effect of these new devices on the health of consumers is not fully understood; also, it is unknown if it is a healthy alternative to replace combustion cigarettes or tobacco, or as a therapy to quit smoking. This review aims to clarify and update the pathophysiological effects of these new cigarettes so that the medical and scientific community can understand them, as well as to compare the damage to health generated by electronic nicotine delivery systems against that generated by the combustion cigarette. The alternative hypothesis was verified by observing that the consulted literature coincided in the concept that the consumption of the electronic cigarettes result in damage to the organism.

Keywords: vaping, tobacco, lung injury, e-liquid, ENAS, EVALI.

RESUMEN. Hoy en día los sistemas electrónicos de administración de nicotina (SEAN) comienzan a ser muy populares entre la población en general, en específico en los adolescentes; sin embargo, no se conocen totalmente los efectos de estos nuevos dispositivos en la salud de los consumidores, y se desconoce si es una alternativa saludable para reemplazar los cigarrillos de combustión o de tabaco, al igual que su uso como terapia para dejar de fumar. Esta revisión tiene como objetivo clarificar y actualizar los efectos fisiopatológicos de estos nuevos cigarros para que la comunidad médica y científica pueda entenderlos, así como comparar el daño a la salud que generan los sistemas electrónicos de administración de nicotina contra el que genera el cigarrillo de combustión. Se comprobó la hipótesis alterna al observar que las referencias que se ocuparon coincidían en el daño al organismo por el consumo del cigarro electrónico.

Palabras clave: vapeo, tabaco, lesión pulmonar, *e-liquid*, SEAN, EVALI.

INTRODUCTION

Electronic nicotine delivery systems (ENDS) are instruments used to aerolize substances without the use of a combustion process; after aerolization these substances are then inhaled.[1,2] The main components of an ENDS are: a rechargeable lithium battery, a vaporization chamber containing an atomizer and heating coil, and a cartridge in which the e-liquid product is stored.[1,2] When the device is turned on, the components of the e-liquid are aerosolized and then inhaled by the user, so the term «vaping» is incorrect because no vapor is generated; however, it is the simplified term that has been standardized to refer to the combustion process of the device. The substances contained in the liquid component of the ENDS generate certain elements that can be harmful to the body and that with their frequent inhalation could have serious consequences on the organism.[1,2]

Currently, the use of the electronic cigarette (EC) has increased as a «healthy alternative» to replace the traditional tobacco cigarette (TC) or as another way to consume nicotine or other substances.[3] However, this is a subject on which little information is available and whose veracity is not fully proven by the scientific community. Furthermore, its use as a replacement for TC has not been approved by the Food and Drug Administration (FDA) or the Center for Disease Control and Prevention (CDC). In fact, these agencies have reported that vaping as a healthy alternative is not recommended, since the health conditions it may cause have not been sufficiently studied.[4] In August 2019, cases of E-cigarette or Vaping Use-

Correspondence:
Marnix Valdemar Martínez-Larenas
Universidad La Salle. Mexico City, Mexico
E-mail: marnix.martinez@lasallistas.org.mx; marnix@prodigy.net.mx

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Associated Lung Injury (EVALI) were reported with deaths associated with its use, even though these are marketed as a safe and healthy strategy to quit smoking. According to several studies, it has been found that vaping used for the purpose of quitting smoking TC has only replaced it and the bad habit of smokers continues, therefore, it is not efficient as a measure to quit smoking.[5] Throughout these years, a notorious increase in its use has been observed in several population groups, in particularly in the youngest age group there has been an increase in its consumption, a population ranging from 18 to 24 years old.[6]

In addition, the *Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas* in Mexico City and other respiratory, cardiology and public health societies worldwide have issued an important alert to the general population about lung damage in vapers.[7] Taking into account these alerts and the increase in EC consumption, the pathophysiological mechanism of EC should be investigated to warn consumers of the possible damage they may present and to improve possible treatments for such damage.[7]

This review aims to find and clarify the possible pathophysiological effects of these new cigarettes so that the medical and scientific community can understand them, as well as the comparison between the health damage generated by the EC and the tobacco cigarette.

EPIDEMIOLOGY

The increase of EC is closely related to the popularity that this product has gained over the years in the general population. It was invented in China in 2003 and first introduced to the US market in 2007, since then it has experienced some success among smokers, non-smokers, pregnant women and even young people, therefore increasing the demand for this product and, consequently, its consumption, with a boom in sales starting in 2013. This clearly increased curiosity and the need for the scientific community to evaluate the safety of its consumption.[1]

It has been shown that the reasons for EC consumption and the pattern of consumption vary greatly depending on the age of the consumer. In the last decade, EC use among the US adult population has increased by 3.8%; of which 16% were cigarette smokers and 22% were former TC smokers.[1] On the other hand, the young population has had the largest increase in EC use, of which 5.3% of all users are middle school students and 16% are high school students.[1] EC use in this age-group is closely related to users' curiosity and the «appealing» flavors contained in e-liquids. The latter is alarming because nicotine exposure at these ages can interfere with brain development and impact academic performance, as well as increase susceptibility to addiction to nicotine or other drugs.[1]

According to the article *Epidemiology of electronic cigarettes: the arrival of JUUL* by Arroyo-Cózar,[6] in the National Health Interview Survey (NHIS) from 2014 to 2018 on «daily use» and «use on at least one occasion in the last month» of EC, it was observed that the prevalence rose markedly in the age-group of minors, with consumers having an approximate age of 18 to 24 years. Likewise, it refers that since 2014, the most consumed product by youth in the United States is EC.

On the other hand, in the context of the consumption of this product in Europe, a survey was conducted in 2017 among almost 28,000 individuals; the investigators reported that 84% had «never consumed EC»; this result differs with the 2015 survey, where this population was 87%.[6]

In the epidemiological notice issued by the National Epidemiological Surveillance Committee (CONAVE) on September 25, 2019, it warns of a possible association between severe lung disease and EC or vape use and presents the epidemiological situation in the United States and Mexico.[7] On September 19, 2019, 530 cases of lung injury and seven deaths were reported in 38 states in the United States, whose specific cause of lung injury was unknown, but it did show that all cases had a history of EC use. Among the 530 cases, 72% were males between the age group of 18 and 34 years. Of the cases, 16% were younger than 18 years and 17% were older than 35 years. These cases showed what is called a pattern of pneumonitis, which are: acute eosinophilic pneumonia, lipoid pneumonia, diffuse alveolar damage and acute respiratory distress syndrome, diffuse alveolar hemorrhage, hypersensitivity pneumonitis and giant cell interstitial pneumonitis.[7]

In Mexico, data obtained in the Tobacco Report of the National Survey on Drug, Alcohol and Tobacco Use (ENCODAT) 2016-2017 revealed that 5.9% of the population aged 12 to 65 years alluded to having ever tried EC. The prevalence of EC consumption in this same survey was 1.1%, resulting in a total of 975,000 Mexicans consumers of this product.[7]

Electronic cigarette components (EC)

The EC is an electronic device for administering nicotine or some other substance, which can be combined with nicotine or administered independently. It generates a mixture of aerosols of the substances contained in the e-liquid to be inhaled by the user.[1,8] Its designs have evolved over the years, creating different generations of this product; however, all models contain three main components: a power source, a vaporization chamber and a cartridge.[1,2] The power source is usually a rechargeable lithium battery *(Figures 1 and 2)* connected to the vaporization chamber where an atomizer is in contact with a heating coil,

which obtains its energy from the battery. The cartridge is the place where the e-liquid is stored and also has a communication with the vaporization chamber. When the user wants to use the device, he must press a button that makes the battery turn on the heating coil (some of them contain a led light that indicates that the device is on), converting the e-liquid components into aerosols, which will be inhaled into the lungs by the user through an attached mouthpiece.[1,2] The industry of this product has been evolving more and more, nowadays there are new EC models that allow to make the use of this device more personalized through a microprocessor, with the ability to modify the resistance, the voltage supplied to the heating coil (modifying the temperature that each user wants) and the desired amount of nicotine.[2]

There are four generations of ECs on the market. The first generation are the so-called ciga like devices,[1] this type of EC is mainly composed of a cartridge, an atomizer and a low voltage battery (3.7 V); usually for users who are just starting to consume this type of product, most of these ECs are disposable.[1] The second generation of ECs are slightly different from the first, as they are quite a bit larger and contain a rechargeable tank for refilling with e-liquid with the flavoring of the user's choice; they also contain a battery that allows the user to adjust the voltage between high or low (3 to 6 V) during the inhalation of the aerosol.[1] The third generation differ only by the size of the battery; these are larger and have a higher voltage, up to 8 volts.[1] Finally, we have the most recent generation of this product, the fourth generation. These have a heating coil that maintains a resistance of less than 1 Ohm. In addition, they have temperature control devices that provide the user with the ability to modify the temperature and thus be able to inhale larger amounts of the aerolized components, which also leads to higher e-liquid consumption per inhalation.[1]

Now, e-liquid is a component that contains three main ingredients: the solvent (which can be vegetable glycerin and/or propylene glycol), various flavorings, and nicotine in various dosages.[2,9] Manufacturing labels are usually incomplete as to all the components that e-liquid contains; however, a large variation in chemicals can be detected in the aerosol resulting from the solvents and flavors used in the reaction.[2] These chemicals *(Figure 2)* that can be detected are carbonyl compounds such as formaldehyde, acetaldehyde, acetone and acrolein; volatile organic compounds such as benzene and toluene; tobacco-specific nitrosamines; particulate matter (suspended particles); and metals such as nickel, copper, zinc, tin and lead.[9] One of the great challenges currently faced in assessing the health effects of ECs is the high variability of the chemical components found in the aerosols produced (even within samples of the same product, differences have been observed);[9] this is due to the customization of ECs, which allows some components to be adjusted as mentioned above.[2] This has led to great confusion regarding whether these types of cigarettes are healthier than traditional tobacco cigarettes. Concentrations of these chemicals have been reported to be below those found in conventional cigarettes and below occupational safety standards, although this is not a consistent finding, so not all studies have had this result.[2]

Besides electronic nicotine delivery devices, there are also ECs used for the delivery of tetrahydrocannabinol (THC), a psychoactive component found in cannabis. The structural components of these devices are similar to those of ECs for nicotine delivery, but one of the main components that differentiates them is the vitamin E acetate used as a solvent.[10] This is one of the main components involved in the pathophysiology of lung injury associated with ENDS.

Adverse effects and attributed diseases

It should be taken into account that the effects of EC depend on several factors. According to the evidence investigators propose the following: the type of device, content of the liquid to convert to aerosol, user behavior and experience.[11] Still, both the long-term effects,[11] the rate of adverse effects (AE) and the impact to health are not well known.[12]

In a cross-sectional study conducted by Pénzes *et al.* in 2018, it was found that 44.6% of 65 Hungarian adults who are daily EC users reported AEs. The most common AEs in daily users were: dry mouth and pharynx, cough, burning

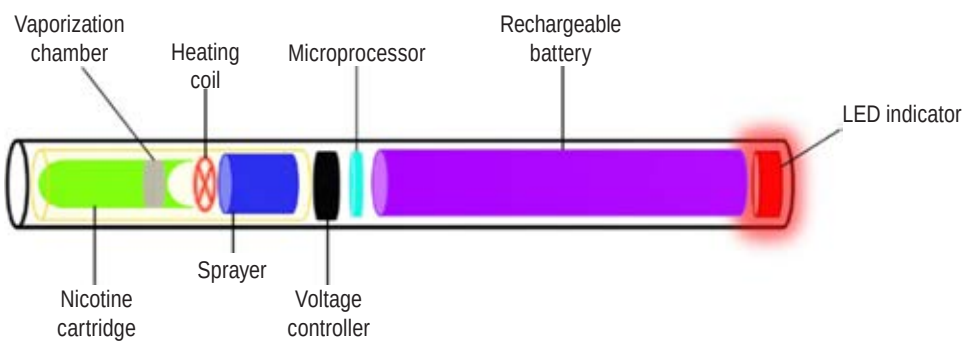

Figure 1:

Constitution and design of an electronic cigarette with microprocessor. Modified from: Qasim H, et al.[1]

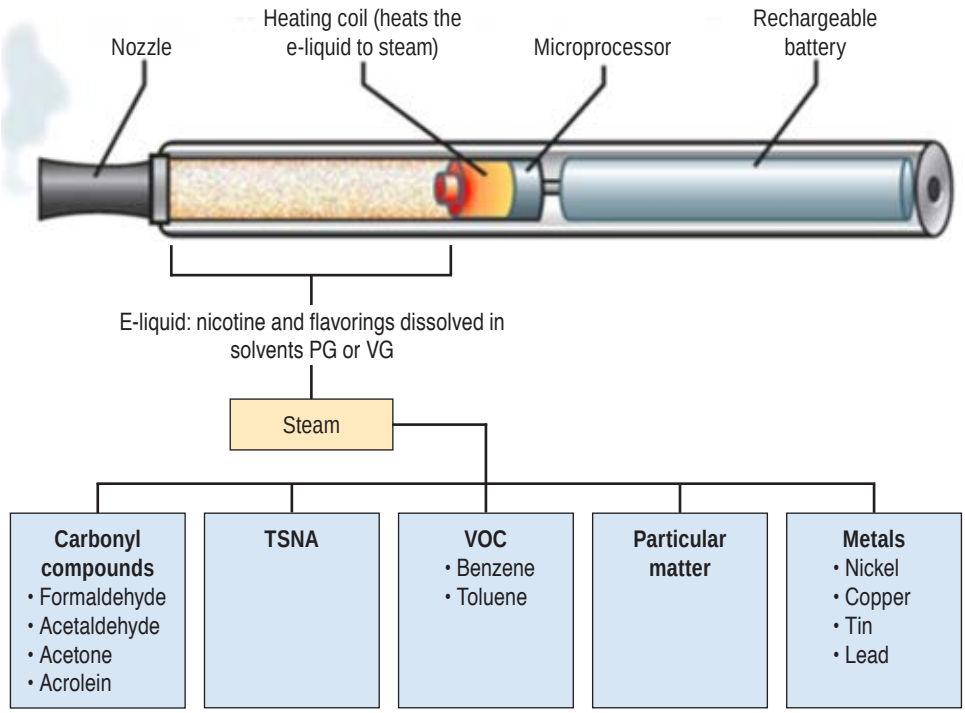

Figure 2:

Composition and design of an electronic cigarette. The electronic cigarette is made up of three main components: power source, vaporization chamber and a cartridge. By heating the e-liquid its substances are aerolized and subsequently inhaled by the user. Modified from: Sood AK, Kesic MJ, Hernandez ML. Electronic cigarettes: One size does not fit all. J Allergy Clin Immunol. 2018;141(6):1973-1982.
PG = propylene glycol.
VG = vegetable glycerin.
TSNA = tobacco-specific nitrosamines.
VOC = volatile organic compounds.

sensation in mouth, lips and pharynx, and headache. In contrast, former users reported a variety of other AEs such as: palpitations, breathing problems, dizziness, decreased taste and drowsiness.[12]

EVALI. An entity has been recognized in the medical literature associated with EC use, EVALI.[4,13,14] The CDC established the epidemiologic surveillance definition of this lesion as «cases of patients who have used e-cigarette and vaporizer products 90 days prior to symptom onset, with pulmonary infiltrates on imaging studies and not attributed to any other entity (either pulmonary infection or other likely diagnosis)».[4]

An investigation conducted in Illinois and Wisconsin revealed that 98 patients exhibited a clinical picture that included respiratory, gastrointestinal, and constitutive manifestations. The most common symptoms were shortness of breath (85%), cough (85%), chest pain (52%), nausea (66%), vomiting (61%), diarrhea (44%), abdominal pain (44%) and subjective fever (84%). Similarly, 83% of cases were found to have leukocytosis (> 11,000 leukocytes/mm^3) with a predominance of neutrophils > 80%.[14] On chest X-ray and CT scan the most common pattern found was ground glass infiltrates with predominance in the lower lobes.[14,15]

Another review found that pathological anatomy showed nonspecific histological changes with patterns of other identities of acute lung injury such as fibrinous pneumonia, diffuse alveolar damage, and organizing pneumonia. The only histopathological finding in all cases was the presence of foamy macrophages and vacuolated pneumocytes.[16]

Myocardial infarction (MI) and other cardiovascular diseases. A cross-sectional study in the United States in 2020 revealed that EC use is associated with MI, although this depended on the user's history. Similarly, current users were found to have an association with one MI event during their lifetime.[17] In the Pénzes study, 46.9% of current users mentioned that they had experienced a MI compared with 35.2% of the ex-users. On the other hand, exclusive EC users reported more MIs than combustion cigarette users, 63.1 vs. 38.6%.[12] In mice, EC has been shown to have effects on hemostasis and to increase the risk of thrombogenic events,[18] although more research is needed.

Lung cancer. EC theoretically has an oncogenic effect because several of the components of vape liquids contain proven human carcinogens, most notably formaldehyde, heavy metals, and nitrosamines. However, there is no research that has been done to confirm this in humans.[19]

Physiopathology

The main causes of the damage generated by ECs are the materials they contain, ranging from flavorings and tobacco to carcinogenic substances such as n-nitrosonornicotine and nitrosamine ketone (substances derived from nicotine). ECs containing heavy metals have also been found in e-liquid, and although not all ECs use the same materials, their unmeasured consumption generates lung damage at best (EVALI) as well as neurological and cardiovascular conditions at worst.[1]

Causes and symptoms of EVALI. Patients with EVALI have presented with a variety of symptoms including: breathlessness, fever, coughing, vomiting, diarrhea, headache, dizziness, and pain after use of vaping devices. Symptoms are generally consistent with chemical pneumonitis, they may appear and worsen suddenly.

In spite of the fact that it is known that EVALI is caused by the use of EC or some other vaping device that provokes biochemical, cellular and molecular changes in the pulmonary epithelium, giving rise to the appearance of this disease, the exact etiology is unknown.[20] Several hypotheses have been generated trying to explain the etiology of this alteration, the most accepted seems to be related to the materials used in vaping products, from the combustion mechanisms they use to the chemical products they contain, among them, the one that seems to be most related is the use of vitamin E acetate, which is a chemical product with a sticky and oily texture, used as a component for the elaboration of ECs containing THC, which when inhaled adheres to lung tissue.[20]

In a study that analyzed bronchoalveolar lavage from healthy patients and patients with or likely to have EVALI, it was reported that 25 patients were confirmed with EVALI and 26 patients with probable EVALI.[20] Of these patients, bronchoalveolar lavage identified vitamin E acetate in the bronchoalveolar fluid obtained in 48 of 51 patients, 94% of the cases. When compared with bronchoalveolar fluid from healthy patients, it was reported that the bronchoalveolar fluid obtained from the healthy comparison group did not show traces of vitamin E acetate.[20]

The role of vitamin E acetate in lung injury. Vitamin E acetate possesses a structure showing a long aliphatic chain that appears to be able to penetrate the surfactant layer to align the molecule in parallel with the surfactant phospholipids.[21] Several biochemical properties of vitamin E acetate have been proposed that may be responsible for the occurrence of EVALI, which are:

1. Role as an inducer of the crystalline to gel-liquid phase transition: phosphatidylcholine appears to undergo a transition from gel to a crystalline liquid phase. This transition to a crystalline liquid phase allows the surfactant to lose the ability to maintain the lung surface tension necessary for ventilatory mechanisms to occur in the lung, making this situation the main mechanism of respiratory dysfunction by vitamin E acetate.
2. Acts as an inducer of exogenous lipoid pneumonia: in the biological system vitamin E acetate has the characteristic of having a lipid droplet deposition. It has been shown that one of the most prominent features of lung biopsies from patients with EVALI is the observation of intraalveolar lipid-laden macrophages, which may be evidence of vitamin E acetate accumulation.
3. It is a modulator of the DGK-PKC pathway: vitamin E acetate may antagonize the catalytic activity of PKCα K, as studies indicate that the substance is able to compete with diacylglycerol (DAG) for its binding site on PKCα.[22] For this reason, vitamin E acetate could play an analogous anti-inflammatory role in the pulmonary system, interfering with the normal inflammatory response of the lung to irritant compounds such as dust or even components present in the EC itself.[22]
4. It can behave as a pregnane X receptor (PXR) agonist: when administered to the biological system, vitamin E is transformed into a large number of bioactive metabolites, most notably PXR agonists, which function as a transcription factor of cytochrome P450 monooxygenase genes. If vitamin E acetate behaves as a PXR agonist, a transcriptional activator of cytochrome P450 genes could contribute to the pathogenesis of EVALI where there is a large increase in cytochrome P450 activity.

These biochemical properties of vitamin E acetate may explain the participation of this compound in the pathophysiogenesis of EVALI. It is of utmost importance to think of vitamin E acetate as the main compound responsible for the pathophysiogenesis of EVALI because of the strong relationship between the presence of this compound in bronchoalveolar fluid with the presence of EVALI, which is 94%.[20]

Although vitamin E acetate is the chemical component that has the strongest relationship with lung damage, it is not present in all ECs, so the pulmonary pathophysiology in these cases is associated more with the other chemicals contained in the EC. The main ones are the flavorings and the processes used to generate the vapor that is inhaled, since these can contribute to the accumulation of heavy metals derived from this process. An example of the contribution of chemical products (in addition to vitamin E acetate), as stated above, are the flavorings, since[23] several flavors in the vapor extract of the EC were shown to have a cytotoxic effect on the airway epithelium, causing alterations in the conformation of the airways and, therefore, problems in gas exchange. Variations were reported to exist among different brands.[23] In addition, exposure to EC vapor induces oxidative stress in the respiratory epithelium. Nicotine and flavorings mostly contained in the liquid of EC cartridges have a synergistic effect on the induction of oxidative stress genes,[24] so these products, may contribute to the pathophysiology of lung damage caused by EC.

Impact of vaporizers on the cardiovascular system. The impact that vaporizers will have on the cardiovascular system is directly proportional to various factors, both of the vaporizer and the liquid they contain.[1] It has been shown that vaporizers that handle higher voltages will produce a

higher concentration of aerosols of the elements contained in the e-liquid when vaporized.[25] Another factor to evaluate is the percentage of each substance in each liquid as well as the materials it is made of, as is the case with flavorings, glycerin or propylene glycol, and nicotine.[1] It is important to emphasize that the EC, unlike the conventional cigarette, does not generate a total combustion of the materials it contains, which is extremely important because this was the main advantage or characteristic with which these products were initially sold.[1] However, it has been proven that the aerosol that can be generated can be equally or more harmful to the body and especially to the cardiovascular system than if a conventional cigarette were smoked.

According to the American Heart Association,[1] it is mentioned that although the concentrations of various toxic materials are lower than those of conventional cigarettes, they can still cause significant damage to the cardiovascular system. This may vary according to the studies taken into account, since the results vary according to the wide variety of vaporizers, nicotine concentration, vaping techniques and the experiences of each user. So to understand the damage caused by ECs, we must know the damage caused individually by each element contained in the liquid.[1]

Nicotine. It is probably one of the major components of the solution contained in the EC and all products used for smoking in general. In this same article it is reported that many times the companies that manufacture these solutions do not label them correctly, since some brands specify that their products do not contain nicotine, but when examined, small amounts can be found.[1] It is important to mention that nicotine is a psychoactive substance, which has a high affinity to nicotinic cholinergic receptors, having an activating action at the beginning and later a blocking action. In general, the action at the cerebral level is that of central stimulation, resulting from an increase in the release of several neurotransmitters. However, it also causes an increase in the plasma concentration of adrenocorticotropic hormone (ACTH), activating the adrenal medulla and releasing noradrenaline and adrenaline, which cause the cardiovascular effects of nicotine.

First generation vaporizers have reported a low delivery of nicotine levels to the human body compared to the latest generation devices, where higher concentrations have been reported. This is due to the fact that in the new ECs, both voltage and temperature can be altered to generate more or less aerosol. One of the characteristics that stands out in JUUL devices with respect to the others is their high nicotine concentrations. Qasim et al. explain the risks that nicotine has on the human body when delivered by a conventional cigarette. Although there are not many studies that explain the damage of ECs directly on the cardiovascular system, there is one study that concluded that after five minutes of using different types of ECs, both heart rate and nicotine concentration in plasma are increased, while there are other studies that show the opposite.[1] On the other hand there is a lot of interesting data regarding people who do not smoke but who are exposed to the aerosol generated by the EC. Evidence shows that this is an important source of nicotine exposure.[25] Passive vaping has also become an issue of relevance due to the fact that concentrations of formaldehyde higher than the permitted limit have been documented in environments where vaping is allowed, creating a harmful environment for those who do not consume it.

Carbonyl compounds. Another important component of ECs are carbonyl compounds that are the result of the degradation of propylene glycol and glycerol that are used as solvents in vaporizer liquids.[25] It is important to know that these compounds are found in greater quantities in ECs than in conventional cigarettes and they are quite harmful. They can alter the heart rate by increasing it through the sympathetic nervous system, raise blood pressure, as well as muscle contractility. An association with cardiac oxidative stress and cell damage in this organ has also been seen. Another result showed an increase in the number of circulating platelets which is important to take into account in cases of thrombosis.[25]

Acrolein is another carbonyl that generates excessive toxicity increases systolic and diastolic pressure. An imbalance of this carbonyl can lead to increased risk of arrhythmia in rats,[25] due to the formation of an acrolein protein adduct, induction of oxidative stress and dysregulation of proinflammatory cytokines, as well as inhibition of cardioprotective signaling.[1] Finally, it can lead to vascular injury by impairing vascular repair capacity, risk of thrombosis and atherosclerosis due to endothelial dysfunction, dyslipidemia and platelet activation.[1]

Benowitz concluded that the cardiovascular risk that ECs can produce are more likely to occur in patients with a history of cardiovascular disease.[25] To consider an EC as a risk factor for cardiovascular problems, the toxicity of each element, the levels of exposure to them, mechanisms and above all more studies on the subject should be evaluated there is no direct empirical evidence that ECs can cause cardiovascular disease or that they are a risk factor as cigarettes are; probably they do impose some degree of risk, but at a lower level than the former.[25]

Impact of electronic cigarettes on the nervous system. The effect of vaporizers on the nervous system, as well as on the cardiovascular system, has been a topic for which there is not much research and very few articles discuss vaporizers. An article published by Ruszkiewicz explains the effects of e-liquid in both gaseous and liquid states.[26] The first article reviewed by Nguyen et al. involved exposing pregnant prepartum and postpartum rats to vaporizer-

generated aerosol, where they found a deficit in the short-term memory of the offspring, as well as less anxiety and hyperactivity.[26,27] This was due to the effects of nicotine on the nervous system, while the reduction in anxiety was seen in groups exposed to both nicotine and non-nicotine aerosols. Another meaningful change is that the exposure to non-nicotine aerosols promotes gene methylation and affects histone acetyltransferases causing changes in genes related to neurological activity.[26]

Prenatal nicotine neurotoxicity generates an imbalance in cholinergic transmission, resulting in significant behavioral changes as well as perinatal death.[26] On the other hand, solvents such as glycerol and glycerin do not show a risk to the nervous system unless a significantly overdosed. In this case only damage to the peripheral nervous system has been demonstrated.[26]

Tobacco versus vaping comparison

«Vaping» (electronic cigarette smoking) is a practice that has become very common among adolescents and adults, so it is necessary to know the health implications and compare it with traditional cigarettes. This section will review the common and differentiating components of EC versus TC as well as their effects on the lungs.

As previously mentioned, ECs are composed of the following parts: a lithium battery and a vaporization chamber (atomizer and heating coil and a refillable cartridge for liquid).[28] It is important to remember that e-liquid is made up of propylene glycol, vegetable glycerol, nicotine, among other substances. The TC consists mainly of a tobacco column, a filter and a paper with adhesive covering them.

Regarding the different pulmonary damage caused by both products, studies in murine C57BL/6 strain have shown that the substances that make up the e-liquid are responsible for the toxic effects seen in pulmonary fibroblasts. It was also observed that direct exposure of primary bronchial epithelial cells to EC vapor containing glycerol/propylene and glycol induced oxidative stress, although with less intensity than that induced by TC.

As for e-liquid containing nicotine, it was found that when nicotine was added, the effects already present were aggravated. When e-liquid contained both nicotine and flavoring in a three-day exposure to EC vapor, IL-6 and IL-1β interleukins were increased compared to solutions without flavoring.

In both flavored and nicotine-free EC vapor and TC, elevations were found in the methacholine response, which is a parasympathetic bronchoconstrictor that serves as a marker for determining bronchial hyperresponsiveness. Also in the study by Glynos et al.[28] measurements of mucin production were compared, and it was shown that after a three-day exposure there was an increase in Muc5ac levels in the airways with both EC vapor and TC. This study highlights that lung resistance, elasticity and distensibility were only affected by EC vapor. Thus, CE vapor causes lung inflammation, changes in respiratory mechanics and physiology, and when flavoring is added, these effects are aggravated.

Social impact

The invention of CE dates back to 1963, but it was patented in 2003 by a Chinese pharmacist. The popularity of EC started worldwide in 2009 and 2010, mainly because it was promoted as a novel product and as a useful and pleasant alternative for those who wanted to reduce their tobacco consumption. Companies promote these products as an alternative for tobacco users to quit their addiction. Furthermore, this began to attract the attention of young people who were anxious to start smoking, but were held back by fear of tobacco and nicotine.[29] However, this has not been sufficient reason to allow the free sale of these products in many countries. Due to several studies, in addition to the fact that it is still a tobacco-related product, some countries decided to ban its sale, such as the United States, Canada and Australia. Another important fact is that the World Health Organization (WHO), although it was the first to make reference to the use of these products, did not declare whether there were harmful effects, which gave companies a window of opportunity to sell freely.[30] The popularity of these products is also due to the fact that they make them attractive by adding artificial flavorings (e-liquids) and their eye-catching and fun designs. Having a better smell than tobacco, depending on the flavoring, has been found to be an important factor for people in deciding to try EC or switch from tobacco to EC.

The people most interested in acquiring and consuming ECs are under-age children, adolescents, and people seeking to quit smoking. Several studies have been conducted to gather information about early consumption and its relationship to the onset of tobacco addiction; one study found that adolescents in middle school or early high school who had already consumed ECs were up to seven times more likely to start using TCs, which was found when they were interviewed half a year later.[31] In contrast, students who had already tried TC showed no interest in starting to consume EC. This study, as well as other similar studies, suggests that there is a relationship between starting to consume EC at an early age and smoking.[32] As to whether it really helps to quit smoking, the FDA today has not accepted EC as an aid for people who wish to quit smoking, as it does not meet the necessary requirements stipulated by the organization. In addition, there is still not enough research on the safety of these products as a tool. A study in Europe showed that

the use of EC is not beneficial for smoking cessation; in this research more than 800 people were interviewed who were interested in quitting smoking and who currently use EC as an alternative, of these, only 9% (72 people) reported having quit smoking when asked one year later.[30]

For its part, the management of ECs in Mexico has undergone several changes. At the beginning, the government, through the General Law for Tobacco Control in its article 16, prohibited the sale of ECs: «to trade, sell, distribute, exhibit, promote or produce any object that is not a tobacco product, that contains any of the elements of the brand or any type of design or auditory signal that identifies it with tobacco products».[33] This law was drafted in 2008, its last modification was two years later, but it is still in force. Likewise, the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) at the time supported these declarations by stating that these products «do not have a sanitary registration». The above is called into question because on October 19 of this year, the Supreme Court declared unconstitutional the prohibition that had been discussed just a few days before regarding the commercialization of ECs and other related products. The proclamation went directly to the aforementioned Article 16.[34,35] While declaring something unconstitutional does not mean that it is law, it does open the possibility that in the future there may be changes in the law.

The facts indicate that due to the premise that the majority of the population considers ECs to be less harmful than conventional cigarettes, they continue to be consumed. Today, in many countries where their sale is prohibited, they are readily available to the general public, the only requirement being that the person can afford the product rather than demanding that they are of legal age.

DISCUSSION

The impact that these products have had on a cultural level since their appearance and popularity a little more than 10 years ago until today is still observed in a greater tendency in adolescents and young adults. Their popularity lies in several aspects that depend mainly on the age group, as people decide to try EC or change the TC, either because of popularity or because it is sold as an alternative to quit smoking, which, thanks to several studies and the FDA itself, has been shown not to be the case.

The purpose of this review is to guide the reader to learn more about the functioning of EC, as well as its possible repercussions in order to provide the necessary knowledge and make a decision as to whether or not to continue using EC. Because EC is a recent product, the pathophysiological mechanisms have not yet been fully established, but it is known that the impact on the homeostasis of EC users can vary greatly depending on the history and habits of the user as well as the composition of the EC.[11] It is important to conduct further research on pathophysiology to understand and prevent the pathologies that EC may generate in the future with its chronic use, as this may be triggering a public health problem, especially in young people.[29]

Due to the attributed manifestations that include life-threatening diseases, such as cardiovascular diseases, EVALI and lung cancer,[1,17,19,20] research will help to establish certain quality controls on the chemical products used for their manufacture, seeking to avoid the appearance of these pathologies, as well as to identify which materials tend to affect the organism the most and which are common in the majority of EC.

CONCLUSION

Evidence indicates that EC consumption can produce adverse effects to serious health consequences such as pulmonary, cardiovascular and even neurological damage.[11,12] Although the pathophysiology of these alterations is not fully understood, it is mainly associated with the chemical components that constitute the EC.[1] It is worth mentioning that the damage that can be caused by EC is multifactorial and includes: type of device, content of the liquid to be converted into aerosol, user behavior and experience. Even combinations can be made in the CE with nicotine, THC and other chemicals. Due to the high variability offered by the customization in product use, it is not possible to establish a specific harm from EC.[11]

Currently, there is still much controversy and uncertainty regarding the harmful effects of EC. The assumptions made by the EC industries that this product is less harmful compared to TC or that it is a healthy alternative are not correct or are not entirely true.[33]

It is important to continue doing research, especially comparative studies between TC and EC in more species to be able to determine with more specificity the differences in lung damage caused by consumption of EC versus smoking TC. It is also urgent to regulate e-liquids because due to the boom in their popularity, many liquids of different composition have been manufactured in the market that need to be analyzed and regulated.

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Ideas and perspectives

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Reflections on the current practice of medicine

Reflexiones sobre la práctica actual de la medicina‡

Antonio Soda-Merhy*

*Hospital Ángeles Lomas.

Receiving an award of this nature is of particular importance to me, because I receive it from the INER, the place where I carried out most of my professional life and where I have developed most part of my career. I can say from with great emotion that this institute is my home, and it gives me great pride to be recognized by you; to share this moment with my peers, students and my family, as well as having the opportunity to express some reflections on the current exercise medicine.

Those of us who decide to dedicate our lives to the exercise of medicine take a path that has no return and that never ends; each answer leads us to new questions and in that dialectic we form our medical awareness and our destiny. We are living in times of sudden changes, science shows us amazing leaps, the novelty happens at a great speed and ideas are renewed substantially from one year to the next, and anyone who wants to leave the study and apply only what they already know, in a short time their knowledge will be obsolete. The doctor's preparation is indispensable for us, to reach a shore is always to set off to a new horizon, to a route full of expectations. In our profession having the degree is not enough, the struggle continues, we must study every day, every year and all life. That is why the commitment we make to ourselves, to our profession and to our patients to keep us constantly updated is important. Fortunately, there are continuing medical professional education programs, which we can access voluntarily and which allow us to update skills and knowledge through courses, workshops, congresses, hospital stays, etc., that result in better care for our patients.

Being a doctor implies being a student for life, actively pursuing continuing education, renewing ourselves, being at the forefront of the knowledge that happens every minute in all corners of the world. In the XX century medicine has incorporated important changes; the development of specialities has been one of them. Therefore, the much-needed figure of the general practitioner has been disappearing. One of the characteristics of a good doctor, and this has been observed since ancient times, is being a subject who naturally tends to educate. The classical family doctor of a few decades ago influenced family members with their advice, opinions and sometimes decisions, that were beyond medical matters. Nowadays, it is being rethought to increase their role, even rich countries are considering them as an important need in health services. Undoubtedly, a well-prepared general doctor plays an important role in preventive medicine, they are able to solve most of the cases presented to them and if not, they can refer the specialist to the patients who need a different level of care.

It is becoming increasingly difficult to hear interns talking of the exercise of general medicine as the ultimate goal of their professional preparation. Nowadays, the recently graduated doctor considers that if they are not specialists they will not succeed. Nothing is further from the truth, since we must now recover the key role of the general doctor for the health service of the population. The general doctor must be the cornerstone of health care. In 1958, the teacher Ignacio Chávez said:

«It is true that the specialization brings within it a huge expansive force of progress, responsible for much of the incredible advancement we are witnessing, but it also contains the seed of a regression in the intellectual and spiritual order. Specialization means fragmentation, parcial

Correspondence:
Antonio Soda-Merhy, MD
E-mail: asodam@prodigy.net.mx

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vision, limited horizon. What is gained in depth, is lost in extension. To dominate a field of knowledge, the rest must be abandoned; the human then confines in on point and sacrifices the integral vision of the science and the universal vision of the world. In this drama the current human of science there is an imminent risk: the dehumanization of medicine and the dehumanization of the doctor».

As we can see, we are bound to keep a balance. Doctors have always cured and relieved the sick, even when the treatment resources were very limited, because the role of the doctor is not limited to curing only with modern methods of diagnosis and treatment. The doctor-patient relationship has two qualities: the necessary attitude of service and the ease of having a relationship with the patient listening to their problems and needs in order to gain their trust. When doctors posses these two qualities, it can be said they have received the gift of healing. Being supportive is also a necessary characteristic, bearing in mind that all the actions we take in our profession must be only motivated by the need to heal, alleviate and comfort the sick. In the oral tradition of our profession it is said that doctors must know how to heal; when this is not possible, they must alleviate suffering and when this is not possible either, they must be able to comfort. In order to do this, is necessary something more than the modern diagnosis methods and the technological advances.

Nowadays, doctor-patient relationship has undergone notorious changes. It is discussed about the medical dehumanization, about large hospitals where patients are numbers, of the despersonalization of medicine, of public institutions and insurance companies that do not allow choosing their doctors, of the lawsuits against doctors for procedures or treatments poorly performed and that force doctors to hire insurance and legal defenses, and we could mention many others. While innovations in technological development applied to medicine have meant breakthrough in diagnosis and treatment, on the other hand, they have transformed medical practice. The tendency to exaggerate the use of technological supports has caused a distance between doctors and patients, the relationship has become cold and distant, and medicine has become excessively expensive.

Working for human health involves very profound aspects that form a medical philosophy and ethics that must always accompany us. Those of us who perform this important task know that the knowledge and skill of which we are capable are not enough. In this struggle for the health of our patients, we must treat them with professionalism, a word that we have heard more and more in recent times and that it is the responsibility that the doctor acquires before society to perform with a conduct that reflects the principles of ethics, humanism, accountability and altruism, based on technically adequate clinical competence to solve the problems that arise. These values must be emphasized and are the basis of the commitment of the medical profession to society.

WHAT IS THE SCENARIO THAT WE ARE LIVING IN OUR COUNTRY?

Some data of the panorama of medical education in Mexico; currently there are 114 schools or faculties of medicine affiliated to the Mexican Association of Faculties and Schools of Medicine (AMFEM); there are approximately 20 more that are not affiliated; there are more than 133 thousand students of medicine, (@secretariadesaludMX), of which they graduate approximately 70%. Mexico has more than 250,000 general doctors, many of them without the possibility of directly exercising their profession and poorly distributed throughout the country.

The scenario of the recently graduated doctor is, in most of cases, to take the exam to enter the residence of the specialty. In 2021, 42,423 people took the exam, 18,173 were selected, which represents an acceptance percentage of 42.2%, compared to 2019 which was 26.4% (www.cifrhs.salud.gob.mx). If we ask ourselves what are the causes of this phenomenon, we can speculate different reasons: 1) did students from one year to the next improve their preparation?; 2) did the degree of difficulty of the exam decrease?; 3) did the minimum grade to pass the test decrease?; 4) did the number of locations increase? The reality is that we have the same teaching staff, the same resources and the same clinical field, so, by increasing the number of places without sufficient infrastructure, the opportunities to comply with university programs become limited and this has an impact on the preparation of students. Despite these adjustments, there are 57.8% of doctors who did not pass, what happens to them?, there is a big discouragement, some of them prepare for the evaluation of the following year, others are frustrated and others accept the challenge of working as general doctors, many of them in the service of pharmacies. A good opportunity for these doctors, who have fresh knowledge and are used to evaluations, is to take the exam to belong to the National Council of General Medicine, regardless they later do a specialization.

Within the framework of the changes in modern medicine since 1963, the creation of the Councils of Medical Specialities was initiated to certify the quality of doctors in professional practice and, at the same time, the recertification every five years in order to keep the doctors updated through continuing medical professional education activities. In 2017, there were 147,910 specialists, of which 69% are certified in 47 Speciality Councils that make up the National Regulatory Council of the Medical Speciality

Councils (CONACEM). In the early 1990s, the general doctor did not have a body with these characteristics, so it was not until 1995 that the National Council for General Medicine was stablished. To date, from the 250 thousand general doctors in the country, only 36,323 are certified by the National Council of General Practitioners. The situation of the other thousands of doctors who practise general medicine only after preparation in a medical school with a variable quality of preparation is worrying; they are largely responsible for the first contact care of the sick in this country.

Doctors with many years of practice have had the privilege of being spectators and actors of the great changes that we have had to live in relation to technological advances in diagnosis and treatment. I'm sure when we finished our bachelor's degree and residency, we didn't even dream that we were going to reach the degree of technification in which we are now. In addition, we must consider the great changes in the near future of genetics, stem cells, neurotropics, nanotechnology, just to mention a few.

As we can see, there are many things that come to mind when writing these lines and sharing them; I believe that a ceremony like this forces us to stop along the way and just start thinking, looking in the rearview mirror, analyzing how time has passed and what we have done to give it content and value. In this exercise, thought forces us to ask ourselves what it has meant to be a medical professional in Mexico in the 21st century, how have we approached medicine? Have we thought about medical philosophy? Have we ever raised our science against humanism? In an article entitled «Medical humanism», the teacher Ismael Cosío Villegas, of whom the institute proudly bears his name, said, and I quote:

«Humanism means culture; understanding of man in his aspirations and miseries; appreciation of what is good, what is beautiful and what is just in life; fixing of the norms that govern our inner world, a desire to overcome that leads us, as in the phrase of the philosopher, to equate with life, thought».

The most important and gratifying thing in any profession and human activity that we develop, without a doubt, is to carry it out with joy and passion; to achieve this vocation is indispensable and, in the case of the doctor, this must be a sine qua non; but we must not allow this vocation to be trapped only in the specialism or in the rigor of knowledge and technological advances. Whatever specialty we dedicate ourselves to, it is necessary to have a horizontal gaze, to prepare ourselves in interdisciplinarity and to always keep in mind the humanism that allows us to understand the individual not only as a sick person who has a condition, but as a human equal to us, who suffers, who has dreams and life hopes.

The doctor's preparation is indispensable, to reach a shore is always to set off to a new horizon, to a route full of expectations. n our profession it is not enough to acquire the title, the struggle continues, the study must be of every day, of every year and of all life.

In conclusion, I would like to congratulate and applaud the directors of our institution for their initiative in promoting this kind of recognition, which is a great encouragement to all doctors, whom I invite to continue to fight for the health of our fellow men with pride of belonging to this beloved institution; doing so from the perspective of medical humanism and with all the strength of their vocation.

Thank you.

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Percutaneous embolization of the thoracic duct in iatrogenic chilotorax. Case report

Embolización percutánea del conducto torácico en quilotórax iatrogénico. Reporte de caso

Jorge Guerrero-Ixtlahuac,* Melissa Pamela Solano-Velásquez,* Estefanía Murrieta-Peralta,* Gustavo Adolfo Villegas-Villa*

*Instituto Nacional de Cancerología. Mexico City, Mexico.

ABSTRACT. Thoracic duct injury is a rare complication of any intrathoracic surgical intervention but potentially severe if proper treatment is not instituted. Early surgical intervention is required in cases with large refractory chyle output but may be associated with substantial morbidity and mortality. Next, we present the case of a 66-year-old male patient with a history of having undergone radical hybrid esophagectomy for neoplasia in the lower third of the oesophagus, who in the mediate postoperative period presented bilateral pleural effusion, compatible with chylothorax. Treatment was initially conservative; given the unfavourable evolution, it was subsequently treated with percutaneous embolization of the thoracic duct, yielding an adequate resolution. This case demonstrates the efficacy of percutaneous thoracic duct embolization as a treatment alternative, as it is a minimally invasive, safe and effective method.

Keywords: chylotorax, thoracic duct, lymphography, embolization.

RESUMEN. La lesión del conducto torácico es una complicación poco frecuente de cualquier intervención quirúrgica intratorácica, pero potencialmente muy grave si no se instaura un tratamiento adecuado. La intervención quirúrgica precoz se requiere en los casos cuando existe una gran producción de quilo, refractaria a tratamientos conservadores, pero puede estar asociada con altas tasas de morbilidad y mortalidad. A continuación presentamos el caso de paciente masculino de 66 años con historia de haber sido sometido a esofagectomía por neoplasia en el tercio inferior del esófago, que en el posoperatorio mediato presentó derrame pleural bilateral compatible con quilotórax. El tratamiento inicialmente fue conservador, dada la evolución desfavorable posteriormente fue tratado con embolización percutánea del conducto torácico, arrojando adecuada resolución del cuadro. Con este caso se demuestra la eficacia de la embolización percutánea del conducto torácico como alternativa de tratamiento por ser un método mínimamente invasivo, seguro y eficaz.

Palabras clave: quilotórax, conducto torácico, linfangiografía, embolización.

INTRODUCTION

Chylothorax is defined as the presence of lymph in the pleural cavity as a result of disruption or obstruction of the thoracic duct. The etiology can be traumatic and non-traumatic, traumatic can be subdivided into iatrogenic and non-iatrogenic.[1] Iatrogenic post-traumatic chylothorax remains a major complication after thoracic surgery and particularly difficult to manage.[2] Thoracic duct injury is an infrequent complication of any intrathoracic surgical intervention, observed in up to 4%[2,3] of thoracic esophagectomies and less than 1%[4] in other types of surgery, but potentially very serious, with a mortality of up to 50%[5] if adequate treatment is not established.

Lymphatic leakage can occur anywhere along the lymphatic pathway beginning in the four extremities. The most clinically important pathway begins from the intestinal lymphatic ducts and continues through the chyle cistern into the thoracic duct. Chylothorax is a serious condition that can rapidly lead to hypovolemia, electrolyte abnormalities, malnutrition and immunocompromise.[6] As a result, early intervention has become the ideal treatment strategy.

In 1998, a new percutaneous method for the treatment of chylothorax was reported by Cope,[7] as well as some larger series[3] since that date. Percutaneous thoracic duct embolization is a minimally invasive technique with low morbidity and mortality rates and a cure or response rate

Correspondence:
Melissa Pamela Solano-Velásquez, MD
Instituto Nacional de Cancerología. Mexico City, Mexico.
E-mail: mao.pame@gmail.com

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of up to 73.8% in patients with nontraumatic etiologies and 71% in patients with posttraumatic etiology;[2,3] so it is accepted as a therapeutic alternative to surgical treatment in cases in which the fistula is not controlled conservatively.[3] However, the procedure is rarely performed. We report a successful case of thoracic duct embolization in iatrogenic chylothorax.

CASE REPORT

A 66-year-old man with a history of radical hybrid esophagectomy for neoplasia in the lower third of the esophagus, treated with radiotherapy and neoadjuvant chemotherapy. In the postoperative period he presented bilateral pleural effusion. Pleural drainage tubes were placed through which milky fluid drained; biochemical analysis of the fluid showed high amounts of triglycerides (176 mg/dL), a finding compatible with chylothorax. After conservative treatment, the chest tube debit did not decrease, so it was decided to discuss the case with the interventional radiology service. With the diagnosis of iatrogenic chylothorax, intranodal lymphangiography and embolization of the thoracic duct with coils and cyanoacrylate were performed.

Technique

There are two methods of lymphangiography (LG): bipedal lymphangiography and intranodal lymphangiography. Conventional bipedal LG involves the injection of methylene blue into the subcutaneous cellular tissue between the first and third toes to identify the course of the lymphatic vessels on the dorsum of the foot. Subsequently through

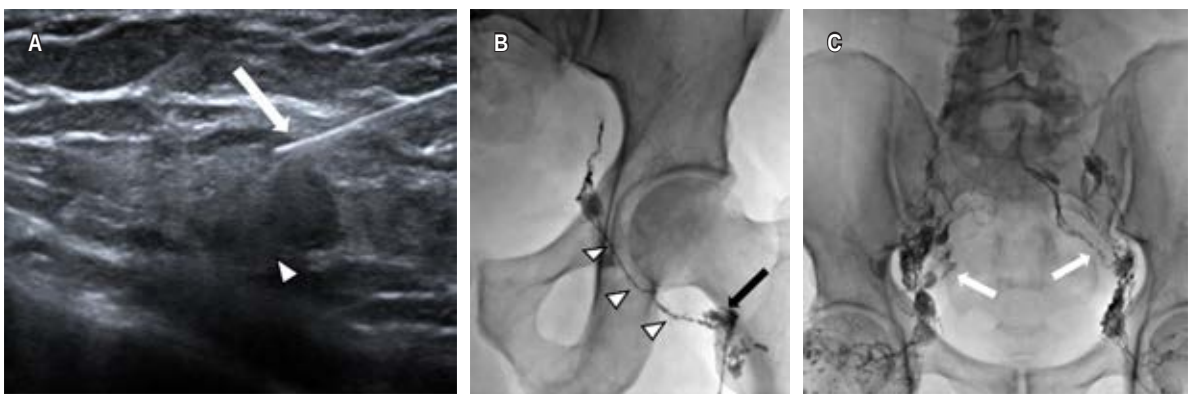

Figure 1: A) Ultrasound image showing access to the lymph node (arrowhead) of the groin with a needle, the tip of the needle is placed in the transition zone between the cortex and hilum (arrow). **B)** Fluoroscopic image obtained during intraganglionic lymphangiography showing a lymph node as a subtle nodular staining (arrow), which then follows the lymphatic vessels continuous with it (arrowheads). **C)** Progression of it through bilateral pelvic lymphatic ducts is seen (arrows).

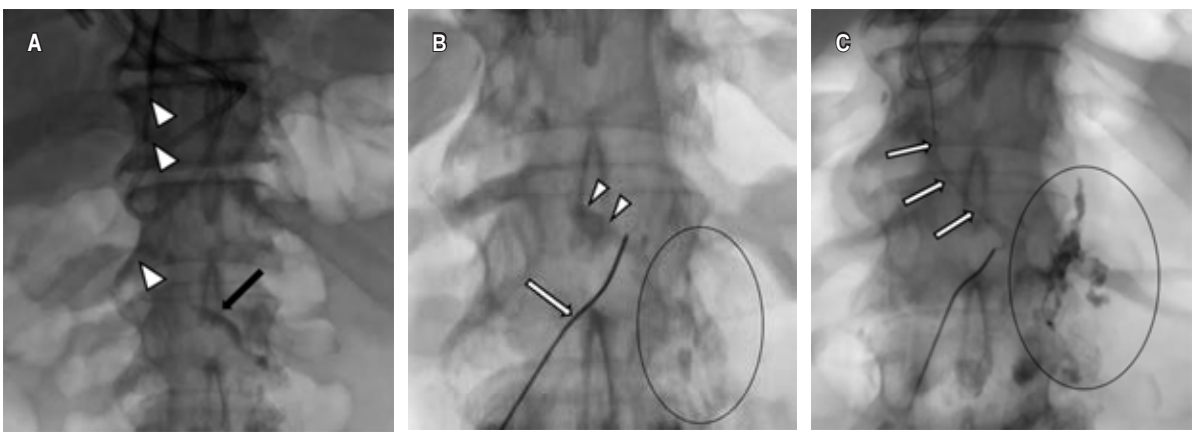

Figure 2: A) Follow-up image showing continuous ascending flow with filling of the thoracic duct (arrowheads) and chyle cistern (arrow). **B)** Percutaneous access with a 22G needle (arrow) to the thoracic duct (arrowhead) shows extravasation of contrast medium (circle). **C)** A microguide (arrow) is used to ensure access, then a microcatheter is introduced. Extravasation of the contrast medium is corroborated (circle).

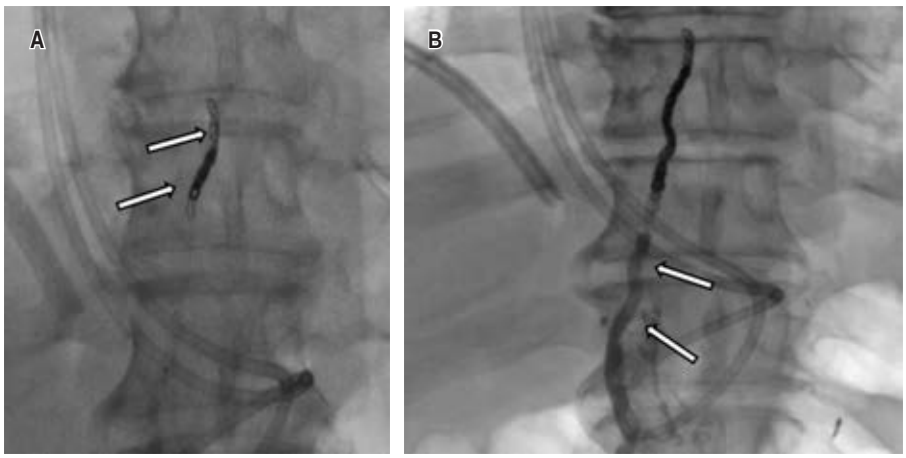

Figure 3:

A) 2 and 3 mm microcoils were released in the thoracic duct proximal to the leak (arrows). **B)** Embolization was completed with NBCA (arrows). Control ductography showed resolution of the leak.
NBCA = N-butyl-2-cyanoacrylate.

a skin incision a lymphatic vessel is isolated to administer Lipiodol®. This method is time consuming and the foot incision can become infected.[8,9]

Intranodal LG was developed to assess tumor involvement of the inguinal, pelvic and lumbar lymph nodes. Several techniques are described for intranodal LG such as direct puncture of the inguinal nodes blindly or after surgical isolation, as well as ultrasound-guided puncture, which is currently the most widely used,[8] as it allows greater precision, is technically simpler, and does not require incisions, thus reducing procedure time, radiation dose and volume of contrast medium.[2]

Besides identifying the leakage point, LG may have a therapeutic role attributed to the embolizing properties of Lipiodol®, which generates a granulomatous inflammatory reaction during its extravasation and which, due to its viscosity, has the capacity to accumulate at the leakage point as well as in the lymphatic ducts.[9]

Intranodal lymphangiography

The largest bilateral inguinal nodes distal to the inguinal region were identified under ultrasonographic guidance; Lipiodol® was then injected using a 22 G needle, the tip of the needle being placed in the transition zone between the cortex and hilum of the lymph node. A slow manual injection of Lipiodol® was performed and observed under fluoroscopic guidance in order to confirm the correct position of the needle. A total volume of 10 to 20 mL of Lipiodol® was injected. Images were obtained under fluoroscopic control every five to 10 minutes during the course of the Lipiodol® injection to observe progression through the pelvic and abdominal lymphatic ducts *(Figure 1)*.

Intranodal LG is considered technically satisfactory if the target lymph node is successfully selected and the lymphatic channels of interest, including the chyle cistern, are adequately visualized with Lipiodol®.

Thoracic duct embolization

Once the chyle cistern was opacified, a disruption of the thoracic duct and contrast leakage into the left pleural cavity was visualized, under fluroscopic control the thoracic duct was catheterized using a 22 G Chiba needle by percutaneous abdominal approach in the epigastric area and with a slightly cranial angulation. Once accessed, a 0.014-inch guidewire was introduced into the thoracic duct and the needle was exchanged for a microcatheter, which was placed as close as possible to the site of the thoracic duct lesion, ideally joining the point of extravasation *(Figure 2)*. Subsequently, it was embolized with microcoils of 2 and 3 mm in diameter proximal to the leak and the embolization was completed with cyanoacrylate. Control ductography showed the resolution of the leak *(Figure 3)*.

DISCUSSION

Chylothorax is diagnosed by the presence of milky fluid during thoracentesis with a triglyceride content greater than 110 mg/dL and a cholesterol level lower than that of the blood.[10,11] Conservative treatment is traditionally used for low-volume chylothorax (< 1,000 mL/dL); however, mortality remains high, up to 50%.[5,12] The main causes of surgical traumatic chylothorax include esophagectomy (28%), congenital heart surgery (28%), lung cancer resection (6-27%).[13] Overall, esophagectomy is more frequently associated with traumatic chylothorax: 3.9 versus 0.42% in general thoracic surgery.[2,3]

Thoracic duct embolization was first described by Constantine Cope in 1996 as an alternative to treatment of chylous leaks that were previously not possible without surgical exploration.[7] It is recommended when a leak persists for more than two weeks despite conservative treatment, when leakage exceeds 1,000 mL per day for more than five days, or when severe metabolic and

nutritional complications occur.[1,9] The initial description required pedal LG to opacify the lymphatic system; however, this method is technically challenging and time-consuming, so it has been replaced by ultrasound-guided percutaneous nodal LG.[8,14]

Thoracic duct embolization has proven efficacy in the treatment of chylous leaks caused by thoracic duct injury. The largest series published in the literature is that of Itkin et al. who evaluated the results of the technique in 109 patients with traumatic chylothorax, reporting a success rate of 71%.[2] Pamarthi et al. evaluated the results in 105 patients with traumatic and non-traumatic chylothorax treated by percutaneous techniques, achieving a success rate in traumatic patients of 62%, higher than in patients with non-traumatic chylothorax.[15] In the series published by Cope et al.[3] where they evaluated the result of percutaneous treatment in 42 patients with chylothorax, they obtained a success rate of 76% in traumatic cases. Therefore, it is considered as a surgical alternative, leaving surgery as the last treatment option in many cases.

In the largest series, no deaths were reported and the complication rate was 3% and included one case of asymptomatic pulmonary artery embolization with cyanoacrylate, two cases of leg edema and foot suture dehiscence.[2] This is significantly lower than the mortality of 82.1% and morbidity of 38.3% in surgical cases.[4]

In our case, a good technical and clinical result was obtained, with no recurrence of the chylothorax, no need for reinterventions and no morbidity. It is in support of the new approach to chylothorax treatment advocated by some other authors,[2,3,15] who consider thoracic duct embolization as a first-line option in patients with refractory chylous effusions. Despite superior results, thoracic duct embolization is a technically challenging procedure performed in very few centers due to unfamiliarity with LG.

CONCLUSIONS

Lymphangiography remains an important tool in the localization of chylous leaks. It has evolved from a laborious and time-consuming procedure that relied on foot lymphangiography to one in which inguinal intraganglionic lymphangiography shortens time and minimizes risks. With proper case selection, thoracic duct embolization is a minimally invasive alternative to surgery in the treatment of traumatic and nontraumatic cases of chylothorax.

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Use of bedaquiline during pregnancy in a patient with MDR-TB. First case reported in Mexico

Uso de bedaquilina durante el embarazo en una paciente con TB-MDR. Primer reporte de caso en México

Paola L. López-de la Cruz,* Samuel Ruiz-Pérez,* Rafael Laniado-Laborín‡

*School of Medicine, Autonomous University of Baja California, Mexico, Tuberculosis Clinic, Tijuana General Hospital, Mexico.
‡ School of Medicine, Autonomous University of Baja California, Mexico, Tuberculosis Clinic, Tijuana General Hospital, Mexico, SNI II, CONACYT.

Hospital General Tijuana, INSABI.

ABSTRACT. Treatment of rifampin-resistant and multidrug-resistant tuberculosis in pregnant women is more complicated since little is known about the safety of second-line antituberculosis drugs during pregnancy and lactation. Drug-resistant tuberculosis, not having many options in the past, has been treated with regimens that include drugs with teratogenic potentials, such as thioamides and second-line injectables. Currently, there are new oral drugs, including bedaquiline, for the treatment of drug-resistant disease; however, the safety of bedaquiline during pregnancy and lactation has not been satisfactorily demonstrated so far. We report the first case in Mexico treated with a regimen that includes bedaquiline for multidrug-resistant tuberculosis during pregnancy, with favorable results, and without maternal-fetal complications.

Keywords: tuberculosis, rifampin-resistant, multidrug-resistant, pregnancy, bedaquiline.

RESUMEN. El tratamiento de la tuberculosis resistente a la rifampicina y multirresistente en mujeres embarazadas es complicado ya que se sabe poco sobre la seguridad de los fármacos antituberculosis de segunda línea durante el embarazo y la lactancia. La tuberculosis farmacorresistente, no tenía muchas opciones en el pasado, se ha tratado con regímenes que incluyen medicamentos con potencial teratogénico, como tioamidas e inyectables de segunda línea. Actualmente, hay nuevos medicamentos orales, incluida la bedaquilina, para el tratamiento de enfermedades resistentes a los medicamentos de primera línea; sin embargo, la seguridad de la bedaquilina durante el embarazo y la lactancia no se ha demostrado satisfactoriamente hasta el momento. Reportamos el primer caso en México tratado con un régimen que incluye bedaquilina para la tuberculosis multirresistente durante el embarazo, con resultados favorables, y sin complicaciones materno-fetales.

Palabras clave: tuberculosis, resistencia a la rifampicina, multidrogo-resistencia, embarazo, bedaquilina.

INTRODUCTION

The World Health Organization (WHO) estimates that in 2020 there were 31,000 cases of tuberculosis (TB) in Mexico[1] which represents 10.3% of all patients in America and the third-highest prevalence of TB in the continent. Also, Mexico has the third-highest number of rifampin-resistant or multidrug-resistant TB (RR-TB and MDR-TB) cases in America.[2]

The prevalence of tuberculosis during pregnancy in low-burden countries (< 20 cases per 100,000 h), such as Mexico, ranges between 0.06 and 1%.[3] Tuberculosis during pregnancy has been associated with maternal-fetal complications; in a study of pregnant women with tuberculosis in Mexico,[4] the neonatal outcome was compared with pregnant women without TB. There was a significantly higher neonatal morbidity rate, a significantly lower birth weight (including weight < 2,500 g), and a significantly higher risk of prematurity in the group of women with TB. In this study, TB treatment included exclusively first-line drugs (isoniazid, rifampicin, ethambutol, or pyrazinamide), currently considered as safe during pregnancy.[4]

Treatment of RR-TB and MDR-TB in pregnant women is more complicated since little is known about the safety of

Correspondence:
Rafael Laniado-Laborín
E-mail: rlaniado@uabc.edu.mx

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second-line anti-TB drugs during pregnancy and lactation.[5] Treatment of drug-resistant TB has traditionally required drugs with teratogenic potential, including thioamides (ethionamide and prothionamide) and second-line injectables (amikacin, kanamycin, and capreomycin).[6] Since 2019, based on new evidence, the WHO recommends an exclusively oral treatment regimen for drug-resistant TB, including new drugs (bedaquiline, delamanid and pretomanid) and repurposed drugs (linezolid, clofazimine and fluoroquinolones).[7] However, all of these drugs are currently classified as category C during pregnancy, that is, those for which animal reproduction studies have shown an adverse effect on the fetus and for which there are no adequate and well-controlled studies in humans, but whose potential benefits may justify the use of the drug during pregnancy despite the potential risks.

We report the first case in Mexico of MDR-TB during pregnancy, treated with a regimen that included bedaquiline (BDQ).

PRESENTATION OF THE CASE

A 21-year-old female was referred for evaluation to the Tuberculosis Clinic of the Tijuana General Hospital with TB and pregnancy; primiparous, with 16 weeks of gestation (WOG) at the time of reference; seronegative for HIV. Her main complaints are productive cough, occasionally hemoptoic, unquantified fever, and diaphoresis for the previous three months. She denies drug addiction or comorbidities. The chest radiograph shows bilateral airspace opacities and a cavitation in the lingula. The Xpert® MTB/RIF (Cepheid, Sunnyvale, CA) assay detects *Mycobacterium tuberculosis* complex (MTBC) with a high load of mycobacterial DNA, and resistance to rifampicin; subsequently, the line probe assay (LPA; GenoType®MTBDRplus VER 2.0, Hain Life Sciences, Nehren Germany) for the analysis of the *rpoB* and *katG* genes and the *inhA* promoter reported resistance to isoniazid (detected) and rifampicin (inferred); second-line LPA (GenoType®MTBDR sl VER 2.0) did not detect mutations associated to fluoroquinolones or second-line injectable antibiotics. Despite the lack of evidence on the safety of their use in pregnancy and lactation, the need for second-line is explained to the patient, for which she is requested and gives her informed consent to initiation of outpatient treatment with home video supervision (videoDOT).

Treatment included Bdq 400 mg for two weeks and 200 mg three times a week for 22 weeks, linezolid 600 mg/day, levofloxacin 750 mg/day, clofazimine 100 mg/day, and pyridoxine 100 mg/day. After a few days of treatment, she complained of nausea and vomiting; thus, sucralfate (2 g) and ondansetron (8 mg) are prescribed every 24 hours. After two months of treatment, serum magnesium was reported at 1.5 mg/dL, and the regimen was supplemented with 250 mg of magnesium every 24 hours.

Spontaneous labor begins at 39 WOG, obtaining a single, live female product. APGAR was graded 8/9 and CAPURRO at 39 weeks. Birth weight 3,090 g, height 49 cm, head circumference 33.5 cm, thoracic perimeter 32 cm, abdominal perimeter 30 cm, lower segment 20 cm, and foot length 8 cm.

After completing six months of treatment with BDQ, the patient continues with the rest of the initial regimen without any other complications; converted sputum smears by the second month and the culture by the third month of treatment. BCG vaccination was recommended for the child, and she was referred to the HGT Pediatric TB Clinic for follow-up. It was decided not to recommend breastfeeding, given the little information on the safety of these drugs during lactation.

DISCUSSION

This is the first case in Mexico treated with a regimen that includes BDQ for MDR-TB during pregnancy, with favorable results, and without maternal-fetal complications. Our case adds to the growing body of evidence on the effectiveness and safety of BDQ during pregnancy.

Biological changes during pregnancy double the risk of pregnant women developing tuberculosis compared to non-pregnant women. Pregnancy itself complicates the treatment of tuberculosis, and untreated tuberculosis may be associated with mortality up to up to 40%.[3] Treatment of RR/MDR-TB, not having many options, traditionally required including drugs with teratogenic potential, including thioamides (ethionamide and prothionamide) and second-line injectables.

The WHO currently recommends a long-term treatment regimen for patients with MDR/RR-TB and pregnancy, with at least four effective drugs, which must include all group A drugs (levofloxacin or moxifloxacin, BDQ and linezolid) for which there is no resistance or contraindication and at least one group B drug (clofazimine or cycloserine).[7]

However, the safety of BDQ during pregnancy and lactation has not been satisfactorily demonstrated so far. In the largest cohort of pregnant women with RR/MDR-TB reported to date with 108 South African women, 81% of which were HIV-positive and 83% were on antiretroviral treatment. At the start of treatment, the median gestational age was 22 weeks (IQR 14-28); 45% of fetuses were exposed to BDQ with a median fetal exposure of 118 days (IQR 70-208). When the group of newborns exposed to BDQ (49) was compared with those not exposed to this drug (60, there was a twin birth), no significant differences were found in the percentage of live births, gestational age at delivery, and fetal/neonatal deaths. Forty-five percent of the products exposed to BDQ had a birth weight under 2,500 g vs 26% of the unexposed products (p = 0.03).

However, at the end of twelve months of follow-up, both groups had already reached the expected weight for their age.[8] Even though no significant congenital malformations were reported, the number of fetuses exposed to BDQ during the critical period of the first trimester was too low (17%) for this study to provide a reliable assessment of safety in this regard.[9]

Our case did not have low birth weight as reported in the South African study, where 45% of the products had low birth weight, even though BDQ exposure in our case was higher (154 days vs 118 days in the South African study).

Although it would be essential to have more information, there is no justification for denying pregnant women with drug-resistant TB (DR-TB) access to innovative therapeutic regimens containing new drugs such as bedaquiline or delamanid and repurposed drugs such as linezolid and clofazimine. The development of clinical trials to include pregnant women with DR-TB would undoubtedly provide high-quality information; however, since pregnant women are routinely excluded from such clinical trials, it would likely take decades for information on the safety of these drugs to be obtained. This evidence gap could also be supplemented by developing and using registries of pregnant women with DR-TB treated with these drugs.[10]

CONCLUSIONS

Pregnant and postpartum women have traditionally been underrepresented in clinical trials. We have minimal evidence on the use of new drugs against drug-resistant TB in pregnant women, which constitutes a critical knowledge gap. The exclusion of pregnant women from drug-resistant TB treatment trials constitutes a significant research challenge.

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Coccidioidomycosis and aspergillosis in a patient with pulmonary tuberculosis sequelae

Coccidioidomicosis y aspergilosis en un paciente con secuelas por tuberculosis pulmonar

Rogelio Flores-Acosta,* Miroslava Félix-Ponce,* Alejandra Isabel Jiménez-Gracia,* Rafael Laniado-Laborín*,‡

*School of Medicine, Autonomous University of Baja California, Mexico, Tuberculosis Clinic, Tijuana General Hospital, Mexico.
‡School of Medicine, Autonomous University of Baja California, Mexico, Tuberculosis Clinic, Tijuana General Hospital, Mexico, SNI II, CONACYT.

ABSTRACT. Introduction: coccidioidomycosis is exclusive to the American continent, being endemic in the southwestern United States and northwestern Mexico. Aspergillosis is an opportunistic mycosis caused by the saprophytic soil fungus *Aspergillus spp.* The main risk factors that favor the presence of these mycoses are structural lung damage and immunocompromise. **Clinical case:** we present a case of coinfection by *Aspergillus spp.* and *Coccidioides spp.* in a patient with a history of pulmonary tuberculosis and diabetes *mellitus*. Sputum examination reported the simultaneous isolation of *Coccidioides spp.* and *Aspergillus spp.* **Conclusions:** in patients with respiratory symptoms and a history of tuberculosis and fibrocavitary sequelae, it is essential to rule out initially a tuberculosis relapse, but at the same time, investigate the presence of endemic and opportunistic fungi.

Keywords: coccidioidomycosis, aspergillosis, tuberculosis, sequelae.

RESUMEN. Introducción: la coccidioidomicosis es una micosis exclusiva del continente americano, siendo endémica en el suroeste de Estados Unidos y noroeste de México. La aspergilosis es una micosis oportunista causada por el hongo saprófito del suelo *Aspergillus spp.* Los principales factores de riesgo que favorecen la presencia de estas micosis son el daño pulmonar estructural y el compromiso inmunológico. **Caso clínico:** se presenta un caso de coinfección por *Aspergillus spp.* y *Coccidioides spp.* en un paciente con antecedentes de tuberculosis pulmonar y diabetes *mellitus*. El examen de esputo informó el aislamiento simultáneo de *Coccidioides spp.* y *Aspergillus spp.* **Conclusiones:** en pacientes con síntomas respiratorios y antecedente de tuberculosis y secuelas fibrocavitarias es fundamental descartar inicialmente una recidiva tuberculosa, pero al mismo tiempo investigar la presencia de hongos endémicos y oportunistas.

Palabras clave: coccidioidomicosis, aspergilosis, tuberculosis, secuela.

INTRODUCTION

Pulmonary tuberculosis is the most frequent cause of pulmonary cavities[1] and is recognized as a predisposing factor for colonization by *Aspergillus spp.*, a severe and life-threatening complication.[2] However, pulmonary coccidioidomycosis can present similar clinical and radiographic patterns, especially in immunocompromised patients.[3]

Correspondence:
MSP Rafael Laniado-Laborín
E-mail: rlaniado@uabc.edu.mx

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This report describes a case of coexistence of *Coccidioides spp.* and *Aspergillus spp.* in a patient with a history of diabetes *mellitus* and fibrocavitary sequelae from pulmonary tuberculosis, highlighting the relevance of comorbidity due to endemic or opportunistic mycoses in immunocompromised patients.

CLINICAL CASE

48-year-old Mexican woman, diabetic with poor metabolic control (central glycemia 265 mg/dL); two years earlier, she was diagnosed with pulmonary tuberculosis receiving treatment and discharged as cured.

She developed night sweats, cough, hemoptysis, and weight loss one year later. Her sputum smear microscopies are reported negative for acid-fast bacilli, so she is referred to the Tuberculosis Clinic at the Tijuana General Hospital for tuberculosis molecular and phenotypic diagnostic tests. Smear microscopy, Xpert® MTB/RIF test (Cepheid, Sunnyvale, CA), and cultures (MGIT® BD, Franklin Lakes,

Neumol Cir Torax. 2022; 81 (2): 138-140

NJ, and Lowenstein Jensen) are reported negative for tuberculosis.

The chest radiograph showed multiple bilateral thin-walled cavities, with an intracavitary mass in several of them. Chest computed tomography *(Figure 1A and 1B)* confirmed the findings and allowed the identification of a greater number of cavities with an intracavitary mass.

Sputum fungal culture showed the simultaneous isolation of *Coccidioides spp.* and *Aspergillus spp. (Figure 1C)*. The hospital unit does not have access to serology tests for these mycoses. She was started with itraconazole 300 mg every 12 hours, showing clinical improvement after a month of treatment.

DISCUSSION

The search in PubMed, Google Scholar, EMBASE, and the Cochrane Library did not yield reports on the simultaneous presence of *Coccidioides spp.* and *Aspergillus spp.* in patients with fibrocavitary sequelae of tuberculosis.

Residual lung damage even after successful treatment of pulmonary tuberculosis includes fibrocavitary lesions, bronchovascular distortion, emphysema, and bronchiectasis.[4]

The main risk factors that favor disease by these mycoses are a history of structural lung damage and immunocompromise. In our patient, residing in an endemic area of tuberculosis and coccidioidomycosis and being immunocompromised due to diabetes with poor metabolic control,[5] were the predisposing factors that favored the concomitant development of these mycoses.[6-8]

The patient was referred to the tuberculosis clinic, suspecting a tuberculosis relapse. However, based on the negative results of the phenotypic and genotypic tests for tuberculosis and the presence of multiple cavitations with an intracavitary mass, fungal sputum cultures were requested, suspecting colonization by *Aspergillus spp.*, which was indeed detected, reporting in addition, the unsuspected presence of *Coccidioides spp.*

Coccidioidomycosis is exclusive to the American continent, being endemic in the southwestern United States and northwestern Mexico,[9,10] where our patient lives. Aspergillosis is an opportunistic mycosis caused by the saprophytic soil fungus *Aspergillus spp.*, with *Aspergillus fumigatus* the most frequently identified species.[11]

The culture of respiratory samples is the study of choice for the diagnosis of coccidioidomycosis.[9]

Serologic tests identifying anticoccidial humoral antibodies (IgM and IgG) are an alternative method (and the most frequently used) for the diagnosis and prognosis of coccidioidomycosis.[10]

Aspergillosis has different clinical presentations, which frequently overlap. Chronic cavitary aspergillosis (CPA) usually shows multiple cavities that may or may not contain an aspergilloma, in association with pulmonary and systemic symptoms, as well as elevated inflammatory markers. Without treatment, these cavities increase in diameter and coalesce, developing pericavitary infiltrates, which a bronchopleural fistula can complicate.[12]

The diagnosis of CPA requires a combination of different criteria: a consistent appearance on radiological images, direct evidence of *Aspergillus* infection, an immune response to the fungus, and the exclusion of an alternative diagnosis. Patients with CPA are not usually immunosuppressed by HIV infection, chemotherapy, or immunosuppressive therapy.[12] Proven diagnosis of aspergillosis requires histopathological documentation of the infection, or a positive culture result

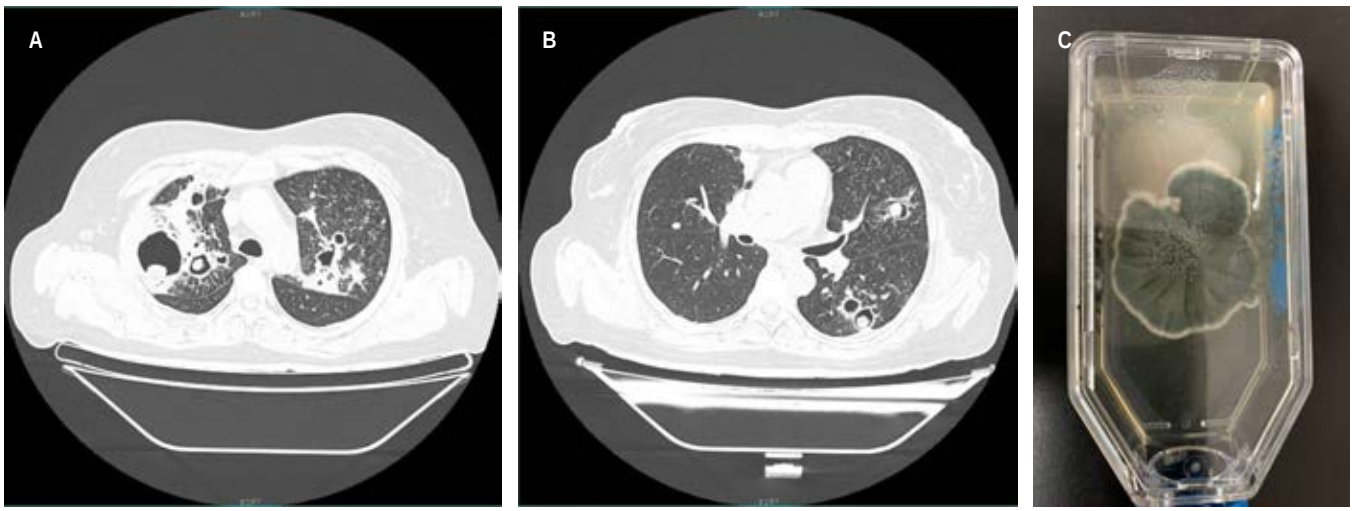

Figure 1: Chest axial tomography and culture. **A)** Multiple cavitations in both upper lobes with intracavitary mass in the right upper lobe lesions. **B)** Left lower lobe cavitation with intracavitary mass. **C)** Culture in Sabouraud medium showing simultaneous growth of *Coccidioides spp.* and *Aspergillus spp.*

from a sample taken from a sterile site.[11] Additionally, the detection of galactomannan (GM) in plasma should support the diagnosis of aspergillosis.[13] In our case, isolation of *Aspergillus* was from a non-sterile sample, and it must be classified as probable aspergillosis infection based on the predisposing factors, suggestive clinical and tomographic data, and mycological evidence.[7,8]

The presence of *Coccidioides* spherules in respiratory samples always represents disease, while the presence of *Aspergillus* can be associated with disease or colonization.[12,14]

CONCLUSIONS

In patients with tuberculosis sequelae with respiratory symptoms, tuberculosis relapse should be initially ruled out, and opportunistic and endemic fungi such as *Aspergillus spp.* and *Coccidioides spp.* should be considered in the differential diagnosis algorithm.

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Giant lung cryptococcoma in immunocompetent patient: case report

Criptococoma pulmonar gigante en paciente inmunocompetente: reporte de caso

Laura Mestre-Orozco,* Rosa María Vicuña-González,*
Freddy Rafael Domínguez-Sosa,* Julio César López-Valdés*

*Hospital Central Sur de Alta Especialidad PEMEX. Mexico.

ABSTRACT. Lung cryptococcosis is a rare entity whose epidemiology hasn't been entirely reported in Mexico. It is frequently found as a complication of HIV or other cases of immunosuppression. We present a case of a young immunocompetent man who debuted with neurological manifestations and was later found to have a giant lung cryptococcoma. This is a particularly interesting case because although the clinical manifestations were normal, the patient was not immunocompromised and the lung damage was important with later development of meningitis that led to complications and a lung resection.

Keywords: cryptococcoma, giant, lung, immunocompetent.

RESUMEN. La criptococosis pulmonar es una entidad poco frecuente, cuya epidemiología en México no se encuentra del todo descrita. Se presenta como complicación de la infección por VIH u otros cuadros de inmunosupresión. Se expone el caso de un hombre joven, inmunocompetente, quien inició con manifestaciones neurológicas y se evidenció un criptococoma pulmonar gigante. Este caso representa un ejemplo habitual de la criptococosis pulmonar, cuyo inicio clínico suele ser incipiente hasta presentar manifestaciones sistémicas asociadas con la infección. La particularidad del caso aquí descrito se relaciona a que aun sin presentar inmunocompromiso, la afectación pulmonar fue importante y hubo progresión a meningitis con déficit neurológico asociado, que llevó a complicaciones y resección pulmonar.

Palabras clave: criptococoma, gigante, pulmón, inmunocompetente.

INTRODUCTION

Pulmonary cryptococcosis is a rare entity, whose epidemiology in Mexico is not fully described; however, according to data provided by Carrada BT et al.[1] in Mexico the fungus was isolated in 20.7% of pigeon droppings samples in urban areas; in addition, they mention that in 1970 only 25 cases of cryptococcosis were registered in the hospitals of the Distrito Federal (now Mexico City).

On the other hand, they mention 13 cases confirmed after *post mortem* histopathological study out of a total of 22,088 studies (0.59 diagnoses per 1,000). However, it should be remembered that it frequently occurs as a complication of HIV infection or other immunosuppression (leukemia, use of glucocorticoids, among others), thus isolated cases in immunocompetent patients are considered even scarcer.[2] However, the clinical picture in immunocompetent patients usually has a pulmonary onset with subsequent extension to the central nervous system (meningitis).[3] The following is the case of a young, immunocompetent man who presented with an incipient clinical picture with neurological manifestations and in whom a giant pulmonary cryptococcoma was evidenced.

Correspondence:
Laura Mestre-Orozco, MD
E-mail: laura.mestre.orozco@gmail.com

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CASE PRESENTATION

A 23-year-old man, originally from Oaxaca and resident of Monterrey, Nuevo León; he confirmed coexistence with animals such as urban pigeons, with no other relevant history. Four days after the application of the second dose of vaccine against the SARS-CoV-2 virus, he started with moderate to severe oppressive headache, which did not

present irradiation and did not improve with analgesics; after two days of evolution, gait instability was added, as well as visual hallucinations and tonic-clonic convulsive crises.

He went to the hospital unit where a simple cranial tomography was performed, which showed the presence of multiple circumscribed lesions of heterogeneous distribution in both hemispheres of the brain. Laboratory studies were performed, consisting of serological tests for antibodies against HIV, HBV and HCV, which were negative. Treatment was started with amphotericin B deoxycholate 100 mg every 24 hours intravenously and fluconazole 100 mg every 12 hours orally, with clinical improvement after administration; however, he presented progressive decrease in visual acuity, as well as repeated febrile symptoms.

A simple chest CT scan of the lung was performed *(Figure 1A and 1B)*, which showed a left lower lobar lesion. After three days without improvement, posterolateral thoracotomy and left lower lobectomy were performed, showing whitish-yellow consolidation of 10 × 10 cm in the lower lobe, upper lobe without alterations *(Figure 1C)*. PAS, Grocott and mucicarmin stains were performed, showing abundant *Cryptococcus* throughout the lung parenchyma *(Figure 2)*.

The patient was discharged after 27 days of stay, with outpatient management and antifungal regimen until further evaluation.

DISCUSSION

The aforementioned case represents a common example of pulmonary cryptococcosis, whose clinical onset is usually incipient until presenting systemic manifestations associated with the infection; however, its particularity is related to the fact that even without presenting immunocompromise, pulmonary involvement was significant and there was progression to meningitis with associated neurological deficit that led to complications and pulmonary resection. Although it was not possible to determine the association with the second dose of the vaccine, in some way the evidence presented and the abrupt response after its application may imply an association related to the immunosuppression-immunocompetence status.

On the other hand, it has been described that when it is cryptococcosis isolated to the lung, the diagnosis is relatively good, however, this is drastically associated with a bad evolution when it has extrapulmonary extension, as in our case, and it is reported with up to 55% mortality.[4] The dimensions of the exposed cryptococcoma are comparable to the largest pulmonary cryptococcoma published to date: the case of Menon A. et al.[5] of 14 × 13 × 0.5 cm in a 48-year-old immunocompetent male patient without extrapulmonary extension. In that case, the patient had a two-year evolution time until he underwent a right upper lobectomy with subsequent resolution of the condition, and at eight-month follow-up showed no recurrence.

Due to the low incidence of cryptococcosis in Mexico, there is no consensus on the therapeutic regimen.[6] Immunocompetent patients with isolated pulmonary cryptococcosis have an excellent prognosis without the need for antifungal therapy or surgical resection, which is why they are often left for observation only.[7] B. Saag et al.[8] recommend only initiating antifungal therapy if the patient is symptomatic. Nadrous HF et al.[9] follow these recommendations, as well as indicating treatment when extrapulmonary extension is present as in the case of

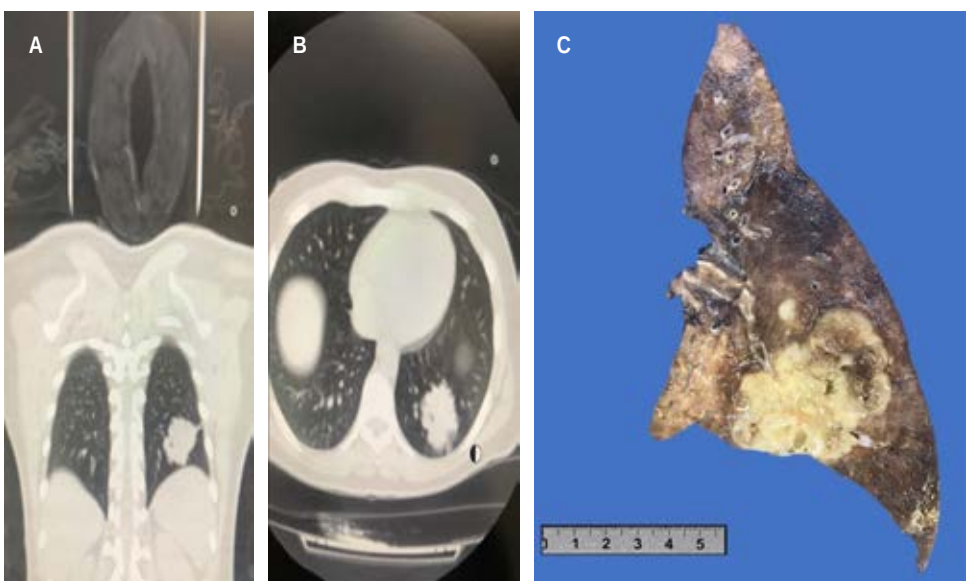

Figure 1:

A and B) thoracic tomography scan with diffuse border lesion in the left lower pulmonary lobe, homogeneous hyperdense. **C)** in the lower third, a well-demarcated nodular lesion measuring 8.3 × 5.5 × 5.0 cm of whitish-yellow color, hard consistency, with areas of microcystic appearance containing mucoid material.

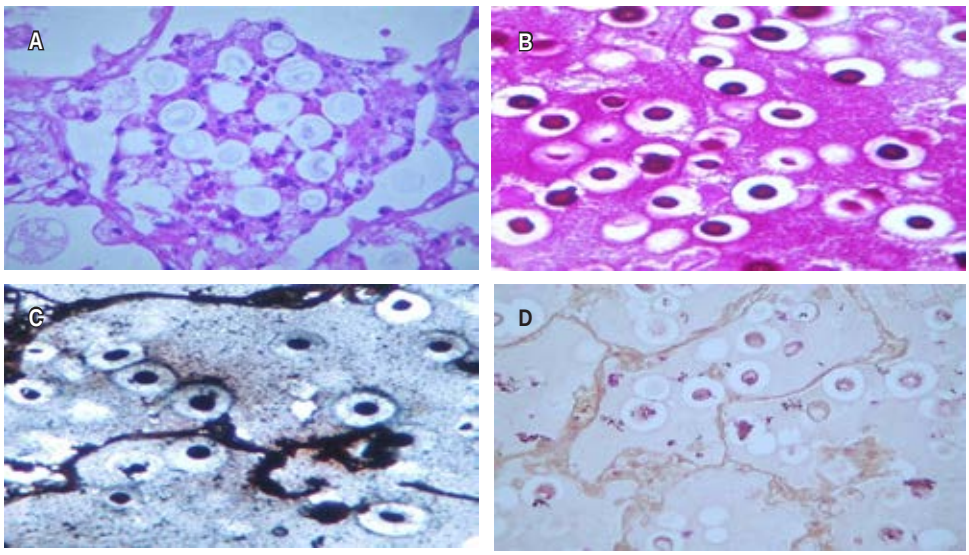

Figure 2:

H&E, PAS, Grocott and Mucicarmin stains showing *Cryptococcus* in lung parenchyma and phagocytosed by macrophages.

the patient presented here. Surgical treatment should be considered for cases with vital organ obstruction, persistent radiographic abnormalities, or cases refractory to treatment after one month. In this case, surgical treatment was decided because of continued neurological deterioration with no response to antifungal therapy.

CONCLUSIONS

This case represents a common example of pulmonary cryptococcosis, whose particularity lies in its presentation in a patient without immunocompromise. Even so, both pulmonary and neurological involvement was important. Although it was not possible to determine a relationship with the application of the second dose of the vaccine, the evidence presented and the abrupt start after its application may imply an association with the immunosuppression-immunocompromised state.

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Respiratory world

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Congresses and contagions. Pulmonologists as patients

Congresos y contagios. Neumólogos como pacientes

José Luis Sandoval-Gutiérrez*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas and vice president of the Sociedad Mexicana de Neumología y Cirugía de Tórax. Mexico City, Mexico.

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Onward, onward along this endless road that is the great adventure of our life, the march of humanity.
«The march of humanity».
David Alfaro Siqueiros
(Figure 1)

Within the professional training of a physician, congresses are part of the actions to be taken to receive continuous education and updating.

In recent months, the COVID-19 pandemic led to the suspension of physical participation and the popularization of virtual assistance, which already existed but had not been exploited to its full potential. This type of modality allowed academic exchange and knowledge to continue with the necessary dissemination in the present respiratory emergency situation.

The control and containment of the aforementioned respiratory disease by means of new management, vaccines, public health, etc., have allowed medical congresses to offer again the hybrid situation (face-to-face/virtual), but emphasizing physical presence.

Our pneumological society had its last pre-pandemic face-to-face meeting in the city of Oaxaca in February 2020, in the so-called MasterClass, where participation is discreet compared to the National Congress, then the first cases began in our country and the need to suspend the 2020 and 2021 meetings arises, as in the rest of the world.

In the current year 2022 the MasterClass meeting was held in the city of Cabo San Lucas with a great attendance, which was the ideal preamble for the National Congress that was scheduled to be held in the city of Monterrey last June, which was completed with great success and participation of the attendees.

The natural fear of the participants was the possibility of contagion due to being together with many colleagues for several days. The professionals questioned themselves about the need to assist or not to this event, asking themselves «is it right to attend?», «isn't it exactly what I have recommended to my patients not to be in crowded meetings?», «is it a responsible decision?», «I have been so careful!» adding all the situations that it entails such as having seen patients and/or family members hospitalized, getting complicated and dying.

Here the logical question would be: why are there medical congresses in person? The answer could be, because life goes on like science, medicine, and professionals are no strangers to it.

Before the scientific societies restarted activities personally, a large number of establishments such as cinemas, theaters, restaurants, schools, sports centers, entertainment centers, tourist hotels, etc., were already doing it. And why? Because the health authorities allowed it with the evaluation of the specialists in charge.

When meeting with foreign colleagues, especially those from North America and Europe, they comment that not wearing masks or having protective measures in their respective countries is the rule compared to what we have in our country.

The congress organizers recommended a test for SARS-CoV-2 virus prior to attending the event and the possibility of running laboratory studies at the course facilities.

It was mandatory to wear a mask in all activities, there was antibacterial gel at the entrances to the site, a similar device was also provided in the registration bags and in the commercial area, besides the gifts for participants contained solutions of the same characteristics. Several questions could be asked here: what else could have been done? Could something better have been planned? There are probably always points for improvement, but we did what was necessary and recommended; so far, the number of infections does not exceed 5% of the total number of attendees.

It is worth mentioning that in the MasterClass held in Baja California Sur there was no significant number of COVID-19 case detection associated with the attendance; it can be argued that the number of participants was lower than in the National Congress, but it should be emphasized that it was held months prior to the conference in Monterrey, where the presence of the pandemic was still in action.

This year we have witnessed the fifth wave of this emerging situation in our nation, unfortunately it overlapped with the month of the national meeting, but fortunately there is no data on the severity

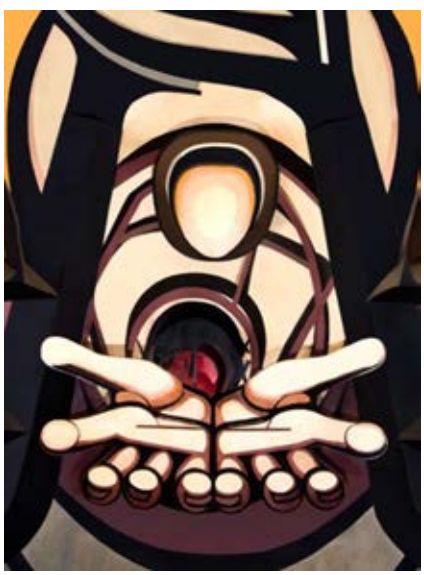

Figure 1: Mural «The march of humanity». David Alfaro Siqueiros. Available at: https://www.pinterest.es/pin/473440979550239251/

Neumol Cir Torax. 2022; 81 (2): 144-145

of infected patients who have required in-hospital care, being managed on an outpatient basis.

After two years, the respiratory health specialist had to restart his academic life at some point and the place was in Monterrey.

It is up to us as a society and professionals to follow up on all these situations; in two years we will be 85 years old as a medical school, we have survived several pandemics, the «white plague», as pulmonary tuberculosis was called, was the origin of its formation.

We will move forward!

With everyone's participation and support, for the benefit of our patients.

Correspondence:
José Luis Sandoval-Gutiérrez, MD
Sociedad Mexicana de Neumología y Cirugía de Tórax, Mexico City, Mexico.
E-mail: sandovalgutierrez@gmail.com

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Dr. Antonio Soda Merhy. Recognition of Academic Merit Dr. Jaime Villalba Caloca 2022, INER

Dr. Antonio Soda Merhy. Reconocimiento al Mérito Académico Dr. Jaime Villalba Caloca 2022, INER

Armando Castorena-Maldonado*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

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Dr. Antonio Soda Merhy *(Figure 1)* was born in Mexico City on December 28, 1940. He studied medicine and afterwards the specialization in otolaryngology and head and neck surgery with the recognition from the Faculty of Medicine of the UNAM. He married to Mrs. Rocío González de Soda with whom formed a family of three children: Antonio, Anuar and Yamil. Dr. Soda was a physician attached to the Otolaryngology Department of the General Hospital «La Raza» Medical Center of the Mexican Institute of Social Security (1970-1982). He arrived to the National Institute of Pulmonary Diseases in 1980 as a key strategy for its transformation into National Institute of Respiratory Diseases (INER). He began as a inter consultative specialist and in less than a decade he managed to form the otolaryngology service and afterwards the otolaryngology and head and neck surgery department, which included the opening of the specialization course and the training of the first generation of specialists with the endorsement of the Faculty of Medicine of the UNAM.

Dr. Soda has fulfilled the fundamental responsibilities of our institute such as high speciality medical care, and he has trained the best level of human resources that practice the speciality from the Northern border of our country to the Southern cone of Latin America. He influenced the applied research that impacted several paperwork's that are still cited in the international texts of the speciality. He has always been characterized by his high level institutional nature, which led him to accomplish multiple distinctions of national and international order, among which are: member of the National Academy of Medicine, of the Mexican Academy of Surgery, of the American Academy of Otolaryngology Head and Neck Surgery, former Coordinator of the Academic Committee of Otolaryngology and Head and Neck Surgery of the Faculty of Medicine of the UNAM and he was Coordinator of the Medical Education Committee of the Ángeles Lomas Hospital and President of the Mexican Society and Councils of the speciality. In addition, he has received nearly 30 distinction and recognitions: Member of the Governing Board of the General Hospital «Dr. Manuel Gea González» (1998-2002), to University Merit for 40 years of academic services, UNAM (2012), Lifetime Achievement Award in the National Institute of Respiratory Diseases Ismael Cosío Villegas (2014), Ángeles Award 2014 (given by the Ángeles Health Services Group and the National Academy of Medicine), Biblos Award to a Lifetime Achievement 2019 and founder of The Ibero-American Group Cochlear Implants and Related Sciences (GICCA). All the previous could be enough to recognize the work of Dr. Soda, but I would like to add the last point about what may have more impact for the medical community and for our country, the National Cochlear Implants Program initiated under his leadership in 1999. This program has had the opportunity to rehabilitate children from low-income families and with one of the disabilities of more isolation and without the possibility of a full life, deafness. To this day, this program continues to put our institute as a leader. Based on all this baggage, Dr. Soda is considered by his peers as one of the pillars of the speciality in our country.

Figure 1: Dr. Antonio Soda Merhy.

Correspondence:
Armando Castorena-Maldonado, MD
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico.
E-mail: armando_iner@yahoo.com.mx

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