4 - 2022

ISSN 2594-1526

VOL. 81 NO. 4 OCTOBER-DECEMBER, 2022

NCT

Neumología y Cirugía de Tórax

New treatments for rifampin resistant tuberculosis. Safe and effective?

ORIGINAL ARTICLES

- Efficacy and safety of a new short regimen for treatment of tuberculosis resistant to rifampicin. A pilot study
- Use of an electrolyzed superoxidation solution to disinfect non-invasive mechanical ventilation masks

REVIEW ARTICLE

- Recommendations for diagnostic approach and management of bronchiectasias

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REVISTA OFICIAL DE:
SOCIEDAD MEXICANA DE NEUMOLOGÍA Y CIRUGÍA DE TÓRAX,
INSTITUTO NACIONAL DE ENFERMEDADES RESPIRATORIAS ISMAEL COSÍO VILLEGAS

ISSN 2594-1526

Volume 81 / Number 4 / October-December 2022

NCT

Neumología y Cirugía de Tórax

www.revistanct.org.mx

Oficial journal:
Mexican Society of Pneumology and Thoracic Surgery
National Institute of Respiratory Diseases Ismael Cosío Villegas

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Neumología y Cirugía de Tórax
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Editorial
doi: 10.35366/112949

New treatments for rifampin resistant tuberculosis. Safe and effective?

Nuevos tratamientos para la tuberculosis resistente a rifampicina. ¿Seguros y eficaces?

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Due to the impact of the COVID-19 pandemic, the World Health Organization (WHO) predicts a global increase, in 2022-2023, of half a million cases annually of rifampicin-resistant tuberculosis (RRTB/MDR).[1] Added to the above, even before the pandemic, only one in three patients has received treatment,[2] in addition, with a very low cure rate. The regimens used to treat RRTB/MDR, traditionally consisted of many oral drugs, expensive, toxic and of little activity, which motivated the implementation of a multi-drug regimen; to these was added an injectable agent, at least for six months, which produced very serious side effects, such as irreversible hearing loss or renal failure, causing many dropouts.

With the meta-analysis published by the MDR-TB analysis collaborative group, headed by Dr. Menzies, where they reported that the injectable agents proved not to have the efficacy that was believed. In contrast, in the study, both third-generation quinolones, linezolid, clofazimine and carbapenems were shown to have greater effectiveness in treatments;[3] this had already been reported also by Palomino and Martín.[4] There are three new oral drugs with high effectiveness for the treatment of RRTB/MDR: bedaquiline,[5] delamanid[6] and pretomanid.[7] With the advent of these new drugs, different trials of short, safe and effective treatments have been implemented. These regimens include a new six-month treatment based on the combination of bedaquiline, pretomanid and linezolid, in combination with moxifloxacin (BPaLM), or without the latter (BPaL), which were highly recommended by the WHO[8] and which appeared in important publications.[9-11]

Laniado-Laborín *et al.*[12] publish in this issue the results of the treatment for RRRT/MDR with a shortened schedule in 26 consecutive patients with drugs suggested by the WHO[13] of groups A and B to demonstrate their efficacy and safety; the conversion to culture was 1.42 ± 0.82 months (six weeks) and the conversion time of bacilloscopy was 1.75 ± 0.95 months (seven weeks), much higher than the previously used schemes where an injectable and drugs of poor activity were integrated, and which lasted up to more than 18 months. The activity of the new drugs, with significant bactericidal and sterilizing activity, has given hope of curing the greatest number of patients with RRTB/MDR. A major drawback is adverse reactions, but they can be managed without the scheme losing its effectiveness. However, the follow-up must be very punctual to be able to identify them; and the doctor must have experience to identify them. Unfortunately, there are not many specialists who are interested in treating this situation, so I twill be very important to train first contact doctors so that these safe and effective schemes offer a cure for this disease and prevent cases from continuing to increase.

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How to cite: Salazar-Lezama MÁ. New treatments for rifampin resistant tuberculosis. Safe and effective? Neumol Cir Torax. 2022; 81 (4):219-220. https://dx.doi.org/10.35366/112949

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NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022

Original

doi: 10.35366/112950

Efficacy and safety of a new short regimen for treatment of tuberculosis resistant to rifampicin. A pilot study

Eficacia y seguridad de un nuevo esquema corto para el tratamiento de la tuberculosis resistente a rifampicina. Estudio piloto

Rafael Laniado-Laborín,* Gerardo Castro-Mazon,* Jorge Salcido-Gastelum*

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ABSTRACT. Introduction: a fundamental problem in the treatment of drug-resistant tuberculosis has been the long duration of treatment regimens; globally successful treatment rates are less than 60%. The World Health Organization has proposed that through operational research new shortened all-oral regimens be tested for the treatment of rifampicin-resistant and multidrug-resistant tuberculosis. **Objectives:** a pilot study was conducted to determine the efficacy of a 4-drug all-oral regimen, through the conversion time of the culture, and the safety based on the presence of adverse reactions grade ≥ 3. **Material and methods:** twenty-six consecutive patients who have received this regimen, were included. Rigorous clinical and bacteriological follow-up was carried out to evaluate efficacy and safety. **Results:** the culture conversion time from the start of treatment was 1.42 ± 0.82 months (six weeks) and the smear microscopy conversion time was 1.75 ± 0.95 months (seven weeks). Regarding the safety of the regimen, 73.1% of the patients reported some type of adverse effect. **Conclusions:** this all-oral regimen shows excellent effectiveness with culture conversion within two months and by including three drugs with sterilizing activity (bedaquiline, levofloxacin, and clofazimine), it offers the possibility of reducing the duration of treatment, which could reduce losses to follow-up. The toxicity of the regimen is significant, and its implementation requires expert management in drug-resistant TB, and rigorous clinical and laboratory monitoring.

Keywords: tuberculosis, drug-resistant, short-course, treatment, efficacy.

RESUMEN. Introducción: un problema fundamental en el tratamiento de la tuberculosis resistente a fármacos ha sido la larga duración de los esquemas de tratamiento; globalmente las tasas de éxito son inferiores a 60%. La Organización Mundial de la Salud ha propuesto la aprobación de nuevos esquemas acortados, todos orales, a través de investigación operacional para el tratamiento de la tuberculosis resistente a rifampicina y multidrogorresistente. **Objetivos:** este estudio piloto fue realizado para determinar la eficacia de un esquema de cuatro fármacos, todos orales, a través del tiempo de conversión del cultivo, y seguridad con base en la presencia de reacciones adversas grado ≥ 3. **Material y métodos:** se incluyeron a 26 pacientes consecutivos que han recibido este esquema. Se llevó a cabo un riguroso seguimiento clínico y bacteriológico para evaluar la eficacia y seguridad. **Resultados:** el tiempo de conversión del cultivo desde el inicio del tratamiento fue de 1.42 ± 0.82 meses (seis semanas) y el tiempo de conversión de la baciloscopia fue de 1.75 ± 0.95 meses (siete semanas). En cuanto a la seguridad del esquema, 73.1% de los pacientes reportaron algún tipo de efecto adverso. **Conclusiones:** este régimen todo oral muestra excelente efectividad con conversión del cultivo antes de dos meses, al incluir tres fármacos con actividad esterilizante (bedaquilina, levofloxacino y clofazimina), ofrece la posibilidad de reducir la duración del tratamiento, lo que disminuirá las pérdidas a seguimiento. La toxicidad es significativa y su uso requiere manejo experto en tuberculosis resistente a fármacos y riguroso monitoreo clínico y de laboratorio.

Palabras clave: tuberculosis, resistente a fármacos, acortado, tratamiento, eficacia.

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Received: V-10-2023; accepted: VII-07-2023.

How to cite: Laniado-Laborín R, Castro-Mazon G, Salcido-Gastelum J. Efficacy and safety of a new short regimen for treatment of tuberculosis resistant to rifampicin. A pilot study. Neumol Cir Torax. 2022; 81 (4):221-223. https://dx.doi.org/10.35366/112950

INTRODUCTION

A fundamental problem in the treatment of drug-resistant tuberculosis (TB) has been the long duration of treatment regimens.[1] This is one of the factors that contribute to a success rate in the Americas region of less than 60% with traditional treatment regimens and rates of loss to follow-up above 20%.[2] The World Health Organization (WHO) has proposed that, through operational research projects, new shortened all-oral regimens be tested for the treatment of rifampicin-resistant (RR-TB) and multidrug-resistant (MDR-

TB) tuberculosis. The Special Programme for Research and Training in Tropical Diseases (TDR) in close collaboration with the Global TB Programme at WHO has developed ShORRT (Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis), an operational research package to assess the effectiveness, safety, feasibility, acceptability, cost and impact (including on health-related quality of life).[3]

The National Tuberculosis Program of Mexico plans to implement a new shortened standardized nine-month regimen with four oral drugs under operational research conditions. To this end, a pilot study was conducted to determine the efficacy of the drug regimen, evaluated through the conversion time of the culture, and the safety based on the presence of adverse reactions grade ≥ 3.

MATERIAL AND METHODS

The subjects with RR-TB/MDR were diagnosed and treated at the Tuberculosis Clinic of the Tijuana General Hospital. The diagnosis was established by molecular (Xpert® MTB/RIF, Cepheid, Sunnyvale, CA) and phenotypic (MGIT, Becton-Dickinson, NJ) methods. The standardized regimen includes four oral drugs, three from group A and one from WHO group B:[4] bedaquiline, levofloxacin, linezolid, and clofazimine. Twenty-six consecutive subjects who have received this regimen, currently indicated in Mexico for 18 months, were included. Subjects underwent a strict protocol to determine the effectiveness of the regimen by smear microscopy and monthly cultures during treatment; to determine the safety of the regimen, clinical evaluation (including visual acuity test and color discrimination ability) and safety laboratory tests (blood count, biochemical profile) were performed monthly. In addition, electrocardiograms at baseline, on day 15 of treatment, and monthly thereafter while the subjects were receiving bedaquiline.

The study was approved by the Institutional Review Board of the Tijuana General Hospital (CONBIOETICA-02-CEI-001-20170526) and performed under the principles of the declaration of Helsinki. Written informed consent was obtained from every participant.

RESULTS

The mean age of the group was 38.2 ± 17.7 years; the majority were male (65.4%). Nineteen subjects (73%) had rifampicin-resistant (RR) tuberculosis and seven multidrug-resistant tuberculosis (MDR-TB). Sixteen subjects (61.5%) had some comorbidity, the most frequent being diabetes (12 cases, 46.1%) and infection by the human immunodeficiency virus (HIV; six cases, 23.1%). Most of the subjects with diabetes presented uncontrolled glucose levels at the time of diagnosis, with a baseline glycosylated hemoglobin (HbA1c) of 7.51 ± 2.9%; 60% of subjects with diabetes had a baseline HbA1c of ≥ 9%. Eleven subjects (42.3%) reported addictions, methamphetamine being (27.7%) the most frequent.

The culture conversion time from the start of treatment was 1.42 ± 0.82 months (six weeks) and the smear microscopy conversion time was 1.75 ± 0.95 months (seven weeks).

Regarding the safety of the regimen, 73.1% of the subjects reported some type of adverse effect, with gastrointestinal adverse reactions being the most frequent (42.3%). Hematologic toxicity attributable to linezolid occurred in six subjects (23.1%) as anemia and/or thrombocytopenia.

During the monthly follow-up, five subjects had a corrected QT interval (QTc) value ≥ 490 ms on at least one occasion; these five subjects (19.2%) required a temporary suspension of bedaquiline due to prolongation of the QTc interval. Twelve subjects (46.1%) presented an increase of ≥ 60 ms compared to the baseline QTc. In general, an adverse reaction made it necessary to adjust the dose of one of the drugs in nine subjects (34.6%) and to suspend a drug in seven cases (26.9%) *(Table 1)*.

DISCUSSION

Globally, only 59% of subjects with rifampicin-resistant tuberculosis who started treatment in 2018 were successful and this figure has not improved much in the last five years.[5] As mentioned, one of the contributing factors to this low success rate is the long duration of traditional RR/MDR TB treatment of 18-20 months. For this reason, shortened oral treatments have been proposed; the results of the TB-PRACTECAL study were recently published, which included a 24-week all-oral regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin, with higher success rates than those of the traditional regimen.[6]

The regimen proposed for the treatment of RR-TB/MDR in Mexico as an operational research protocol includes the

Table 1: Most frequent adverse reactions associated with the anti-tuberculosis drugs that make up the regimen.

Adverse reaction	n (%)
Gastrointestinal (nausea, vomiting)	11 (42.3)
Elevated liver enzymes (< 3 times the upper limit of normal)	8 (30.8)
Skin adverse reactions	7 (26.9)
Visual (green/red color discrimination/visual acuity)	7 (26.9)
Hematologic (anemia/thrombocytopenia)	6 (23.1)
QTc prolongation ≥ 490 ms	5 (19.2)
Elevated liver enzymes (≥ 3 times the upper limit of normal)	3 (11.5)

three drugs from WHO group A (bedaquiline, levofloxacin, and linezolid) and one drug from group B (clofazimine) for nine months. This combination demonstrated in our pilot test an excellent bactericidal effect with culture conversion in only six weeks.

As with all second-line drug treatment regimens, adverse effects are reported in the majority of subjects[7-9] when active pharmacovigilance is carried out. The most toxic medication in the regimen is linezolid,[4] with hematologic and neurologic toxicity. Hematological toxicity attributable to linezolid occurred in one out of every four subjects in the form of anemia and/or thrombocytopenia, which in some cases forced the definitive suspension of the drug; similarly, in cases with optic neuritis (26.9%), it was necessary to reduce the dose or permanently suspend linezolid. Bedaquiline, fluoroquinolones (especially moxifloxacin), delamanid, pretomanid, and clofazimine, drugs currently used to treat drug-resistant TB, prolong the QTc interval of the cardiac electrical cycle. QTc prolongation is a risk factor for life-threatening polymorphic ventricular tachycardia (torsade de pointe), and sudden death.[10]

CONCLUSION

This all-oral regimen shows excellent effectiveness with culture conversion within two months, and by including three drugs with sterilizing activity (bedaquiline, levofloxacin, and clofazimine), it offers the possibility of reducing the duration of treatment, which could reduce losses. To follow-up[4] by shortening the treatment from 18 to 9 months. However, the toxicity of the regimen is significant, and its implementation requires expert management in drug-resistant TB, and rigorous clinical and laboratory monitoring. It is important to emphasize that this is a pilot study whose results cannot be extrapolated to the national level.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022

Original

doi: 10.35366/112951

Use of an electrolyzed superoxidation solution to disinfect non-invasive mechanical ventilation masks

Uso de una solución electrolizada de superoxidación para desinfectar mascarillas de ventilación mecánica no invasiva

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ABSTRACT. Introduction: non-invasive mechanical ventilation masks are non-reusable supplies in high demand in respiratory therapy services. Determining whether they can be successfully disinfected could help to optimize resources. Neutral pH electrolyzed superoxidation solutions are effective and harmless high-level disinfectants used in the hospital environment. **Objective:** to evaluate the effectiveness of an electrolyzed neutral superoxidation solution to eliminate the bacterial load of noninvasive mechanical ventilation masks and its effects on the mask material. **Material and methods:** 49 masks used in patients with non-infectious diseases or pneumonia of the Respiratory Therapy Service of the Ismael Cosío Villegas National Institute of Respiratory Diseases were randomly distributed into the experimental group of electrolyzed solutions of neutral pH superoxidation (n = 22) and the orthophthalaldehyde control group (n = 27). Bacteriological sampling was performed before and after disinfection and the bacterial load was characterized in five of each group. Disinfection was by immersion in electrolyzed solutions of neutral pH 0.004% superoxidation, for five minutes or for 45 minutes in orthophthalalaldehyde. New masks subjected to three disinfection cycles were analyzed by scanning electron microscopy. **Results:** disinfection with neutral pH electrolyzed superoxidation solutions eliminated 100% of the bacterial load. The neutral pH electrolyzed superoxidation solution was effective against the nosocomial opportunistic bacteria *Staphylococcus aureus, Corynebacterium striatum, Enterobacter cloacae, Enterobacter aerogenes* and *Enterococcus faecalis* from the masks. Scanning electron microscopy revealed that three disinfection cycles did not generate structural damage to the material. **Conclusion:** the disinfection method with neutral pH

RESUMEN. Introducción: las mascarillas de ventilación mecánica no invasiva son insumos no reutilizables de alta demanda en los servicios de terapia respiratoria. Determinar si pueden ser desinfectadas exitosamente podría ayudar a optimizar recursos. Las soluciones electrolizadas de superoxidación de pH neutro son desinfectantes de alto nivel efectivas e inocuas utilizadas en el ámbito hospitalario. **Objetivo:** evaluar la efectividad de una solución electrolizada de superoxidación neutra para eliminar la carga bacteriana de mascarillas de ventilación mecánica no invasiva y sus efectos sobre el material de éstas. **Material y métodos:** 49 mascarillas utilizadas en pacientes con enfermedades no infectocontagiosas o neumonía del Servicio de Terapia Respiratoria del Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas se distribuyeron, de manera aleatoria, en el grupo experimental de soluciones electrolizadas de superoxidación de pH neutro (n = 22) y el grupo control ortoftalaldehído (n = 27). Se realizó un muestreo bacteriológico antes y después de la desinfección y en cinco de cada grupo se caracterizó la carga bacteriana. La desinfección fue por inmersión en soluciones electrolizadas de superoxidación de pH neutro al 0.004%, por cinco minutos o por 45 minutos en ortoftalaldehído. Las mascarillas nuevas sometidas a tres ciclos de desinfección, se analizaron mediante microscopia electrónica de barrido. **Resultados:** la desinfección con soluciones electrolizadas de superoxidación de pH neutro eliminó 100% de la carga bacteriana. La solución electrolizada de superoxidación de pH neutro fue efectiva contra las bacterias oportunistas nosocomiales *Staphylococcus aureus*, *Corynebacterium striatum*, *Enterobacter cloacae*, *Enterobacter aerogenes* y *Enterococcus faecalis* de las mascarillas. La microscopia electrónica de barrido reveló que tres ciclos de desinfección

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Received: IV-11-2023; accepted: VII-25-2023.

How to cite: Toral-Freyre SC, Castillejos-López M, Hernández A, Becerril-Vargas E, Mújica-Sánchez MA, Mendoza-Romero VM *et al*. Use of an electrolyzed superoxidation solution to disinfect non-invasive mechanical ventilation masks. Neumol Cir Torax. 2022; 81 (4):224-231. https://dx.doi.org/10.35366/112951

Neumol Cir Torax. 2022; 81 (4): 224-231

electrolyzed superoxidation solutions was effective in eliminating the bacterial load without causing damage to the mask material.

Keywords: electrolyzed superoxidation solution, noninvasive mechanical ventilation mask, high-level disinfection, reuse of medical devices.

no generan daños estructurales en el material. **Conclusión:** el método de desinfección con soluciones electrolizadas de superoxidación de pH neutro fue efectivo para eliminar la carga bacteriana sin generar daños en el material de las mascarillas.

Palabras clave: solución electrolizada de superoxidación, mascarilla de ventilación mecánica no invasiva, desinfección de alto nivel, reúso de dispositivos médicos.

INTRODUCTION

The use of single-use masks for the administration of nebulized drugs, oxygen therapy and non-invasive mechanical ventilation (NIMV) results in a high consumption of material and economic resources for respiratory therapy services in the country's public hospitals. Applying effective disinfection techniques that allow reuse of these supplies could be a strategy to optimize this area. Since this type of equipment is semi-critical, it should be subjected to standardized high-level disinfection protocols to ensure its effectiveness and guarantee the integrity of the material.[1-3]

Currently, at the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER), Mexico City, a disinfection protocol is applied for reusable semi-critical equipment consisting of an enzymatic washing cycle and a 40-minute orthophthalaldehyde (OPA) immersion cycle, followed by rinsing with sterile water and drying.[4,5] However, the use of OPA has disadvantages such as skin, clothing and surface staining.[6,7] In addition, there have been reports of health effects on technical personnel and anaphylaxis in patients treated with materials disinfected with this substance.[8,9]

In contrast, neutral pH superoxide electrolyzed solutions (SES) are non-toxic, non-corrosive and environmentally friendly high-level disinfectants.[10-13] They are produced through the controlled electrolysis of an aqueous solution of sodium chloride that generates active oxygen and chlorine species, such as hydrogen peroxide and hypochlorous acid.[14] These act by scavenging electrons and breaking chemical bonds of the outer envelopes in microorganisms.[15] Consequently, it generates protein denaturation in viruses and osmotic lysis in single-celled organisms.[16] The effectiveness of neutral SES has been documented on fungi, spores, viruses and bacteria, including multidrug-resistant strains and biofilms.[17-19] Because of these properties, they are used in the disinfection of hospital environments such as intensive care units, in healthcare settings and in rooms with specialized equipment, such as radiology and tomography rooms.[10-13]

This study evaluated the effectiveness of a SES with neutral pH at 0.004% of active species of chlorine and oxygen to eliminate the bacterial load of single-use NIMV masks used by patients with non-infectious diseases of different types of pneumonia, in parallel with a disinfection control protocol for semicritical equipment routinely applied in the INER using OPA. The effects of three disinfection cycles with SES on the mask material were also analyzed by scanning electron microscopy (SEM).

MATERIAL AND METHODS

Collection of non-invasive mechanical ventilation (NIMV) masks. Experimental study. The sampling method used to collect the NIMV masks (AcuCare™ F1-0 NV LGE, ResMed) was by convenience. They belonged to consecutive cases that met the selection criteria. Those from patients admitted to the clinical area of the Respiratory Therapy Service of the INER with non-infectious diseases were included. Specifically, with chronic obstructive pulmonary disease (COPD), obesity-hypoventilation syndrome, asthmatic crisis, pleural effusion, pulmonary tumor, type II respiratory failure, pulmonary cancer, venous thrombosis, pulmonary multinodular disease and pulmonary hypertension. Masks used by patients with pneumonia, nosocomial pneumonia and multiloculated empyema were also included. Masks used by patients diagnosed with tuberculosis, human immunodeficiency virus (HIV), hepatitis B and C were not included.

Five to six masks were collected per week according to the guidelines of the Manual for Cleaning and Disinfection of Reusable Equipment in the Respiratory Therapy Service.[4] Each mask was assigned with an identification number and randomly assigned to two groups identified as: the experimental group SES and the control group OPA. At the end of the study, 22 were in the SES group and 27 in the OPA group. Likewise, each week, one to two masks, from those assigned to each group, were randomly selected for bacteriological contamination typing until there were a total of five per type of disinfectant.

Determination of bacteriological load. Microbiological control of the internal part of the masks was performed by swabbing (sterile rayon-headed plastic swabs, 3M™ RediSwab). The swabs were placed inside tubes containing 10 mL of Letheen broth (3M™ RediSwab Letheen Broth RS96010LET). 100 μL of broth and a 1:10 dilution was seeded in duplicate on trypticasein soy agar (TSA) plates and incubated for 48 hours at 37 °C. The bacterial load was determined by counting colony forming units (CFU) and adjusting for the total volume of Letheen broth. The

identification of microorganisms was carried out with biochemical tests and the VITEK® 2 automated method, based on the protocols established in the Institute's Clinical Microbiology Laboratory.

Disinfection process for non-invasive mechanical ventilation masks. The masks of the experimental group SES were disinfected following the steps: 1) immersion of the device for three minutes in a 4 mL/L water dilution of the enzymatic detergent (Endozime® AW Plus); 2) rinsing with tap water; 3) immersion for five minutes in SES at 0.004% active chlorine and oxygen species and REDOX potential 750-950 mV (Estericide® QX, Sanitary Reg. No.: 0363C2006 SSA); 4) drying; and 5) wiping with sterile gauze.

Those in the OPA control group received the routine process of washing and disinfection of the institution's semi-critical material consisting of: 1) immersion for three minutes in the enzymatic detergent dilution (Endozime® AW Plus); 2) rinsing with flowing water; 3) immersion for 40 minutes in 0.55% OPA solution (CIDEX® OPA); 4) thorough rinsing with sterile water; 5) drying; and 6) wiping with sterile gauze.

At the end of the protocols, a microbiological control was performed as described above. Both disinfectant solutions were used according to the manufacturer's instructions, and were changed when the appearance of suspended particles was detected. Adequate OPA activity was verified using the test strips indicated by the supplier, while reuse of the SES was carried out according to the manufacturer's indications. The technical personnel in charge of performing the disinfection processes were informed about the characteristics of SES and its safety. However, they were asked to apply the same biosafety measures as with the use of OPA: use of gloves, mask and gown. They were also required to report any discomfort during the process. Personnel were not blinded to the treatments that each mask must receive. This work was performed from November 2017 to August 2018. The masks disinfected in this protocol were not reused on patients.

Analysis of structural damage in the material of non-invasive mechanical ventilation masks by scanning electron microscopy. Six new single-use NIMV single-use BiPAP masks (AcuCare™ F1-0 NV LGE, ResMed) were used. They were randomly assigned to the experimental group SES (n = 3) or the control group OPA (n = 3). All masks were subjected to three consecutive disinfection cycles as described above. Photographs were taken of the masks under the same light and perspective conditions. The analysis of structural changes in the material was performed with a JEOL JCM-600Plus scanning electron microscope (SEM). The samples were covered with graphite and gold. Images were acquired using a high vacuum SED detector with a spot size of 4.5, a working distance of 8.1 and at 15 kV. Micrographs were obtained at magnifications of 5,000× and 10,000×. The studies were carried out at the Department of Metallurgical Engineering, Faculty of Chemistry, National Autonomous University of Mexico, Mexico City.

RESULTS

The SES disinfection protocol was effective in decontaminating NIMV masks used by patients. Immersion of NIMV masks in SES for five minutes eliminated 100% of the bacterial load, regardless of the initial amount, both in masks used in patients with non-infectious diseases and in masks used in patients with pneumonia of different etiology *(Table 1)*. The same result was obtained when OPA was used as a disinfection control. It was evident that the two disinfection processes completely eliminate bacterial contamination; therefore, no statistical analysis was applied since there are no differences between them that can be compared. That is, SES had the same results as the OPA used as a control.

Regarding bacterial typing, in the five masks randomly selected from the SES group, prior to disinfection, two were found to be colonized by Enterococcus faecalis, one by Enterobacter cloacae, another by Enterobacter aerogenes and the last by Staphylococcus aureus and Corynebacterium striatum *(Table 2)*. Immersion in SES for five minutes completely eliminated these typically nosocomial opportunistic bacteria from the masks. In the case of the OPA group, of the five masks chosen at random, two were contaminated with Staphylococcus aureus, one with Enterobacter cloacae, one with Enterococcus faecalis and one with Pseudomonas aeruginosa *(Table 2)*. Similarly, immersion for 45 minutes in OPA eliminated these microorganisms from the masks.

In terms of the duration of each disinfection process, the use of SES required an average of 20 minutes per mask. Fifteen minutes of handling were required, comprising the stages of washing with enzymatic detergent to eliminate organic matter, rinsing with running water, drying after immersion in SES and cleaning with sterile gauze. In contrast, disinfection with OPA requires, in addition to the 40 minutes of immersion, 20 minutes of pre- and post-handling. In particular, thorough washing with sterile water is necessary to remove OPA residues. It is then that the use of SES as a disinfectant save about 40 minutes per mask. Finally, the technical staff did not report any physical discomfort associated with handling SES.

The SES disinfection protocol did not induce structural damage to the NIMV mask material. At the macroscopic level, photographs of the masks at the end of the disinfection protocols, acquired under the same light conditions, showed that those immersed with SES had a translucent appearance after three disinfection cycles *(Figure 1)*. In contrast, those immersed three times in OPA presented a yellowish opacification *(Figure 1)*.

Table 1: Comparison of disinfection methods with neutral pH electrolyzed superoxidation solution and orthophthalaldehyde.

Disinfection method							
Neutral pH superoxide electrolyzed solutions (SES)				Orthophthalaldehyde (OPA)			
Mask ID	Patient diagnosis	CFU (10^3)/mL	Bacterial death (%)	Mask ID	Patient diagnosis	CFU (10^3)/mL	Bacterial death (%)
1	Obesity-hypoventilation syndrome	4.6	100	2	Asthmatic crisis	80	100
5	Obesity-hypoventilation syndrome	110	100	3	Left pleural effusion	68	100
21	Interstitial pneumonia	40	100	4	Left pleural effusion	0	100
25	Lung mass	0	100	8	Left pulmonary tumor	0	100
27	Exacerbated COPD	26	100	12	Multiloculated empyema	4	100
31	Obesity-hypoventilation syndrome	110	100	13	COPD	6	100
34	Nosocomial pneumonia	18	100	17	Multiloculated empyema	290	100
36	Atypical pneumonia	4.2	100	18	Respiratory failure type II	1.3	100
39	Diffuse interstitial pneumonia	380	100	20	Lung cancer	0	100
40	Lung mass	2.8	100	23	Diffuse interstitial pneumonia	45	100
44	Mixed respiratory failure	280	100	26	Obesity-hypoventilation syndrome	98	100
46	Respiratory failure type II	0.4	100	29	Exacerbated COPD	0	100
47	Pneumonia	6.1	100	30	Exacerbated COPD, respiratory insufficiency type II	2,100	100
48	Pneumonia	13	100	33	COPD	1.7	100
59	Venous thrombosis	0	100	38	COPD/respiratory insufficiency type II	120	100
64	Interstitial pneumonia	300	100	45	COPD	230	100
68	COPD	420	100	50	Pneumonia	8.5	100
71	Pulmonary multinodular disease	0	100	51	Lung tumor	460	100
72	Pneumonia	600	100	52	Diffuse interstitial pneumonia	140	100
73	Pneumonia	680	100	53	Unspecified	11	100
75	Respiratory failure type II	1.1	100	54	Pulmonary hypertension	250	100
83	Pneumonia	22	100	57	Pneumonia	9.6	100
				58	Pneumonia	8.5	100
				61	Diffuse interstitial pneumonia	68	100
				62	Diffuse interstitial pneumonia	0	100
				67	Diffuse interstitial lung disease	0	100
				77	COPD	2	100

ID = identification. CFU = colony forming units. COPD = chronic obstructive pulmonary disease.

Table 2: Typing of microorganisms in five single-use non-invasive mechanical ventilation masks before the disinfection process.

Disinfection method					
Neutral pH superoxide electrolyzed solutions (SES)			Orthophthalaldehyde (OPA)		
Mask ID	Patient diagnosis	Identified MO	Mask ID	Patient diagnosis	Identified MO
31	Obesity-hypoventilation syndrome	*E. cloacae*	50	Pneumonia	*S. aureus*
40	Lung mass	*S. aureus* *C. striatum*	54	Pulmonary hypertension	*E. cloacae*
44	Mixed respiratory failure	*E. faecalis*	57	Pneumonia	*E. faecalis*
64	Interstitial pneumonia	*E. faecalis*	58	Pneumonia	*P. aeruginosa*
73	Pneumonia	*E. aerogenes*	77	COPD	*S. aureus*

ID = identification. MO = microorganism. COPD = chronic obstructive pulmonary disease.

However, analysis of the surface topography of the masks by scanning electron microscopy (SEM) revealed a similar appearance between the samples immersed in SES or OPA. No apparent structural damage was observed that could suggest aggressiveness of the disinfectants with the material of the masks *(Figure 1)*. It is worth mentioning that the SEM detected the presence of metallic particles deposited on the surface of the new masks, this means, before being subjected to the disinfection procedures (data not shown). This could be attributed to the manufacturing or packaging processes of these medical devices. It should be noted that after the disinfection protocols were performed, the load of these particles decreased.

DISCUSSION

In this work it was determined that a 0.004% SES of active chlorine and oxygen species can eliminate the bacterial load of NIV masks used by patients with non-infectious diseases and different types of pneumonias. It was shown to be effective against Enterococcus faecalis, Enterobacter cloacae, Enterobacter aerogenes, Staphylococcus aureus and Corynebacterium striatum, which are of particular medical importance, as they are multidrug-resistant nosocomial opportunists with the ability to form biofilms on medical devices.[20] After immersion for five minutes in the electrolyzed solution, the bioburden was completely eradicated without density dependence at the beginning of the disinfection process. This is consistent with a number of reports demonstrating that SES has bactericidal action against multidrug-resistant strains and biofilms.[17-19,21,22] This antimicrobial activity is due, broadly speaking, to the active species of chlorine and oxygen, which by oxidizing mechanisms generate osmotic lysis, denaturation of proteins and lipids and damage to genetic material.[15,16] It should be noted that currently and to the best of our knowledge, there is no evidence to indicate resistance of any pathogen to the germicidal action of SES. For this reason, they are used as high-level disinfectants and cold sterilants. Likewise, it has been shown that neutral SES is a non-corrosive disinfectant, so it is applied in the disinfection of specialized equipment such as those found in computed tomography and nuclear magnetic resonance rooms.[13] According to this evidence, SES did not induce changes in the masks that were appreciable at the macroscopic level. Consequently, the analysis of their surfaces by SEM showed that immersion in SES for three consecutive cycles does not induce structural damage in the material. In this regard, a recent study established that immersion of polyvinyl siloxane impressions for dental prostheses for 10 minutes in SES does not alter the reproduction of surface details or texture,[23] which corresponds to the results of this work.

To establish whether the disinfection of the masks with SES was efficient, OPA was used as a disinfection control in this study. This is a disinfectant routinely used in the decontamination of semi-critical material, which means that its effectiveness has been validated by health organizations around the world.[1] The results clearly showed that SES eliminates the entire bacterial load as well as immersion in OPA. It was also determined that both have activity against the same bacteria colonizing the masks: Staphylococcus aureus, Enterobacter cloacae and Enterococcus faecalis. The difference between them was, in the scope of this work, in the duration times of the disinfection processes. While disinfection with SES required 20 minutes, decontamination with OPA required 60 minutes. Another difference detected was a yellowish opacification of the masks that was evident at the macroscopic level in those subjected to three cycles of immersion with OPA. However, these macroscopic changes induced by OPA require further evaluation to determine if it affects their functionality.

It is important to point out that there are two aspects that are crucial for the reuse of medical materials. One, to establish that biofilms are not formed on them; and two, to determine that there are no disinfectant residues

that could compromise the patient's health. In this regard, there are reports that associate the presence of traces of OPA in endoscopes with anaphylactic reactions and cytotoxic effects.[8,24] Therefore, the use of this substance requires thorough rinsing of the material exposed to it. However, deficient or careless rinsing is a risk factor for the development of biofilms.[25] Likewise, tolerance of gram-positive and biofilm strains to OPA has been reported.[26,27] On these points, the use of SES has the advantages of not requiring rinsing and of being a non-toxic substance.[28] However, for the use proposed in this work, specific safety studies should be carried out.

SES have proven to be innocuous in animal models, in human cells and in hospital settings.[13,28] In fact, one of their most important applications is in wound disinfection.[29] In relation to this aspect, in this work the technical personnel did not report any discomfort when handling SES. However, it should be noted that biosecurity measures were used and that no objective measure of this point, such as a questionnaire, was made, so this is an anecdotal observation.

In summary, the results suggest that it is feasible to use a SES to decontaminate this type of masks, since in short times it was effective in eliminating the bacterial load, without depending on the amount of biomass. In addition, it did not induce structural damage in the mask material when subjected to three consecutive immersion processes. This could indicate that their useful life would be extended by up to three disinfection cycles.

Although the results obtained suggest that SES can be used as a disinfectant for this type of mask, we recognize the limitations of the present work. Firstly, the sample size, which should be increased to be statistically representative. Furthermore, bacterial load typing should be carried out on all the masks to clearly establish against which species the biocidal action of SES is effective or if there are any resistant bacteria. Additionally, the study must be extended to other pathogens such as fungi and viruses before it can be validated for use in patients. In this sense, if it is planned to reuse the masks, it is also necessary to make sure that there are no biofilm growths on them. In addition, the assessment of the quality of the material should be carried out on masks coming from patients and then subjected to disinfection. Likewise, it is imperative to include physical analyses that establish the correct functionality of this material after disinfection, considering that it is designed to be used only once.

CONCLUSIONS

Five-minute immersion in SES at 0.004% active chlorine and oxygen species was effective in decontaminating

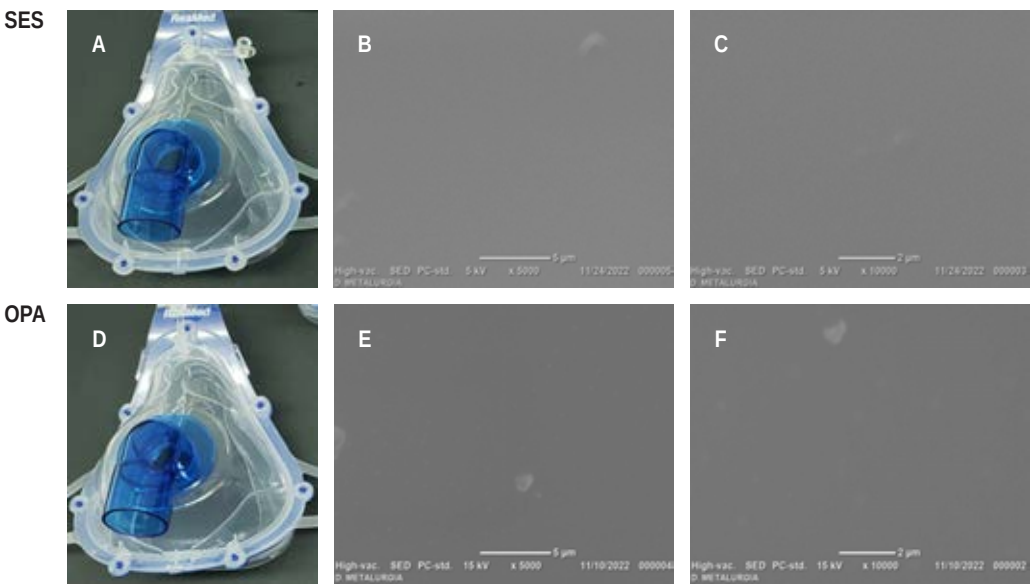

Figure 1: Material analysis of noninvasive mechanical ventilation (NIMV) masks subjected to three cycles of disinfection with superoxide electrolyte solution (SES). After three consecutive cycles of disinfection with SES or orthophthalalaldehyde (OPA) the masks were processed for examination by scanning electron microscopy. **A)** Photograph of the physical appearance of the SES-treated masks is shown. **B)** Scanning electron microscopy micrograph at 5,000× magnification is shown. No fractures or any damage to the material are visible. **C)** 10,000× magnification is shown. No fractures or damage to the material are visible. **D)** Corresponds to the physical appearance of a mask subjected to three disinfection cycles with orthophthalalaldehyde. A yellowing of the mask can be seen. **E and F)** Scanning electron microscopy micrographs at 5,000× and 10,000× magnification, respectively. No fractures or other changes in the topology of the material were observed at any magnification.

bacterially loaded single-use NIMV facemasks. This broad-spectrum disinfectant eliminated nosocomial opportunistic species Enterococcus faecalis, Enterobacter cloacae, Enterobacter aerogenes, Staphylococcus aureus, and Corynebacterium striatum from the masks. In addition, after three consecutive immersion cycles, the disinfectant did not cause damage to the mask material. All of the above suggests that it is feasible to use SES to disinfect single-use NIMV masks and extend their useful life. However, this is a first approach that must be complemented with other studies and validated before it can be used in patients. Specifically, it must be determined whether it eliminates other pathogens, such as viruses and fungi, as well as multidrug-resistant strains and biofilms. Functionality and safety studies must also be performed.

Acknowledgments

To the company Esteripharma, S.A. de C.V. for supplying the neutral pH superoxidation electrolyzed solution Estericide® QX with Health Reg. No. 0363C2006 SSA. To Dr. Brenda Paz-Michel and Dr. Mario Alfredo Rodríguez León for their critical comments on the content of this work.

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Conflict of interest: The authors Saraí Del Carmen Toral-Freyre, Mario Alberto Mujica-Sánchez, Eduardo Becerril-Vargas, Manuel Castillejo-López and Andrés Hernández declare that they have no conflict of interests. The authors Ariana Cabrera-Licona and Nicolas Mervitch-Sigal declare that they work for the company Esteripharma, but state that they did not participate in the acquisition or analysis of the data or in the decision to publish the results of the study.

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022

Review
doi: 10.35366/112952

Recommendations for diagnostic approach and management of bronchiectasis

Recomendaciones para abordaje diagnóstico y tratamiento de las bronquiectasias

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ABSTRACT. Bronchiectasis is a syndrome of chronic cough and production of viscous sputum associated with dilation of the airways and thickening of the bronchial wall. Exacerbations are usually caused by bacterial infections. It is a chronic disease that requires rapid responses for the treatment of exacerbations. Bronchial secretions should be cultured. Evaluate and treat underlying diseases to interrupt progression. In patients who have recurrent exacerbations (two to three in the last year) and do not have *Pseudomonas aeruginosa* infection, preventive therapy with a macrolide is recommended, excluding nontuberculous mycobacterial infections. In patients with recurrent exacerbations, or significant morbidity, and *Pseudomonas aeruginosa* in sputum, a therapeutic trial of nebulized tobramycin is useful. Nebulized tobramycin may also be for patients not infected with *Pseudomonas aeruginosa* in whom oral antibiotic prophylaxis is contraindicated, not tolerated, or ineffective. Patients who have *Pseudomonas aeruginosa* but cannot receive a nebulized antibiotic may benefit from macrolides as an alternative. Inhaled glucocorticoids are only indicated in patients with asthma or COPD. For patients who respond to bronchodilators on spirometry, the use of inhaled beta-adrenergic agents is suggested. All patients are candidates for pulmonary rehabilitation and bronchial hygiene. The prognosis is influenced by the underlying disease process, the frequency of exacerbations, and comorbidities, but in general, age-adjusted mortality is increased compared with the general population.

Keywords: bronchiectasis, approach, diagnosis, treatment.

RESUMEN. Las bronquiectasias son un síndrome de tos crónica y producción de esputo viscoso asociado con la dilatación de las vías respiratorias y el engrosamiento de la pared bronquial. Las exacerbaciones casi siempre son causadas por infecciones bacterianas. Es una enfermedad crónica que requiere respuestas rápidas al tratamiento de las exacerbaciones. Se deben cultivar las secreciones bronquiales, evaluar y tratar las enfermedades subyacentes para interrumpir la progresión. En los pacientes que tienen exacerbaciones recurrentes (dos a tres en el último año), y no tienen infección por *Pseudomonas aeruginosa,* se recomienda terapia preventiva con un macrólido, excluyendo infecciones por micobacterias no tuberculosas. En pacientes con exacerbaciones recurrentes o morbilidad significativa y *Pseudomonas aeruginosa* en el esputo, es útil una prueba terapéutica con tobramicina nebulizada. La tobramicina nebulizada también puede ser para pacientes no infectados con *Pseudomonas aeruginosa* en quienes la profilaxis con antibióticos orales está contraindicada, no se tolera o no es efectiva. Los pacientes que tienen *Pseudomonas aeruginosa*, pero no pueden recibir un antibiótico nebulizado pueden beneficiarse de los macrólidos como alternativa. Los glucocorticoides inhalados sólo están indicados en pacientes con asma o enfermedad pulmonar obstructiva crónica. Para pacientes con respuesta a broncodilatador en la espirometría se sugiere uso de agentes beta-adrenérgicos inhalados. Todos los pacientes son candidatos a rehabilitación pulmonar e higiene bronquial. El pronóstico está influenciado por el proceso patológico subyacente, la frecuencia de las exacerbaciones y las comorbilidades pero, en general, la mortalidad ajustada por la edad aumenta en comparación con la población general.

Palabras clave: bronquiectasias, abordaje, diagnóstico, tratamiento.

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Received: V-18-2023; accepted: VI-15-2023.

How to cite: Hernández-Zenteno RJ, Velázquez-Montero A, Suárez-Landa TJ, Pérez-Padilla JR. Recommendations for diagnostic approach and management of bronchiectasis. Neumol Cir Torax. 2022; 81 (4):232-245. https://dx.doi.org/10.35366/112952

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Neumol Cir Torax. 2022; 81 (4): 232-245

Abbreviations:

NSAI = Non-stereoidal anti-inflammatory NSAI.
BSI = bronchiectasis severity index.
CFTR = cystic fibrosis transmembrane conductance regulator.
CV = cardiovascular.
CVID = common variable immunodeficiency.
DLCO = diffusing capacity of the lungs for carbon monoxide.
COPD = Chronic obstructive pulmonary disease.
ERS = European Respiratory Society.
FACED score = FEV_1, Age, Chronic colonization, Extension, Dyspnea Score.
FEV_1 = forced expiratory volume at one second.
CF = Cystic fibrosis.
GC = Glucocorticoids.
IGC = Inhaled glucocorticoids.
IV = Intravenous.
LABA = long acting beta agonist.
mMRC = Modified Medical Research Council Scale
NET = neutrophil extracellular traps.
P. aeruginosa = *Pseudomonas aeruginosa*.
PEP = Positive Expiratory Pressure
PZP = pregnancy zone protein.
GER = Gastroesophageal reflux.
PR = Pulmonary rehabilitation.
RR = Relative risk.
SABA = short acting beta agonist.
SGRQ = Saint George Respiratory Questionnaire.
HRCTS = High resolution CT scan.
ICU = Intensive Care Unit.

INTRODUCTION

Bronchiectasis is an acquired disorder of bronchi and bronchioles, characterized by a permanent abnormal dilatation and destruction of their walls. Its induction requires an infectious insult plus drainage alteration, airway obstruction or defects in the defenses of the host. Bronchiectasis share many clinical presentations with chronic obstructive pulmonary disease (COPD), including collapsible airway inflammation, expiratory airflow obstruction, frequent exacerbations that require scheduled or unscheduled consultations or hospitalization. Diagnosis based on the clinical history (daily cough, tenacious discharge expectoration, recurrent expectorations and, by imaging, bronchial dilatations).[1]

Epidemiology, diagnostic approach, pharmacological and non-pharmacological management are the objective of this review that aims to be a proposal for recommendations.

EPIDEMIOLOGY

Prevalence increases with age eight to 10 times after the 60 years of age (300-500/100,000) when compared to < 40-50 years of age (40-50/100,000).[2] In United States a prevalence of 350,000-500,000 is estimated in adults.[3] Medicare (≥ 65 years of age) has an annual prevalence of 701/100,000 inhabitants.[4]

The greatest risk factor for chronic cough in the non-smoking population is bronchiectasis (OR = 5), among the former smokers it is OR = 7. It is more common in women, they make an extensive use of health resources (consultations, antibiotics, CT scans and hospitalization),[2,4] its prevalence is higher in the marginalized population, affects young people and impacts survival.[5,6] Social and environmental factors undoubtedly play a rol, including smoke exposition, limited access to health services and delayed antibiotic prescription.

Mortality: some small studies have described mortality rate of 16-20% at five years, which increase with the hospitalization in the Intensive Care Unit (ICU) and comorbidity. A study in United Kingdom found that mortality adjusted by age for adults with bronchiectasis was approximately twice that of the general population, regardless of age difference.[7] A report of 48 patients from France found 19% mortality in the ICU and 40% mortality per year.[8] In one series of 57 patients in Singapur a 26% general hospitalization mortality was reported without difference if the patients received non-invasive ventilation or intubation with mechanical ventilation.[9] Severe hypoxemia and high APACHE II scores were the worst prognosis factors.

In one series of 245 patients with bronchiectasis in Belgium between 2006 and 2013, mortality was 20%, increasing to 55% among those with COPD.[10] The cause of death was mainly respiratory (58%).

Pathophysiology: the consequent host response, immune effector cells (mainly neutrophils), neutrophils proteases (elastase), oxidative stress (hydrogen peroxide, H_2O_2) and inflammatory cytokines create a transmural inflammation, mucosa edema, ulceration and neovascularization in the airways.[11] The following factors may contribute to the physiopathology of bronchiectasis:

1. **Neutrophils effects and neutrophil elastase:** progressive destruction of airways. Serum and local neutrophils have increased variability (reduced apoptosis), reduced phagocytosis, increased release of myeloperoxidase and damaged bactericidal activity (for *Pseudomonas*).[12] Pregnancy zone protein (PZP) correlates with exacerbations, worsening and the presence of Pseudomonas aeruginosa *(P. aeruginosa)*.[13] Neutrophil extracellular traps (NETs) are networks of strings of DNA that contain histone, elastase, PZP and other inflammatory mediators that are formed as part of a cellular death process of neutrophils, which also contributes to anormal and permanent destruction and dilatation of the bronchial and bronchiole walls.[14]
2. **Physical properties of the sputum/mucus:** it is more tenacious, viscous and less elastic, contains concentration of DNA, mucin (mainly MUC5B), and other solid components.[15] These differences may explain divergent responses to bronchial hygiene.

3. **Atopy as conductive of inflammation:** it leads to a worse course, allergen test and serum inmunoglobulin E are associated with reduced pulmonary function and worse bronchiectasis severity index (BSI) score.[16]
4. **Variants of heterozygous of the cystic fibrosis transmembrane regulator (CFTR):** contributes to the development of bronchiectasis through dysfunction of sodium and chloride channels.[17] There are one to two CFTR mutations.
5. **Vitamin D deficiency:** potential role in vicious cycle of the recurrences and more probability to have *Pseudomonas* colonization, worse respiratory symptoms and greater inflammation.[5]
6. **Common variable immunodeficiency (CVID):** it is associated with small airway damage (air entrapped) as incipient and potentially reversible damage.[5]
7. **Gastroesophageal reflux (GER):** there is great concern about this association.[18,19] Among patients with advanced pulmonary disease that were waiting lung transplant, patients with bronchiectasis had higher prevalence of GER (50%).[20] In a retrospective study of 81 patients with bronchiectasis in a center in Irland, 36% had a hiatal hernia and 62% had symptomatic GER. There was no predilection for any affectation of a particular lobe, the severity of the bronchiectasis was greater in subjects with hiatal hernia.[21]

RISK FACTORS

History of pneumonia (in childhood), alcoholism (bronchoaspiration, GER), pertussis, measles, tuberculosis (and granulomatosis), asthma, allergies, rheumatism, infertility, inhaled agents.[22-24] In *Table 1* shows the causes grouped by etiology and their diagnostic approach base on studies.[22-24]

IMPLICATIONS AND COMPLICATIONS

Decreased pulmonary function: patients with bronchiectasis have a mean annual decrease in forced expired volume in the first second (FEV_1) of 50-55 mL/year.[25] This is higher than in normal individuals (20-30 mL/year), but similar to patients with COPD (approximately 60 mL/year). Among patients with bronchiectasis, FEV_1 decrease accelerates when there is *Pseudomonas* colonization, frequent exacerbations, or increased inflammatory markers (e.g., C reactive protein).

Pulmonary vascular disease: an observational study evaluated 94 patients with bronchiectasis by echocardiography.[26] There was evidence of pulmonary hypertension (defined as an estimated systolic pulmonary arterial pressure > 40 mmHg) in 33% of patients and right ventricular systolic dysfunction in 13%. Right ventricular dysfunction was correlated with low FEV_1, low diffusing capacity for carbon monoxide (DLCO), hypercapnia and hypoxemia. Only 15% of patients had evidence of left ventricular dysfunction.

Hemoptysis: the origin of bleeding in bronchiectasis is due to the rupture of a tortuous bronchial artery or submucosal capillary plexus. It is a frequent and serious complication of the bronchiectasis. Hemoptoics are common in stable patients, while, the occurrence of increased amount of fresh blood or clots during an acute exacerbation is less common; bronchiectasis is a common cause of life-threatening bleeding. The most common causes of hemoptysis in bronchiectasis are mycobacteria and fungi. When bleeding is present, the time, amount and condition of the patient should be evaluated. The approach to bronchiectasis based on hemoptysis escapes the approach of these recommendations.

Cardiovascular morbidity: respiratory tract infections are associated with increased cardiovascular events (CV): myocardial infarction, stroke.[27] In a revision of patients with bronchiectasis from primary care practices in the United Kingdom, an increase in CV events was observed in the first 90 days after higher relative risk (RR) respiratory infection in the first three days.[28] In a separated study, bronchiectasis was an independent risk factor for the coronary artery disease and strokes after the adjustment for age, sex, smoking and other known CV risk factors.[29] Serum desmosine, is a marker of elastin degradation, it may be a marker of CV mortality.[30]

Classification of severity and prognosis

Few studies have examined the frequency of exacerbations, the hospitalization, comorbidities and mortality, as well as the rate of pulmonary decline function among patients with bronchiectasis; long-term outcome studies are limited.[8,25,31] Score systems have been propose to help guide prognosis assessment and identify patients who exacerbate frequently.[32,33] The bronchiectasis severity index (BSI) *(Table 2)*, was derived from 608 patients with bronchiectasis in a center in Scotland and was validated in 597 patients in other centers of the United Kingdom and Europe.[32] The predictors of hospitalization included prior hospitalization high index of dyspnea, low FEV_1, presence of *Pseudomonas* in the sputum and more extensive involvement (> 3 lobes) in high Resolution CT Scan. Mortality was correlated with advanced age, low FEV_1, prior hospitalization and three or more exacerbations in the last year. This score system presented a prognosis capacity for all the causes of mortality at four year of diagnosis, it also presented value for future hospitalization.[34]

FACED score *(Table 3)* is an easy scale to use composed by five variables and 10 points (**F**EV_1, **A**ge, presence or not of

Table 1: Diagnostic approach: characteristic causes and tests.[22-24]

Category	Specific examples/traits	Diagnostic test
Acquired bronchial obstruction (several produce localized bronchiectasis)		
Foreign body suction	Peanuts, bone, tooth, etc.	X-ray, CT scan; FBC
Tumors	Laryngeal papillomatosis; adenoma, endobronchial teratomas	X-ray, CT scan; FBC
Adenopathy	Tuberculosis; histoplasmosis; sarcoidosis	PPD; X-ray, CT scan; FBC
COPD	Chronic bronchitis	PFT, symptoms
Connectivopathies	Polychondritis, amyloidosis	Cartilage biopsy
Mucoid impaction	ABPA; bronchocentric granulomatosis; post-surgical	Total and specific IgE aspergillosis; skin reaction, X-ray, CT scan; bronchial biopsy
Congenital anatomical defects causing bronchial obstruction		
Tracheo-bronchial	Bronchomalacia; bronchial cyst; cartilaginous deficiency (Sx Williams-Campbell); tracheobroncomegaly (Sx Mounier-Kuhn); ectopic bronchus; tracheoesophageal fistula	X-ray, CT scan
Vascular	Intralobar sequestration, pulmonary arterial aneurysm	X-ray, CT scan
Lymphatics	yellow nail syndrome	History of dystrophy, slow-growing nails
Immunodeficiencies		
IgG	Congenital (Bruton type), agammaglobulinemia; selective deficiency (IgG2, IgG4); acquired Ig deficiency; variable common hypogammaglobulinemia; Nezelof Syndrome; «Naked lymphocyte syndrome»	Quantitative Ig and subclasses; damaged response to pneumococcal vaccine
IgA	Selective deficiency with or without ataxia-telangiectasia syndrome	Quantitative Ig
Leukocyte dysfunction	Chronic granulomatous disease (NADPH oxidase dysfunction)	Dihydrorhodamine 123; oxidation test; tetrazolium nitroblue test, genetic testing
Humoral immunodeficiencies (CXCR4 mutation, CD40 and ligand deficiency)	WHIM syndrome; hypergammaglobulinemia M	Neutrophil count; Ig levels
Abnormal clearance of secretions		
Mucociliary defects	Kartagener syndrome; ciliary dyskinesias	X-ray, CT scan (situs inversus); bronchial biopsy; ciliary motility; electron microscopy of sperm or respiratory mucosa
Cystic fibrosis	Typical early infantile LH; late presentation with sinopulmonary symptoms	Chlorine in sweat; genetic testing
Young syndrome	Obstructive azoospermia with sinopulmonary infections	Spermatocrit
Miscellaneous disorders		
Alpha-1 antitrypsina deficiency	Absence or synthesis/abnormal function	Alpha-1 antitrypsin levels
Recurrent bronchoaspiration pneumonia	Alcoholism; neurological disorders; lipoid pneumonia	Medical record; X-ray, CT scan
Connectivopathies	Sjogren syndrome and Rheumatoid Arthritis	Rheumatoid factor; antiSSA/antiSSB; salivary gland biopsy
Toxic inhalation of fumes and dusts	Ammonium; nitrogen dioxide, irritant gases; fumes; talc; silicates	Medical record; X-ray, CT scan

Contents

Table 1 continues: Diagnostic approach: characteristic causes and tests.[22-24]

Category	Specific examples/traits	Diagnostic test
Miscellaneous disorders		
Post-transplant rejection	Bone marrow, bronchiolitis obliterans (lung transplant)	PFT; X-ray, CT scan
Childhood infections	Pertussis; measles	Medical record
Bacterial Infections	Staphylococcus aureus, Klebsiella, Pseudomonas aeruginosa	Medical history; cultures
Viral Infections	Adenovirus (types 7 and 21), influenza, herpes simplex	Medical history, evidence of infection
Other infections	Histoplasmosis; Mycobacterium tuberculosis, non-tuberculous mycobacterium; mycoplasma	Cultures; stains

X-ray = simple chest X-ray. CT scan=computed tomography of the chest. FBC = fibrobronchoscopy. COPD = chronic obstructive pulmonary disease. ABPA = allergic broncho pulmonary aspergillosis. Ig = immunoglobulin. PFT = pulmonary function tests. Sx =syndrome. NADPH = nicotinamide adenine dinucleotide phosphate. Whim = warts, hypogammaglobulinemia, infections and myelocatexis. PPD = purified protein derivative. antiSSA =antibody Sjögren'ssyndrome A/Ro. antiSSB = antibody Sjögren's syndrome B/La.

Colonization/ chronic bronchial infection for *Pseudomonas*, radiological **E**xtension in the high resolution CT Scan mentioning the number of lobes affected and Dyspnoea measured by the modified Medical Research Council scale [mMRC] dichotomized in 0-II and III-IV, the higher score the more dyspnoea). It was developed in 397 subjects from a multi center cohort of 819 patients from Spain.[33] This scale presented an excellent predictive capacity for all causes of mortality five years after diagnosis and for respiratory causes.[34]

The BSI and FACED were evaluated retrospectively over 19 years with respect to mortality estimates in 91 patients followed at the Royal Brompton Hospital in London. Both scores gave equally mortality estimates at five years, with the FACED slightly higher at 15 years.[35] Regarding, other clinical results, in an additional analysis of 1,612 subjects of seven European cohorts, the BSI more accurately predicted exacerbations, hospitalizations, respiratory symptoms, and quality of life than the FACED score.[36]

Daily sputum production and the presence of *Pseudomonas* or other potential infectious pathogens in sputum culture were the main characteristics related to quality of life (QoL = *quality of life*), inflammatory markers and the clinical results at three years.[37]

Clinical criteria to guide management

1. Criteria for close or specialized monitoring:
   a. Congenital/genetic bronchiectasis (cystic fibrosis [CF], dyskinesias and immunodeficiencies).
   b. BSI score ≥ 9 points.
   c. Diffuse multilobe (multi-segmental) bronchiectasis with extensive involvement in pulmonary function tests ($FEV1_1$ < 50%p).
   d. Recurrent relapses ≥ 3 times/year.
   e. History of multiple hospitalizations.
   f. Chronic infection by *Pseudomonas*, *Staphylococcus aureus* or others.
   g. Candidate for eradication treatment (*Pseudomonas* or others).
   h. Candidate for resection for localized bronchiectasis.
2. Criteria for prophylactic outpatient antibiotic treatment:
   a. Unexacerbated patient (stable and without respiratory compromise) with positive isolation culture (chronic infection) or empirical.
3. Criteria for acute antibiotic treatment (exacerbation):
   a. Stable exacerbated patient without respiratory compromise for ambulatory management, or unstable, or with respiratory compromise for hospitalization, with positive cultures or empirical.
4. Criteria for eradication treatment *(Pseudomonas)*:
   a. New isolation of *Pseudomonas* in exacerbated or non-exacerbated patients.
5. Criteria for hospitalization:
   a. Unstable exacerbated patient or with respiratory compromise.
   b. Intravenous (IV) eradication treatment.

TREATMENT

The goals of bronchiectasis treatment are to prevent exacerbations, reduce symptoms, improve quality of life, and stop disease progression.

The underlying cause should be treated specifically, CFTR (cystic fibrosis transmembrane conductance regulator) modulators in CF; DNase in primary ciliary dyskinesia; antibiotics for non-tuberculous mycobacterial infections; macrolides in diffuse panbronchiolitis; intravenous or subcutaneous immunoglobulins in immunodeficiencies; inhibitors of acid secretion in gastroesophageal reflux (GER); oral and antifungal corticosteroids in allergic broncho pulmonary aspergillosis; smoking withdrawal; intravenous

alpha 1 antitrypsin in PIZZ phenotypes, management of associated diseases (COPD, asthma, inflammatory bowel disease, systemic diseases);and surgery or bronchial dilatation in bronchial obstruction.

An exacerbation of bronchiectasis is defined as a deterioration in three or more of the following symptoms: cough, sputum volume or consistency, sputum purulence, shortness of breath or exercise intolerance, fatigue or malaise, hemoptysis lasting at least 48 hours, accompanied by a change in the treatment of bronchiectasis, and exclusion of other possible causes of clinical deterioration.[38] It may be accompanied by changes in respiratory examination, deterioration of lung function, or increased markers of inflammation. The pathogens that are most often isolated in an exacerbation are: *P. aeruginosa, H. influenzae, S. pneumoniae, S. aureus, Moraxella catarrhalis* and enterobacteria.[39] Viruses are isolated in 25% of cases (coronavirus, rhinovirus, influenza, SARS-CoV-2).[25]

Table 2: Bronchiectasis Severity Index (BSI).[32,34]

	Score
Age (years)	
< 50	0
50-69	2
70-79	4
> 80	6
Body mass index	
< 18.5	2
18.5-25	0
26-29	0
≥ 30	0
FEV_1 (% of predicted value)	
> 80	0
50-80	1
30-49	2
< 30	3
Medical research council dyspnea scale	
1-3	0
4	2
5	3
Colonization by *Pseudomonas aeruginosa*	
No	0
Yes	3
Colonization by other organisms	
No	0
Yes	1
Radiological severity > 3 lobes or cystic bronchiectasis	
No	0
Yes	1
Hospitalization in the last year	
No	0
Yes	5
Exacerbations in the last year	
0	0
1-2	0
≥ 3	2

Score: mild 0-4 points, moderate 5-8 points, severe ≥ 9 points.

Table 3: FACED Score.[33,34]

Variable	Values	Scores
Exacerbations with hospital admission (previous year)	No	0
	At least 1	2
FEV_1 (% of predicted)	At least 50%	0
	Less than 50%	2
Age (years)	Under 70 years of age	0
	At least 70 years of age	2
Chronic bronchial infection (colonization) by *Pseudomonas aeruginosa*	No	0
	Yes	1
Radiological extension (number of lobes)	1-2	0
	More than 2	1
Dyspnoea (modified mMRC scale)	0-II	0
	III-IV	1

FACED = FEV_1 Age, Chronic colonization, Extension, Dyspnea. FEV_1 = expiratory volume in the first second. mMRC = modified Medical Research Council. Score: mild 0-2 points, moderate 3-4 points, severe 5-7 points.

Exacerbations

Antibiotic therapy is the cornerstone of treatment because it reduces the bacterial load and systemic and airway inflammatory mediators.[40] Ideally, it should initially be adapted to previous sputum cultures and sensitivities, where possible rather than chosen empirically. Other factors in antibiotic selection are the route of administration, oral or parenteral, the history of success or failure, and the presence of allergy or intolerance. Do not use nebulizad antibiotics as single agents in an acute exacerbation.[41]

Mild exacerbation: most afebrile and clinically stable patients (mild exacerbation) can be treated on an outpatient basis with an oral antibiotic guided by the most recent sputum culture results, and by the patient's experience with previous regimens. In the absence of culture, a respiratory fluoroquinolone (e.g., levofloxacin, moxifloxacin)is a reasonable and broad-spectrum option. In cultures without positive beta-lactamases (*H. influenzae* or *Pseudomonas*), the options are amoxicillin or macrolide. It can be modified based on response to therapy and culture results and sputum sensitivity. In beta-

lactamase positive culture (*M. catarrhalis* or *H. influenzae*) the options are amoxicillin-clavulanate, second or third generation cephalosporin, azithromycin or clarithromycin, doxycycline or a fluoroquinolone.[41] In positive culture of *P. aeruginosa*, the initial selection is ciprofloxacin. Given previous courses of antipseudomonal, resistance to quinolones often requires IV. Due to the propensity of *P. aeruginosa*, it is recommended to add nebulized tobramycin to ciprofloxacin.[42,43]

Clinical experience favors a duration of 10-14 days for patients with a first time or few exacerbations. The European Respiratory Society (ERS, 2017) guidelines suggest a 14-day cycle. When there is no response or relapses in a short time, repeat culture them *(Table 4)*.[44]

Severe exacerbation: when there is increased respiratory rate ≥ 25/minute, hypotension, temperature ≥ 38 °C, hypoxemia (pulse oxygen saturation < 92%) or lack of improvement after oral antibiotics (no intravenous therapy at home), hemoptysis, severe cardiopulmonary instability, or the presence of resistance to available oral agents, initial intravenous and hospital treatment is appropriate.[45]

Always obtain sputum culture before starting antibiotics. A significant number of severe exacerbations are by *Pseudomonas* and if they are resistant to oral quinolones, antipseudomonas penicillin can usually be used as ceftazidime; in case the patient looks seriously ill or has incipient *Pseudomonas* pneumonia a second agent (e.g. fluoroquinolone, aminoglycoside) can be added *(Table 5)*.[45]

Treatment of severe exacerbation should be 14-21 days; a short treatment of seven days will depend on exacerbation severity, patient conditions, and expectoration cultures.[41]

Antivirals are indicated when the etiology is due to influenza virus (oseltamivir or oral baloxavir). For SARS-CoV-2 should be individualized based on symptoms, risk factors and severity of disease.

Eradication of P. aeruginosa

When there is evidence of new isolation and clinical deterioration. Multiple treatments have been suggested. A practical way is as seen in *Figure 1*.

Table 4: Treatment of mild exacerbation.

Agent	Selection	Alternative	Duration (days)
Haemophilus influenzae	Amoxicillin/clavulanate 875/125 mg every 8 h	Amoxicillin 1-2 g every 8 h Ciprofloxacin 750 mg every 8 h Azithromycin 500 mg every 24 hours	10-21 Azithromycin 3-5
Staphylococcus aureus	Amoxicillin/clavulanate 875/125 mg every 8 h	Amoxicillin/clavulanate 875/125 mg every 8 h	10-21
MRS	Linezolid 600 mg every 12 h PO	Clindamycin 300-450 mg every 8 h	10-21
Pseudomonas	Ciprofloxacin 750 mg every 12 h PO	Levofloxacin 750 mg every 24 h PO	14-21

MRS = Methicillin-resistant *Staphylococcus aureus*. PO = PER OS (orally).

Table 5: Treatment of severe exacerbation.

Agent	Selection	Alternative	Duration (days)
Haemophilus influenzae	Ceftriaxone 2 g/24 h IV	Amoxicillin/clavulanate 500/125 mg 2 tab every 8 h PO	14-21
Staphylococcus aureus	Vancomycin 15-20 mg/kg/8 - 12 h IV	Vancomycin 15-20 mg/kg/8-12 h IV	14-21
MRS	Linezolid 600 mg/12 h IV	Vancomycin 15-20 mg/kg/8-12 h IV Ceftriaxone 600 mg every 12 h IV	14-21
Pseudomonas	Ceftazidime 2 g every 8 h IV + tobramycin 5-10 mg/kg every 24 h IV	Imipenem 1 g every 8 h or piperacillin/tazobactam 4-8 g every 24 h or cefepime 2 g every 8 h or meropenem 2 g every 8 h or ciprofloxacin 400 mg every 12 h + amikacin 15-20 mg/kg every 24 h or gentamicin 5-7 mg/kg every 24 h	14-21

MRS = Methicillin-resistant *Staphylococcus aureus*. PO = PER OS (orally). IV = intravenous.

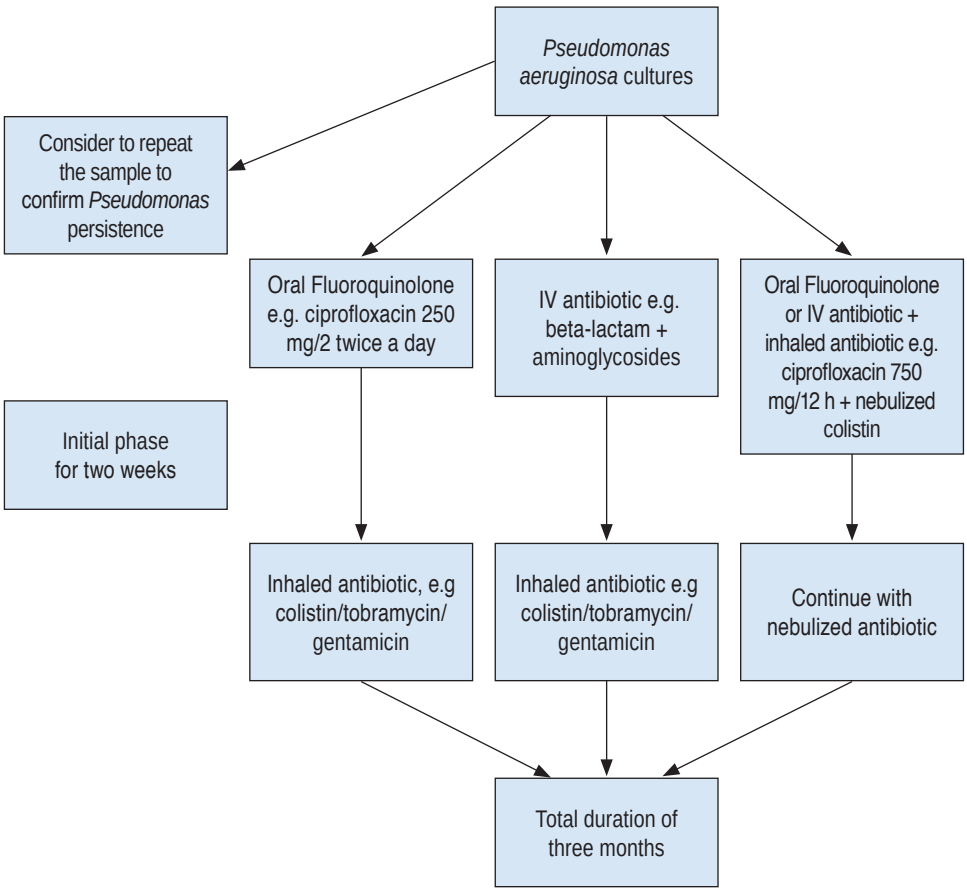

Figure 1:

Schematic eradication of *P. aeruginosa*.

After completing the eradication treatment, a monthly sputum culture must be performed for the first three months and then every two months for a year. It would be a failure of eradication if a positive culture returned during the first year. We will add a nebulized treatment if it had not been added initially, if it had been added we must repeat the same regimen of ciprofloxacin plus nebulized antibiotic, or change the nebulized treatment used in the first regimen. If at least two strategies with nebulized and oral antibiotics fail, the use of nebulized plus IV treatment is recommended. If at least three strategies fail, it should be considered a chronic infection.[46]

Treatment of chronic infection

It is defined as having two or more isolates of the same organism at least three months apart in a year.[11] The most commonly associated germs are *Haemophilus influenzae* and *P. aeruginosa*, less commonly *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*.[46,47]

Chronic infections, particularly *P. aeruginosa*, potentiate airway inflammation and are associated with increased frequency of exacerbations, hospitalizations, reduced quality of life, increased mortality, and increased health care costs.

For treatment, the nebulized route is recommended because it reduces exacerbations and decreased lung function, possibly by reducing bacterial load and airway inflammation. It has also been shown to provide consistent antibiotic deposition, high concentrations in ventilated areas of the lung with a lower risk of toxicity or systemic adverse effects versus other routes. A systematic review and meta-analysis of 16 studies, with a treatment duration between four weeks to 12 months demonstrated significant reduction in the number of exacerbations with nebulized treatment. It was well tolerated with low proportions of adverse effects (bronchospasm), which disapeared with drug discontinuation. There was an increase in antimicrobial resistance at the end of the study, but it appeared to decrease after discontinuation. Nebulized antibiotics did not improve quality of life.[48]

Spanish regulations *(Table 6)*[44] recommend maintaining the nebulized route for long periods of time according to risk/benefit and depending on the selection of the antibiotic with continuous or intermittent guidelines. If with the intermittent form there is clinical worsening, it may be considered to alternate with another nebulized antibiotic without rest periods

Table 6: Treatment of chronic infection.

Agent	Nebulized	Oral or intravenous
Pseudomonas	Tobramycin (solution for nebulization): 300 mg/5 mL twice daily 28 days of treatment followed by 28 days of rest in e-Flow®, Pari LC plus® Gentamicin (inhaled intravenous formulation): 80 mg twice daily continuous treatment	If despite nebulized treatment poor clinical control persists, associate an oral or intravenous antibiotic with activity according to antibiogram, on demand or in cycles
MRS	Vancomycin (intravenous formulation administered by nebulized route): 250 mg/2 times a day continuous treatment	If the response is insufficient or there is intolerance, add or replace vancomycin with IV linezolid
Other germs	Gentamicin: 80 mg/2 times daily or any of those used for pseudomone continuous treatment	If the response is insufficient or there is intolerance, consider adding (or replacing) the nebulized antibiotic with an oral one according to sensitivity

MRS = Methicillin-resistant *Staphylococcus aureus*.

between them. If poor control persists, oral or intravenous antibiotic therapy should be associated every 1-2 months.

Long-term treatment (prophylactic)

To those who have ≥ 3 exacerbations per year (frequent exacerbators), to prevent exacerbation. Macrolides (azithromycin, erythromycin) are suggested as the first line due to the high quality, evidence in decreasing exacerbations and acceptable side effect profile. In the case of *P. aeruginosa* infection add a long-term nebulized treatment.

British Thoracic Society (BTS) guidelines suggest for colonization by *P. aeruginosa*:[49]

1. Nebulized colistin.
2. Nebulized gentamicin as a second-line alternative to colistin.
3. Azithromycin/erythromycin as an alternative (intolerance to nebulized antibiotics).
4. Azithromycin/erythromycin as an add-on treatment to a nebulized antibiotic in chronic *P. aeruginosa* infection with frequent exacerbations.

No colonization by *P. aeruginosa*:[49]

1. Azithromycin/erythromycin.
2. Nebulized gentamicin as a second-line alternative to azithromycin/erythromycin.
3. Doxycycline as an alternative to macrolide intolerance/ineffectiveness.

Muco active and mucolytic treatment

In those who frequently have difficulty in expectorating, or abundant secretions where standard airway cleaning techniques have failed to control symptoms, hypertonic substances and mannitol can be used long-term (≥ 3 months).[49]

Nebulized hypertonic saline (6-7%) is related to improved mucus clearance, increased ciliary motility, and improved cough clearance. Low mucus salinity contributes to mucus retention. It may improve FEV_1 combined with chest physiotherapy and is not superior to 0.9% saline.[50,51]

Mannitol is a hyperosmolar agent that is believed to hydrate secretions, improving mucus clearance. There is insufficient evidence. In a therapeutic multicenter trial (the largest in bronchiectasis) 461 patients inhaled mannitol dry powder 400 mg or mannitol 50 mg (control) twice daily for 52 weeks, showed only modest significant improvements in time to first exacerbation, antibiotic days and quality of life according to St. George Respiratory Questionnaire (SGRQ). A post hoc analysis of 333 patients showed that the greater the burden of symptoms, the time to first exacerbation and fewer exacerbations against placebo were reduced.[52,53]

Aerosolized dornase alpha (recombinant deoxyribonuclease, also called DNase), which breaks down DNA (gelatinous product of neutrophils), improves FEV_1 and reduces hospitalizations in CF patients,[53] but is not effective in another etiology and is potentially harmful.[54]

Mucolytics, essentially N-acetylcysteine, for one year were associated with a reduction in exacerbations and sputum volume, and also improved quality of life.[55]

Other medical therapies

Bronchodilators: should be used in patients with asthma or COPD[49,56] or with significant dyspnea. Airflow obstruction should be assessed by pre- and post-bronchodilator spirometry. If there is reversibility inspirometry, a trial with short-acting beta agonist (SABA) is almost always initiated.[46] If symptoms improve, continue with SABA or prolonged

(LABA). If no airway obstruction is demonstrated, they are not indicated. Information is missing in this context.

Oral glucocorticoids (GC): their use is reserved. In other types of patients, it is suggested to avoid this treatment because they can depress the immunity of the host, promote bacterial and fungal colonization, which perpetuates the infection. Only in patients with asthma or allergic bronchopulmonary aspergillosis it may be used.

Inhaled glucocorticoids (ICGs): there is no evidence for their use when they do not coexist with asthma or COPD as a concomitant disease.[45,57] The ERS guidelines recommend it only in such a situation.[10] They show no significant effect on spirometry, exacerbation rate or sputum volume. Patients with serum eosinophils > 3% improved quality of life (SGRQ) at six months.[58] Although its use was associated with an increased likelihood of *P. aeruginosa*[59] infection and adrenal insufficiency in 48%.[60]

NSAIDs: there is not enough information to support their role.[61,62]

Statins: they have anti-inflammatory properties, but there is not enough information either.[63]

Non-pharmacological treatment

Avoid lung irritants: avoid lung irritants: exposure to respiratory irritants should be avoided as far as possible, e.g. smoking and vaping, cleaning agents, dusts, fumes, gases, etc.

Systemic hydration: maintaining hydration is important to help decrease thick secretions.

Pulmonary rehabilitation (PR): undoubtedly brings benefit.[64] Indicated for patients with diminished exercise capacity.[65] Aerobic exercise (cycloergometer, elliptical) is recommended in stable patients with dyspnea mMRC = 2-4.[45] To deepen into the subject, we suggest going to the pulmonary rehabilitation guidelines.

Airway clearance therapy: all patients should undergo physiotherapy regularly to remove airway secretions *(Table 4)*.[66]

Bronchial hygiene improves cough[67] by adequately expelling secretions and mucous plugs from the airway with manual techniques or devices *(Table 7)*.[68] The choice of a technique or device should be based on the amount and characteristics of the secretions, patient comfort, cost, and ability to use the device.[69] The drainage of secretions is contraindicated in unstable situations.

Oscillatory positive expiratory pressure (PEP) devices combine with high-frequency oscillations to release secretions and move them into the mouth. Schemes of 6-10 deep inhalation cycles, 2-3 second breath hold, exhalation through the device creating oscillations and coughing. Oscillatory PEP improves quality of life, but not the amount of sputum, dyspnea, or lung function.[70] Information about PEP during exacerbations or long-term use is missing.

Nutritional support. The protein-rich nutritional supplement enriched with hydroxy-beta-methylbutyrate (anti-catabolic and anti-inflammatory effect) showed a greater improvement in strength and physical functioning.[71]

Other medical therapies

Anti-GER: Suppression of gastric acid by use of H2 blocker or proton pump inhibitor is indicated in persistent

Table 7: Airway cleaning /bronchial hygiene.

Technique	Advantages	Comment/disadvantage
Directed cough	Cheap, simple	Chest pain may limit
Regular exercise	Economical, strengthens respiratory and peripheral muscles	
Autogenous breathing	Control your breathing	Requires patient cooperation
Forced expiration	Helps control breathing	Requires patient learning
Thoracic physiotherapy (CPT; postural drainage, mechanical or manual thoracic percussions)	Most tested in cystic fibrosis	Needs assistant, difficult to place, hypoxemia, sometimes worsens gastroesophageal reflux
Positive expiratory pressure (PEP)	Easy, cheap	Device needs cleaning
Oscillatory PEP (e.g., acapella device with flutter valve)	Easy, economical, adds vibration to the airways	Device needs cleaning
High frequency chest wall oscillation vest with inflatable bladder	Extensive experience	Pain may limit; needs power outlet
High frequency chest wall oscillation vest with mechanical oscillators	Doesn't hurt compared to inflatable bladder	May be mobile; small batteries in vest; closest to CPT

CPT = chest physical therapy.

and unexplained symptomatic patients or in those with ≥ 2 exacerbations/year. Anti-reflux measures must also be carried out.

Vaccines: review missing immunizations and promote the application of influenza vaccine (live attenuated viruses except in immunodeficiency). Pneumococcal polysaccharide vaccine or conjugate must be present.[72] Both vaccines significantly reduce the number of acute infectious exacerbations during the first year compared to the influenza vaccine alone.[73]

Lung surgery and transplantation

Surgery (lobectomy or segmentectomy) is indicated in case of localized bronchiectasis or severe hemoptysis that does not respond to conventional treatment. Lung transplantation is the only solution in patients with advanced disease, whose survival is estimated to be < 2 years, once all available treatments have been used without obtaining a response.

Follow-up: patients should be asked at each visit about dyspnea and exercise tolerance, color, consistency, and estimated amount of sputum, as this information is useful in determining if a patient has an exacerbation.

Exacerbations, emergency department visits or hospitalizations, or if they were given antibiotics, including dose and frequency, should be recorded. Must have supervision in pulmonary rehabilitation programs.

CONCLUSIONS

1. Bronchiectasis is a chronic syndrome characterized by irreversible distortion of bronchi and bronchioles, characterized by productive cough and exacerbations, with risk factors and multiple etiology.
2. It is quite common with considerable mortality.
3. It has a complex pathophysiology with many mechanisms.
4. It shares many similarities with COPD because it affects pulmonary function, quality of life, and survival.
5. Exacerbations are usually caused by acute bacterial infections.
6. Always culturing bronchial secretions.
7. Its severity is evaluated through validated questionnaires with predictive value.
8. We recommend clinical criteria to facilitate the way to follow for management.
9. The mainstay of treatment is to treat exacerbations mainly of infectious origin, since they are the cause of pulmonary deterioration, greater symptoms, worse quality of life and increased mortality.
10. Antibiotherapy is the basis for the treatment of exacerbations supplemented with physiotherapy and pulmonary rehabilitation.
11. The most frequent cause of severe exacerbations is *P. aeruginosa*.
12. It is important to culture secretions.
13. In recurrent exacerbations (≥ 2/year) without *P. aeruginosa* or nebulization intolerance, preventive macrolide therapy. Exclude non-tuberculous mycobacteria.
14. In recurrent exacerbations or significant morbidity and *P. aeruginosa* or intolerance/contraindication/ineffectiveness of the oral route inhaled tobramycin is suggested. Requires bronchodilator premedication.
15. More information on benefits of hypertonic solution, mannitol, N-acetylcysteine and DNase is missing. Inhaled glucocorticoids and systemic glucocorticoids only in concomitant asthma or COPD.
16. Other medical therapies in selected patients are inhaled bronchodilators, anti-reflux therapy, and immunization.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022

Ideas and perspectives

doi: 10.35366/112953

Institutional robotic assisted thoracic surgery program: mandatory necessity

Programa institucional de cirugía torácica robótica: una necesidad obligada

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Thoracic surgery is a thriving area in the surgical field in our country; it has become a specialty that has progressively acquired its own personality, with a well-established professional pathway and well-defined competencies for the optimal surgical care of non-cardiac thoracic pathology. As it has happened with all other medical specialties, the development of technology and scientific advances in the understanding and treatment of diseases, has forced the increasingly less invasive surgical treatment of thoracic pathology; this undoubtedly has to go hand in hand with specific training in minimally invasive approaches, in which the same principles and results as conventional surgery are preserved, always seeking to improve them.

Video-assisted thoracic surgery (VATS) is the gold standard in a wide variety of procedures, which favors a faster postoperative recovery, thus reducing hospital costs related to time in the operating room, amount of drugs used, days of hospital stay and lower rate of infectious complications. Worldwide, the emergence of robotic platforms for performing surgeries in various fields has raised a wide variety of questions about the cost-benefit of using this sophisticated equipment. In the field of thoracic surgery, robotic-assisted thoracic surgery (formerly abbreviated as RATS) has been reported since the early 2000's, and the first report of robotic-assisted lung lobectomy as a treatment for lung cancer was published in 2002.[1] In that regard, definitions for robotic thoracic procedures have changed, as the Clinical Guidelines Committee of the American Association for Thoracic Surgeons (AATS) created a working group with the purpose of unifying a system of nomenclature and definitions to standardize robotic-assisted thoracic procedures.[2] A four-letter system was proposed, where the letter R refers to a robotic approach, P when only ports are used, or A if assisted (through a utility or working port); the next part, is the abbreviation of the procedures performed and the final element is the number of robotic arms. Under this system, for example, a robotic lobectomy can be described as RPL (3 or 4) or as RAL (3 or 4).

In Mexico, there are reports of the first robotic thoracic surgeries since 2017 and, although in some specialties its use has become popular, thorax remains a pending task, which depends on multiple factors, not only on training and certification in its use for thoracic surgeons. The final decision to acquire a robotic system is not made by the end users (patients), but by institutions or hospitals that, for the sake of competitiveness and prestige, seek to attract surgeons and patients «seduced» by the benefits of sophisticated, state-of-the-art technology. High equipment acquisition and maintenance costs, limited availability of supplies and still long operating times are important factors that have limited its use; recent studies have shown that a rational and multidisciplinary use of equipment together with optimal postoperative management can improve the cost-benefit relation.[3] It should be mentioned that the benefits in the use of robotic systems cannot be fully achieved until sufficient efficiency in their use is achieved, which according to initial reports could reach between 150 and 250 procedures to feel comfortable in their use,[4] a very high and prohibitive figure for most; Melfi et al. and Gharagozloo recommend at least 20 cases of robotic

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Received: III-28-2023; accepted: VI-20-2023.

How to cite: Hernández-Ramírez I, Espinoza-Mercado F, Corona-Perezgrovas MÁ, Rivera-Navarrete E. Institutional robotic assisted thoracic surgery program: mandatory necessity. Neumol Cir Torax. 2022; 81 (4):246-248. https://dx.doi.org/10.35366/112953

thoracic surgery to acquire sufficient skills, while Jang et al. report that the learning curve for a robotic lobectomy is less than that required for a VATS lobectomy.[5]

Although to date there are still no clear differences between VATS and RATS, some benefits have been recognized with the use of robotic systems. These benefits include: clearer, three-dimensional visualization of anatomical structures, finer and more controlled movements within small spaces, wider range of motion with robotic instruments, as well as better ergonomics for the surgeon while working at the console.[6] Several meta-analyses have been conducted to try to determine the benefit of one approach over the other; to date, most conclude that although robotic-assisted thoracic surgery is a safe and feasible technique that can achieve the same results as VATS, more studies with a larger number of patients are needed to be able to draw definitive conclusions.[7]

The only way to determine the validity of this type of robotic approach is to demonstrate similar results in terms of effectiveness and patient safety when compared to thoracoscopy or open surgery. To achieve the above, it is essential to have an adequate volume of patients to allow us to perform the number of procedures required (which may vary from surgeon to surgeon) and to achieve efficiency in their use.

Taking into account the above, the sooner a thoracic surgeon or resident is involved in robotic surgery, the sooner they will reach an acceptable level of competence in practice, which optimizes the results and reduces the incidence of complications.[8] In this line, it is important to consider that the number of robotic systems available for teaching in the country is very limited; and even more so, the number of thoracic surgeons certified for their use. It also influences the fact that most of this equipment is still concentrated in private hospitals with limited access for surgeons in training.

At the Central Military Hospital, robotic surgery program was initiated in 2014, to date a total of 2,339 robot-assisted surgeries have been performed, making it the hospital center that has performed the most procedures of this type in the country *(Figure 1)*. Of the total number of surgeries, 41 correspond to thoracic robotic procedures *(Figure 2)*, of which 20 have been performed in the last year, representing almost 50% of the robot-assisted thoracic surgeries performed. Since the Central Military Hospital is a teaching hospital where the human resources demanded by the army in health care are trained, doctors and surgical residents in training are involved in robotic surgery from early stages, forming a first-hand concept of the advantages, disadvantages and areas of opportunity for the future.

It is also necessary to understand that the success of a robotic surgery program does not only depend on the surgeon; the training of all the personnel involved in the surgical procedure must be considered: anesthesia, nursing, technicians, providers, etc. *(Figure 3)* and, of course: the institution, which is responsible for the acquisition, maintenance and operation of the equipment. As mentioned above, it is necessary to achieve efficiency in the handling of the robot, which will only be achieved with repeated and constant use.

As surgeons, a large part of our skills should be focused on the aspect of manual dexterity, which will be better the more repetitions of a given procedure are performed. One of the initial disadvantages that have been mentioned in robotic procedures is the absence of the tactile sense, not being in direct contact with the patient and losing the sensation of consistency and texture of the tissues, essential

Figure 1: Plaque commemorating the 2,000 robotic procedures performed at the Central Military Hospital.

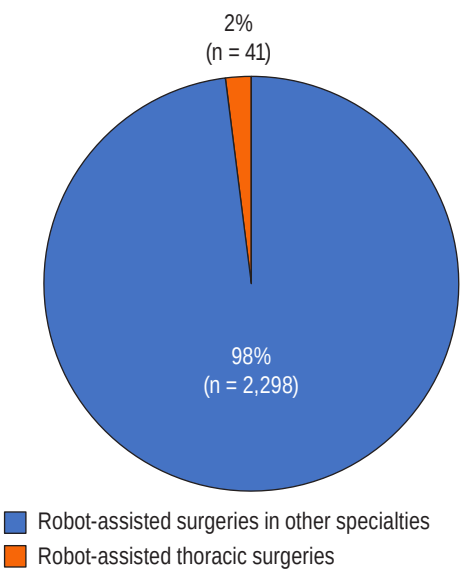

Figure 2: Proportion of robot-assisted thoracic surgeries performed at the Central Military Hospital.
Source: operating room archive.

Figure 3: Panoramic view of an operating room with robotic platform and the equipment involved in its operation.
Source: author's personal file.

for most of us and which, with practice, should be replaced by a better visualization and localization of the anatomical structures. The more time we use the robotic platform, the more we will become familiar with its use, its capabilities, we will compensate for its disadvantages, we will reduce surgical times, we will reduce costs for a greater number of procedures and, as a consequence, we will favor a better evolution and a faster recovery of the patients.

Our work at a personal level will be to be prepared for the changes, with an open and receptive mind to adopt them in the best way, to change the existing paradigms; exactly the same thing that happened with the introduction of laparoscopic surgery at the end of the 80's; it will be the work of the institution to support and provide the necessary means to offer the best possible treatment, only with this collaboration it will it be possible to materialize a successful program of robotic surgery. The passage of time will be responsible for showing the results; for the time being, we must prepare ourselves and do what we must.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022

Clinical case
doi: 10.35366/112954

Symmetrical bilateral effusion and spondylodiscitis: a case report

Empiema bilateral simétrico y espondilodiscitis: informe de caso

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ABSTRACT. Introduction: empyema is defined as a purulent collection in the pleural cavity, its bilateral and symmetrical manifestation is rare, which implies a currently non-existing standardized assessment criterion. Its broad differential diagnoses should consider infectious as well as neoplastic disorders. **Clinical case:** a 60-year-old male with a previous history of tobacco use, alcohol abuse and exposure to biomass fuels. Current complaint of a 2-month history of sharp pain located on right hemithorax, fever, weakness, loss of appetite, weight loss of 10 kg, night sweats and unproductive cough; upon physical examination perceived with cachectic appearance, diminished strength of lower limbs and altered gait. Magnetic resonance imaging showed two T1 hypointense and T2 hyperintense oval lesions extending to the vertebral body of T11, along with manifestations of spondylodiscitis resulting in medullary contact. Analysis of pleural fluid reports a foul-smelling, purulent aspect, increased polymorphonuclear cell count, lactic dehydrogenase 20,376 U/L; culture negative, negative neoplastic histological and cytological typing as well as Ziehl-Neelsen staining negative. **Conclusions:** this case is therefore approached due to respiratory symptoms consistent with a bilateral manifestation empyema associated to a vertebral lesion, an infrequent association, aided by imaging resources to reach a final diagnosis of bone tuberculosis.

Keywords: symmetrical bilateral effusion, spondylodiscitis, extrapulmonary tuberculosis.

RESUMEN. Introducción: el empiema es la acumulación purulenta del espacio pleural, la presentación bilateral y simétrica es rara, no existen algoritmos de abordaje estandarizado. El diagnóstico diferencial es amplio e implica la sospecha de patologías infecciosas o neoplásicas. **Caso clínico:** hombre de 60 años de edad con antecedente de tabaquismo, alcoholismo y exposición a biomasa. Padecimiento de dos meses de evolución con dolor punzante en hemitórax derecho, fiebre, astenia, hiporexia, pérdida ponderal de 10 kg, diaforesis nocturna, tos seca y debilidad de miembros pélvicos, se observó caquéctico y con dificultad para la marcha. La resonancia magnética reportó dos imágenes ovales de interior hipointenso en T1, hiperintenso T2 y comunicación con cuerpo vertebral T11, el cual presenta cambios por espondilodiscitis que condiciona contacto medular. Reporte de líquido pleural de aspecto purulento y fétido, celularidad aumentada por polimorfonucleares, deshidrogenasa láctica 20,376 U/L; fueron negativos el cultivo, estudio histopatológico para células neoplásicas y tinción de Ziehl-Neelsen. **Conclusiones:** se aborda caso por síntomas respiratorios asociado a alteración osteoarticular, relación infrecuente; y con ayuda de información radiológica y epidemiológica se concluye el diagnóstico de tuberculosis ósea.

Palabras clave: empiema bilateral simétrico, espondilodiscitis, tuberculosis extrapulmonar.

INTRODUCTION

Empyema is defined as the presence of purulent fluid in the pleural cavity, which is mostly associated with infections of the pulmonary parenchyma, where pneumonia is the most frequent; other etiological factors are trauma, esophageal rupture, after thoracic surgery or infections of the cervical and thoracic spine.[1]

The presentation of bilateral empyema is rare and there are no guidelines that establish the systematic approach or management. The evaluation of these patients is challenging because the differential diagnosis is broad and includes both benign and malignant, and even life-threatening conditions.[2] Empyema is associated with an increased risk of mortality and therefore requires timely, multidisciplinary intervention.

The following clinical case of symmetrical bilateral empyema associated with spondylodiscitis is presented, in which symptomatology, radiological findings and epidemiological aspects (demography, socioeconomic status, malnutrition) are correlated to reach the final

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Received: VIII-19-2022; accepted: V-17-2023.

How to cite: Tovar-Becerra AI, García-Hernández JA, Sosa-Hernández O. Symmetrical bilateral effusion and spondylodiscitis: a case report. Neumol Cir Torax. 2022; 81 (4):249-252. https://dx.doi.org/10.35366/112954

diagnosis in a timely manner in order to reduce morbimortality.

CASE PRESENTATION

Male, 60 years old, work history in the chemical materials and mining industry, systemic arterial hypertension for eight years of diagnosis, alcoholism for 30 years, smoking for 13 years, smoking rate 6.5, exposure to biomass for 11 years for three hours a day.

Two months of evolution with stabbing pain VAS 9/10 in the right costal region, self-medication with non-steroidal anti-inflammatory drugs (NSAID) without improvement; adding fever, asthenia, adynamia, hyporexia, oral thrush, involuntary weight loss (10 kg), nocturnal diaphoresis, dysphagia and dry cough. One week prior to her admission, she presented weakness in the pelvic limbs with difficulty in standing and inability to ambulate without alteration of sensibility.

On physical examination, the patient was found cachectic, malnourished, body mass index (BMI) 18, chest stethoacoustic, heart sounds without alterations, pulmonary area integrated in posterior region, bilateral basal pleural effusion syndrome in 50%, pelvic limbs hypotrophic, preserved sensitivity, but decreased mobility and strength, Daniels scale 2/5 left and 3/5 in right, respectively, with inability to ambulation, myotatic ++/+++, without data of pyramidal release, the rest of the physical examination without alterations.

Blood cytometry documented leukocytosis 20,700 thousands/UL at the expense of polymorphonuclear (PMN) 16,170 cells, lactate dehydrogenase 122 U/L, albumin 2.4 g/dL, C-reactive protein 28.9 mg/dL. Thoracentesis was performed which revealed fetid purulent fluid *(Figure 1)* documenting cellularity 324,000 mm^3, polymorphonuclear 81%, mononuclear 19%, erythrocytes 23,500 million/UL, crenated 45%, non-crenated 55%, pH 5, glucose 45 mg/dL, lactate dehydrogenase 20,376 U/L, total protein 2. 90 g/dL, albumin 0.05 g/dL, cholesterol 387.50 mg/dL, total bilirubin 0.180 mg/dL.

Magnetic resonance imaging (MRI) was performed, which documented, in pleural space, oval images of hypointense interior in T1, hyperintense T2 and SPAIR with wall thickening up to 11 mm, presented communication with destroyed vertebral body in T12, which presented changes due to spondylodiscitis that conditioned spinal cord contact and increase in its amplitude without change in intensity *(Figure 2)*.

Histopathological report of pleural fluid: yellowish-greenish and fetid fluid is described; in the microscopic description, on a protein background and with necrosis, inflammatory cells, lymphocytes in moderate quantity and abundant neutrophils are observed. Negative for neoplasia, intense acute and chronic inflammation. Pleural fluid culture negative. Gram stain showed no bacterial forms and negative Ziehl-Neelsen stain. As part of the empyema management, bilateral endopleural probe placement was performed without complications, being the evolution of the patient unfavorable and torpid, so the case was discussed with neurosurgery for vertebral lesion approach. However, due to the patient's condition, he did not receive a surgical procedure and was evaluated in conjunction with the Epidemiology Service, which, given the clinical manifestations and the negative biochemical reports for bacterial and neoplastic development, in addition to the MRI findings, considered the possibility of tuberculous etiology and decided to initiate antituberculosis treatment, presenting improvement in his condition and a decrease in acute phase reactants.

The neurosurgical approach to take a biopsy of the vertebral lesion was left pending until the patient's clinical condition allowed it.

DISCUSSION

The incidence of empyema is variable, with 32,000 cases reported per year in the United States (US); however, there are reports of increasing frequency.[3] It has been reported that up to 40% of patients with community-acquired pneumonia will develop pleural effusion; and of these, up to 7% will develop complicated parapneumonic effusion or empyema. The bacterial cause is the most

Figure 1: Purulent pleural fluid.

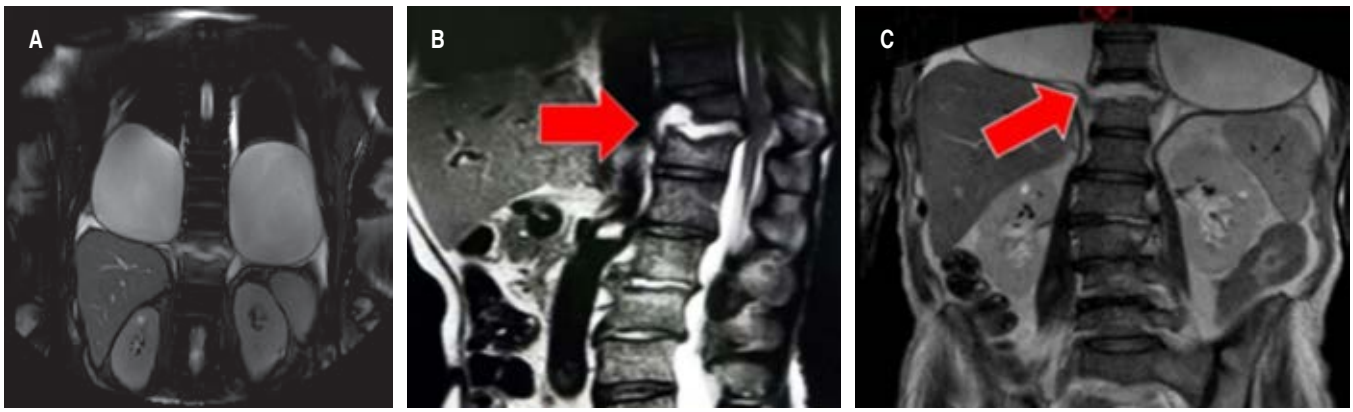

Figure 2: A) Coronal STIR weighted image, coronal, showing two oval images, hyperintense, regular and discreetly thickened wall, bilateral, symmetrical, associated with lytic lesion, with edematous changes characterized by high signal in endplates involving intervertebral disc and vertebral body of T11. **B)** Sagittal T2-weighted image with extension of disc lesion and vertebral erosion, conditioning spinal cord contact and focal thickening. **C)** Fistulous path of collection is shown at the level of the intervertebral disc with right basal empyema.

frequent; Falguera et al. described that, of the 261 patients with empyema, 64% were gram-positive cocci, 6% gram-negative, 10% anaerobic and 4% atypical microorganisms.[4]

Independent risk factors for the development of empyema include diabetes, immunosuppression, gastroesophageal reflux disease, aspiration and poor oral hygiene, alcohol and intravenous drug abuse.[4]

Our case reports a rare association of bilateral empyema and spondylodiscitis. Pleural fluid analysis confirmed exudative features; although pleural fluid cultures did not report development, cytology did not document neoplastic cells and even the search for BAAR was negative. Due to unfavorable clinical conditions the patient was not a candidate for bone biopsy.

In 2021, San Luis potosí, Mexico, ranked seventh nationally in prevalence of extrapulmonary tuberculosis (EPTB), reporting 82 cases.[5] The diagnosis of EPTB is complicated and should be suspected on an epidemiological basis in countries with high prevalence and/or lack of response to conventional treatment.

The simultaneous presentation of vertebral tuberculosis (VTB) with pleural involvement is infrequent, occurring in about 2.5% of patients.[6] Some authors have reported that 10% of extrapulmonary forms correspond to osteoarticular tuberculosis, of which up to half have VTB.[6] In the USA and Europe it represents 10-15% and 2-4.7%, respectively, of all cases of tuberculosis.[7] The lower thoracic and lumbar vertebrae are the most common sites of involvement.[8] The mechanism of infection is considered to be a primary focus at the vertebral level with direct dissemination by contiguity to the pleura. This suggests an atypical natural history of the disease.[6]

The diagnosis of VTB is complex due to the low specificity of clinical and paraclinical data, so it must be based on clinical and epidemiological correlation and radiological findings, with magnetic resonance imaging being the study of choice.[9] The delay in the diagnosis of vertebral involvement leads to neurological complications between 30-80% due to spinal cord involvement, which increases morbidity and mortality.

Considering the aforementioned, the possibility of tuberculous etiology was considered, based on the endemic behavior of this mycobacterium in our country and the adequate response and improvement of the symptomatology with decrease of the systemic inflammatory response to the antituberculosis treatment.

Our case highlights an unusual presentation of bilateral empyema associated with spondylodiscitis, where the imaging findings in a patient with risk factors living in an endemic area for tuberculosis were determinant to consider the diagnosis and initiate a specific treatment.

CONCLUSIONS

Tuberculosis should be considered as a rule-out diagnosis in cases of empyema in patients with or without risk factors and living in endemic areas, especially if associated with vertebral lesions. Management and diagnosis should be multidisciplinary, and this is the justification for initiating antituberculosis treatment. The support of imaging studies allows timely diagnosis and treatment to avoid complications and improve the quality of life of patients.

Acknowledgments

To Dr. Cuellar for his valuable participation in the interpretation of cabinet studies. To Dr. Helena Rodríguez for her contributions.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022

Clinical case
doi: 10.35366/112955

Swyer James MacLeod syndrome. Case report of hyperlucid lung

Síndrome de Swyer James MacLeod. Reporte de caso de pulmón hiperlúcido

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ABSTRACT. Introduction: respiratory infections in childhood can eventually lead to rare diseases such as Swyer James MacLeod syndrome, which, although it does not have a defined etiology, has been associated with these respiratory antecedents. Reports a prevalence of 0.01% of 17,450 chest X-ray. **Clinical case:** we report the case of a young woman who consults for chest pain without irradiation and that imaging studies show greater radiolucency of the left lung, in addition to this, respiratory function tests point to a restrictive process; leading to the diagnosis of this rare syndrome. **Conclusions:** Swyer James MacLeod syndrome is a clinic-radiological entity that is usually asymptomatic and its diagnosis can be considered an incidental finding.

Keywords: James MacLeod Swyer syndrome, hyperlucid lung, case report.

RESUMEN. Introducción: las infecciones respiratorias en la infancia pueden eventualmente desarrollar enfermedades poco frecuentes como el síndrome de Swyer James MacLeod; si bien, no tiene una etiología definida, se ha asociado a estos antecedentes respiratorios. Reporta una prevalencia de 0.01% en 17,450 radiografías de tórax. **Caso clínico:** se reporta el caso de una joven mujer que consulta por dolor torácico sin irradiación y que los estudios de imagen demuestran mayor radiolucencia del pulmón izquierdo. Aunado a ello, las pruebas funcionales respiratorias orientan a un proceso restrictivo, lo que lleva al diagnóstico de este raro síndrome. **Conclusiones:** el síndrome de Swyer James MacLeod es una entidad clínico-radiológica que se presenta habitualmente asintomática y su diagnóstico puede considerarse como un hallazgo incidental.

Palabras clave: síndrome de Swyer James MacLeod, pulmón hiperlúcido, caso clínico.

INTRODUCTION

Swyer James MacLeod syndrome was described simultaneously in 1950 by three professionals, highlighting the interrelation of the different disciplines of medicine, pulmonology and radiology. The three physicians, one of English origin and two Canadians, coincided in the findings of the syndrome that today bears their names. It is related to bronchitis and bronchiolitis obliterans, acquired during childhood from a bacterial or viral infection, and its diagnosis is usually incidental in the course of a radiological evaluation in which unilateral hyperlucency of the lung is revealed.

CLINICAL CASE

A 31-year-old female patient consulted a national hospital with a history of mild retrosternal pain, insidious, not radiating and relieved by sleeping. Due to poorly defined findings in the X-ray, chest tomography was requested and she was transferred to our center. She reported a history of respiratory diseases in childhood and adolescence, such as pneumonia, bronchitis, common colds treated as outpatients, and during the pandemic she suffered from uncomplicated COVID-19.

Admitted in good general and nutritional condition, SO_2 99%, heart rate (HR) 74 beats per minute (bpm), without

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Received: XI-19-2022; accepted: VI-05-2023.

How to cite: Torres-Rodríguez ST, Reyes-Zúñiga KM, Chang-Castillo IE, Herrera-Cruz D. Swyer James MacLeod syndrome. Case report of hyperlucid lung. Neumol Cir Torax. 2022; 81 (4):253-255. https://dx.doi.org/10.35366/112955

dyspnea or cyanosis. Lungs with adequate air entry and rhythmic heart without murmurs. Labs: hemoglobin 13 mg/mL; hematocrit 39%; platelets 224 × 10^9/L; D-dimer 273.59; alpha 1 antitrypsin 98.8 (82.50-320). Pulmonary function tests: spirometry; FEV1 3.09 (52%) 1.55; FVC 3.64 (59%) 2.13; FEF 25-75% 85.39 (88%) 72.89, suggestive of restriction. Body plethysmography/flow-volume uninterpretable. SB diffusion, DLCO 8.18 (80%) mild decrease. Lenin walk, walks 225 m, being 35% of his predicted, without pauses during the test. NADIR: SO_2 88% with no need for supplemental oxygen.

Chest X-ray showed left lung overdistended, displacing the mediastinum to the right and hyperlucent; computed axial tomography (CT) showed, in addition, anomalous distribution of the pulmonary vasculature with areas of hypoperfusion of variable distribution *(Figure 1)*.

Ruling out probable pulmonary thromboembolism (PTE), CT angiography was requested, which showed no evidence of PTE in the digital reconstructions, showing continuity of opacification of first and second order pulmonary arteries. Lung with left hyperclarity and hypoplasia of the ipsilateral pulmonary artery measuring 9 mm in diameter A-P compared to 20 mm on the right. Consider Swyer James MacLeod syndrome *(Figure 2)*. Echocardiogram, reports dextrocardia with EF at 55%. Low probability of PAH with pulmonary systolic pressure at 20 mmHg. Abdominal CT reports no abnormalities.

DISCUSSION

Swyer James MacLeod syndrome is a rare clinical-radiological entity that reports a prevalence of 0.01% in 17,450 chest radiographs.[1,2] We present the case of a young woman with a history of repeated respiratory disorders in childhood, which probably led her to develop structural changes in her lung. Due to the characteristics shown, this syndrome has no defined etiology, but it is related to viral infections such as influenza A virus, respiratory syncytial virus, mumps, paramyxovirus, adenovirus type 3, 7 and 21; as well as a bacterial origin, in which Bordetella pertussis, Mycobacterium tuberculosis and Mycoplasma pneumoniae are involved.[1] It is a rare emphysematous disease characterized by obliteration of the small bronchioles, hypoplasia or absence of pulmonary artery and peripheral vascular bed.[3] The functional abnormality of this syndrome is undoubtedly diffuse chronic expiratory obstruction with distal air trapping.[4] The most distinctive feature compared to emphysema is the absence of chronic obstructive pathology in the small airway,[3] which coincides with the FEF 25-75% 85.39 (88%) 72.89 data obtained from the patient.

A mild chest pain prompted consultation and radiography showed a hyperlucent left lung. It is most commonly diagnosed in infancy, typically occurring in children under eight years of age, before the lung has completed lung development and maturation.[5] It may run asymptomatically into adulthood, present with usually asymptomatic spontaneous pneumothorax,[2] or as a rare emergency condition,[3] as calcified bullae[6] and with placental transfiguration of the lung parenchyma.[7] The patient's chest X-ray and CT scan showed hyperlucent segmental lung with altered vascularity, which is usually described by other authors as unilateral or lobar pulmonary hyperclarity, associated with air trapping of the hyperlucent lung during expiration.[2,5,8] In order to rule out the differential diagnosis of pulmonary thromboembolism, angiotomography was requested, which showed anatomical abnormalities of the left pulmonary artery with a smaller caliber and decreased flow. The spirometric pattern showed restrictive process. Pulmonary scintigraphy was not performed that could show decreased ventilation of the pathologic lung secondary to emphysematous changes and a marked decrease in perfusion, as a consequence of the reduced caliber of the

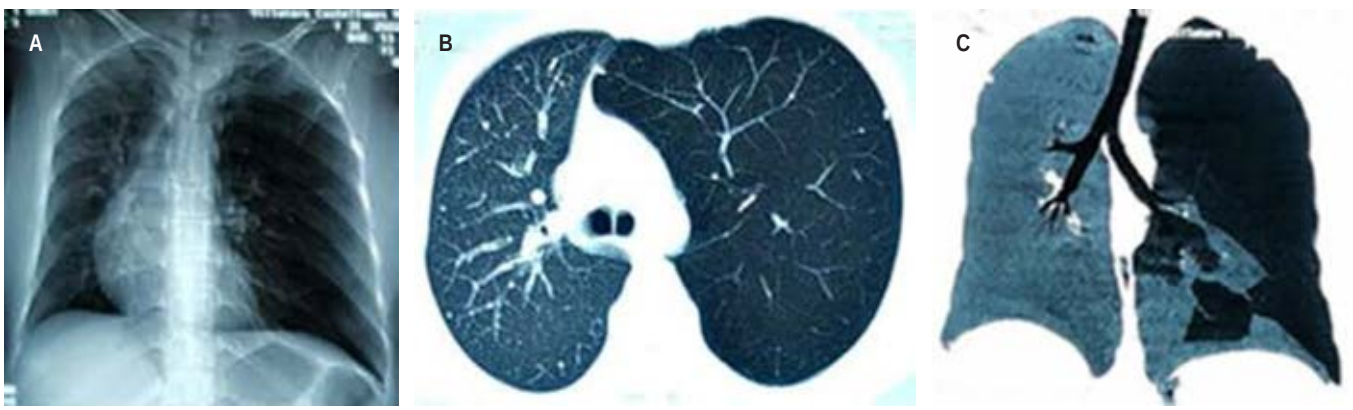

Figure 1: A) Chest X-ray. Left lung. Hyperlucent distended and mediastinal shift. **B)** Computed axial tomography. Axial section. Hyperlucent left lung, over distended. **C)** Digital reconstruction shows hypoperfusion.

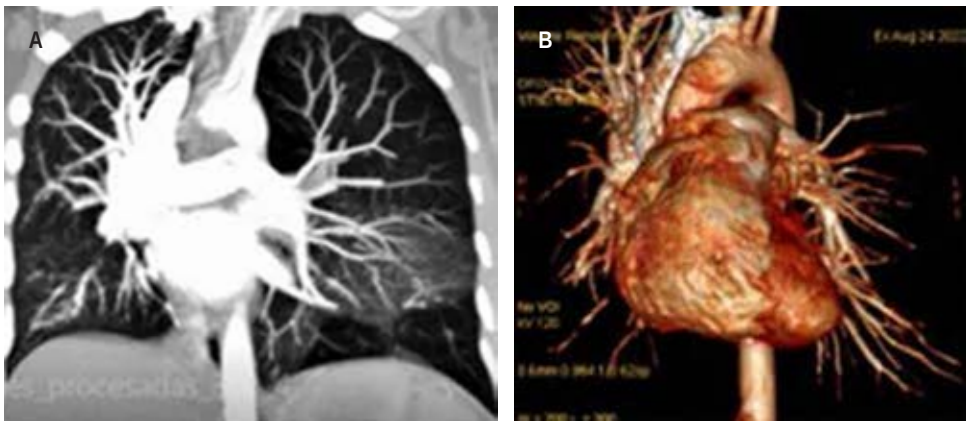

Figure 2:

A) CT angiography. Coronal section, non-uniform vascular distribution. **B)** Coronal section. Digital reconstruction. Superior lobar artery hypoplasia. Redistribution of flow.

pulmonary artery.[5,8] Therefore, diagnostic criteria for this syndrome require one of the following findings: a) unilateral loss of lung volume with hyperlucency demonstrated by chest radiography; b) unilateral reduction of vascularity on chest CT scan; and c) unilateral loss of perfusion on technetium-99m lung scan.[1,2]

Treatment is established according to symptoms and may vary from conservative management to surgical indications. Surgery is reserved for patients with recurrent lung infections that do not respond to conservative treatment or whose symptoms are not adequately controlled with optimal medical treatment. Surgical options include pneumonectomy, volume reduction surgery, lobectomy, or anatomic or non-anatomic segmentectomies,[1] performed by thoracotomy, videothoracoscopy or robotics according to preference, experience and availability of resources. Due to their clinically stable evolution, conservative treatment with outpatient follow-up was chosen.

CONCLUSIONS

Swyer James MacLeod syndrome is a rare entity that usually presents asymptomatic; its diagnosis is usually an incidental finding and treatment is conservative in most patients, with definite surgical indications.

Acknowledgments

To Dr. Sergio Villeda Castañeda, master in general surgery, and Dr. Elka Lainfiesta Moncada, anesthesiologist, for their contribution to the review of this clinical case.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022

Clinical case
doi: 10.35366/112956

Schwannoma, a differential diagnosis in posterior mediastinal tumors

Schwannoma, un diagnóstico diferencial en los tumores de mediastino posterior

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ABSTRACT. Tumors of the posterior mediastinum are predominantly neurogenic tumors. Neurogenic tumors arise from tissues whose origin is the embryonic neural crest, and are classified according to whether they grow from the nerve sheath, nerve cells or are paraganglionic. Among the group of benign nerve sheath tumors, schwannomas and neurofibromas are the most common. Schwannoma is the most frequent intrathoracic neurogenic tumor. The cornerstone of treatment of neurogenic tumors, whether benign or malignant, is complete surgical resection, and is important for diagnostic confirmation and to prevent malignant degeneration.

Keywords: posterior mediastinum, tumor, schwannoma.

RESUMEN. Los tumores del mediastino posterior son predominantemente tumores neurogénicos. Los tumores neurogénicos surgen de tejidos cuyo origen es la cresta neural embrionaria y se clasifican de acuerdo a si crecen a partir de la vaina nerviosa, de las células nerviosas o si son paraganglionares. Entre el grupo de tumores benignos de vaina nerviosa, los schwannomas y los neurofibromas son los más comunes. El schwannoma es el tumor neurogénico intratorácico más frecuente. La piedra angular del tratamiento de los tumores neurogénicos, ya sean benignos o malignos, es la resección quirúrgica completa, y es importante para la confirmación diagnóstica y descartar degeneración maligna.

Palabras clave: mediastino posterior, tumor, schwannoma.

INTRODUCTION

Mediastinal tumors represent a wide variety of diagnostic possibilities. Tumors of the posterior mediastinum are predominantly neurogenic tumors (53.9%), followed by benign cysts (13.9%) and lymphomas (5%). The incidence of mediastinal neurogenic tumors is 4.1%; they can occur in either compartment; however, 71-95% occur in the posterior mediastinum.[1] They typically arise from spinal nerve roots. Most of these tumors occur in adults.[2] Malignancy is unusual and they are usually located in the paravertebral sulcus.[2]

They occur most frequently between the third and sixth decade of life; most are diagnosed incidentally.[3] Between 30-40% are asymptomatic at the time of diagnosis. With growth, symptoms occur due to local compression of adjacent tissues and mainly include chest pain, cough, dyspnea, hoarseness, stridor, superior vena cava syndrome and muscle weakness.[4]

Neurogenic tumors arise from tissues whose origin is the embryonic neural crest; they are classified according to whether they grow from the nerve sheath, from nerve cells, or are paraganglionic.[3] Among the group of benign nerve sheath tumors, schwannomas and neurofibromas are the most common, accounting for 90%.[4] These are benign, slow-growing lesions that most often arise from spinal nerve roots, but can involve any thoracic nerve.

In imaging studies, peripheral sheath tumors are well-defined, hypodense tumors with low attenuation and contrast enhancement on computed tomography (CT). On magnetic resonance imaging (MRI) they are isointense on T1 and hyperintense on T2.[1] MRI is the most sensitive method to define the presence and extent of the intraspinal component of the tumor. It is indicated when the tumor is contiguous to the neural foramen, when there is a widened intervertebral foramen, or when there is erosion of a vertebral body or pedicle.[5]

Schwannoma is the most common intrathoracic neurogenic tumor, accounting for approximately 75% of nerve sheath tumors. It can arise from any neural element

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Received: III-11-2023; Accepted: VI-13-2023.

How to cite: Palomares-Capetillo P, Armas-Zárate FJ, Iñiguez-García MA. Schwannoma, a differential diagnosis in posterior mediastinal tumors. Neumol Cir Torax. 2022; 81 (4):256-259. https://dx.doi.org/10.35366/112956

within the thorax. They are usually friable and encapsulated. Recurrence and metastases are rare.[5-8]

Histologically they are composed of Schwann cells, as well as a well-formed capsule. Verocay bodies are another histologic feature, but are neither sensitive nor specific. They are composed of two areas: Antoni A and Antoni B. By immunohistochemistry, they are positive for S100 protein, SOX10, CD57 and GFAP. The cellular variant may have a higher risk of recurrence, but does not show metastatic potential.[1,2] *Table 1* shows the main differences in the diagnosis of schwannoma and neurofibroma.

The cornerstone of treatment of neurogenic tumors is complete surgical resection, and it is important for diagnostic confirmation and to rule out malignant degeneration.[3]

The surgical approach should be decided according to tumor size, location, and intraspinal/neuroforaminal extension or involvement.[5] The video-assisted thoracic surgical (VATS) approach is preferred for tumors that show no preoperative signs of malignancy and do not involve the spinal cord.[9] As most of these tumors originate from the sympathetic chain, Horner's syndrome is the most feared complication after surgery.[3] In more complex cases with an intraspinal component, a combined neurosurgical and thoracic approach incorporating laminectomy followed by thoracotomy or thoracoscopy is usually required to complete the resection.[5]

Table 1: Histopathologic differences between the main posterior mediastinal tumors.

	Neurofibroma	Schwannoma
Cytology		
Size of the nucleus	+	++
Nuclear hyperchromasia	+	++
Wavy nuclei	+++	+
Histology		
«Shredded carrot»-type collagen	+++	-/+
Capsule	-	+++
Hyalinized vessels	-/+	+++
Fascicular growth pattern	-/+	++
Mitotic activity	-/+	-/+
Necrosis	-	-/+
Immunohistochemistry		
S100	++/+++	+++
Collagen IV	++/+++	+++
EMA	+	-
CD34	+++	+++
Podoplanin	+	++
Calretinin	+	+++
Sox 10	+++	+++

EMA = epithelial membrane antigen.

PRESENTATION OF THE CASE

Female, 67 years old. Important antecedents: allergy to penicillin. Smoking denied. Her condition began after infection by SARS-CoV-2, where a simple chest CT scan was performed with incidental finding of posterior mediastinal tumor *(Figure 1A)*. The study was completed with magnetic resonance imaging *(Figure 1B)* and the patient was sent to the Thoracic Surgery Service of the *Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas*, Mexico City. Preoperative examinations and tumor markers were normal. A two-port VATS approach was decided for tumor resection *(Figure 2A)*, with findings of a nerve sheath-dependent tumor at the level of the second intercostal space, whitish, vascularized, 5 × 4 cm in diameter *(Figure 2B)*, which was resected in its entirety without complications. Postoperative evolution was satisfactory, removing the drain on the third day, with adequate lung expansion. Pathology report of a peripheral nerve sheath tumor compatible with schwannoma, with immunohistochemistry positive for PS100 and enolase. Six-month follow-up with no evidence of tumor recurrence.

DISCUSSION

We present a clinical case of a patient with a definitive diagnosis of schwannoma. In our case it was a posterior mediastinal tumor that was an incidental finding in an asymptomatic patient, as in most cases reported in the literature.

In these cases the main differential diagnosis is between schwannoma and neurofibroma, the former being the most frequent in the literature. For the definitive diagnosis, immunohistochemical support is essential to confirm their neurogenic origin and to distinguish between them. In this case, the anatomopathological study showed a neoplasm of mesenchymal origin, encapsulated, with a biphasic growth pattern (Antoni A and Antoni B), mostly myxoid; with nuclear palisade around a fibrillary process (Verocay bodies). Immunohistochemistry was positive for PS100 and enolase, suggesting a diagnosis of schwannoma. In our case, the patient did not meet the criteria for neurofibromatosis, so it was considered a sporadic tumor.[10]

A minimally invasive approach with two ports was decided based on the size and location of the tumor. This allowed a complete resection and adequate recovery of the

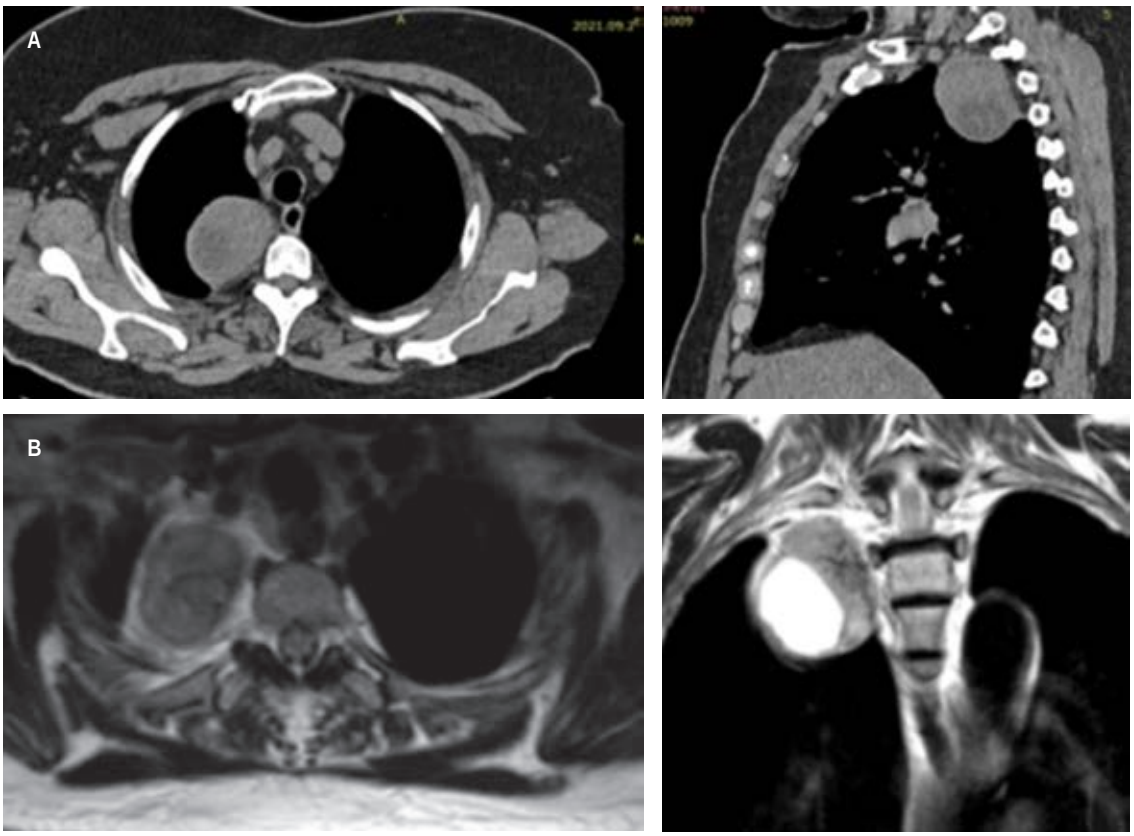

Figure 1: A) Simple computed tomography in axial and sagittal slices showing the tumor in the posterior mediastinum, heterogeneous and with defined borders. **B)** Axial and coronal T2-weighted magnetic resonance images showing the tumor in close communication with the paravertebral sulcus.

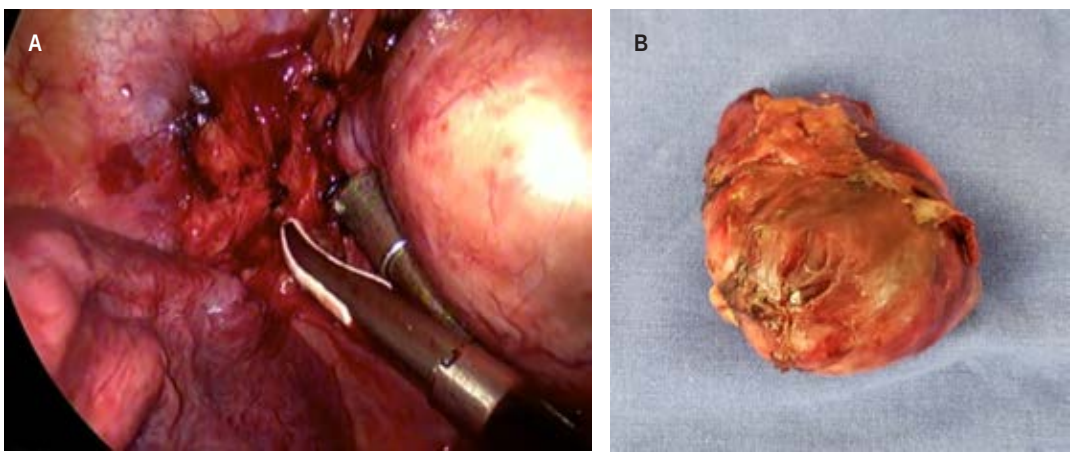

Figure 2: A) Transoperative image showing the tumor pedicle dependent on the peripheral nerve sheath. **B)** Postoperative image of the 5 × 4 cm tumor.

patient. Minimally invasive approaches are recommended in the literature depending on the size of the tumor and when there is no suspicion of spinal cord involvement. This allows a shorter hospital stay, less postoperative pain and the same oncologic results.[9] However, multiple types of approaches have been described, depending on the characteristics of the tumor and spinal cord involvement.[5,9]

Complete resection is the cornerstone of treatment. This allows a high cure rate at five years and low recurrence. Long-term follow-up is not well determined, as these

are slow-growing tumors, a period of five to ten years is commonly stipulated.

CONCLUSIONS

Schwannoma is a differential diagnosis among posterior mediastinal tumors. The studies of choice for diagnosis are computed tomography and magnetic resonance imaging that provide details of the level of tumor involvement. Diagnosis is based on pathology and immunohistochemical features. Treatment is complete surgical resection, ideally by minimally invasive approach, which allows adequate survival and low recurrence.

Acknowledgments

To the Department of Pathology of the National Institute of Respiratory Diseases.

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022

Clinical case
doi: 10.35366/112957

Tracheal lipoma: an unusual case

Lipoma traqueal: un caso poco habitual

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ABSTRACT. Tracheal lipoma is a rare, benign tumor with a very low incidence, whose symptoms are non-specific and variable according to the degree of airway obstruction, causing unnecessary morbidity and mortality if not adequately treated. We describe a case of tracheal lipoma with obstructive airway symptoms in a 70-year-old patient, with symptoms of six months' evolution, productive cough and progressive dyspnea which limited his daily activity. He presented with stridor, without data of respiratory distress, bilateral rales; complementary studies were carried out to rule out tracheal stenosis due to clinical symptoms. The tomography showed an adherent encapsulated lesion in the anterolateral tracheal wall with significant airway obstruction of 95%. The treatment of choice was endoscopic resection using laser or cryotherapy. Interventional treatment via bronchoscopy should only be applied to narrow-based benign tracheal tumors that protrude into the tracheal lumen. In our case, the decision was made to resect using this technique. Follow-up at one month without recurrence, adequate airway patency, and resolution of symptoms prior to the procedure.

Keywords: lipoma, tumor, endotracheal, bronchoscopy, case report.

RESUMEN. El lipoma traqueal es un tumor benigno, raro, con una incidencia muy baja, cuya sintomatología es inespecífica y variable de acuerdo con el grado de obstrucción de la vía aérea, causando una morbimortalidad innecesaria si no se trata adecuadamente. Describimos un caso de lipoma traqueal con cuadro obstructivo de la vía aérea en un paciente de 70 años, con síntomas de seis meses de evolución, tos productiva y disnea progresiva, la cual limitaba su actividad diaria. Se presentó con estridor, sin datos de dificultad respiratoria, estertores bilaterales; se le realizaron estudios complementarios a descartar estenosis traqueal por cuadro clínico. En la tomografía se evidenció lesión encapsulada adherida en pared anterolateral de traqueal con obstrucción importante de la vía aérea de 95%. El tratamiento de elección fue la resección por vía endoscópica mediante láser o crioterapia. El tratamiento intervencionista a través de la broncoscopia sólo debe aplicarse a tumores traqueales benignos de base estrecha que sobresalen en la luz traqueal. En nuestro caso se tomó la decisión de resecarlo mediante esta técnica. Seguimiento a un mes sin recidiva, adecuada permeabilidad de la vía aérea y resolución de síntomas previos al procedimiento.

Palabras clave: lipoma, tumor, endotraqueal, broncoscopia, reporte de caso.

INTRODUCTION

Tracheal primary tumors are rare. In adults, most of them are malignant; only 10-20% of tracheal tumors are benign, including chondromas, papillomas, fibromas, hemangiomas, lipomas.[1-4] Tracheal lipoma is an extremely rare benign neoplasm whose incidence ranges from 0.1 to 0.5%; the symptomatology and signs are nonspecific, such as dry cough, wheezing and sometimes shortness of breath. Due to the slow-growing characteristic, patients with benign tracheal tumors develop symptoms of airway obstruction gradually. They are almost always misdiagnosed as asthma, chronic obstructive pulmonary disease or bronchitis. Definitive diagnosis of these tumors is often delayed.[1-3] They require resection and can be approached endoscopically as well as by open surgery. We present a patient with obstructive symptoms due to the presence of an endotracheal tumor, treated with rigid bronchoscopy and resection.

PRESENTATION OF THE CASE

A 70-year-old man, with clinical picture of six months of evolution, characterized by dyspnea of medium efforts, progressing to small efforts and productive cough, with hyaline expectoration, not cyanosing or dyspneic. During the physical examination, vital signs: blood pressure (BP) 113/101 mmHg, HR 79 bpm, RR 22 rpm, temperature 36.2 °C, oxygen saturation 91% room air, initial arterial blood gasses pH 7.45, PCO_2 36.7 mmHg, PO_2 65 mmHg,

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Received: XII-16-2022; Accepted: VII-14-2023.

How to cite: Midence-Arguello MJ, Morales-Gómez J, Solares-Espinoza AG, Vázquez-Minero JC. Tracheal lipoma: an unusual case. Neumol Cir Torax. 2022; 81 (4):260-262. https://dx.doi.org/10.35366/112957

with stridor, no evidence of respiratory distress, bilateral rales were auscultated in the lung fields. Oxygen was administered through nasal prongs at two liters with oxygen saturation at 94%. Chest X-ray was performed without parenchymal alterations, with an image of tracheal stenosis *(Figure 1A)*. A simple chest CT scan was requested, showing an irregular encapsulated lesion adhered to the anterolateral wall of the middle third of the trachea *(Figures 1B and 1C)*. Fibrobronchoscopy was performed *(Figure 2A)*, and a 3 × 2 cm whitish tumor was identified at the level of the sixth tracheal ring obstructing 95% of its pedunculated tracheal lumen in the anterior wall. Resection was performed by rigid bronchoscopy and total resection of the tumor *(Figure 2B)*. Histopathological examination reported tracheal lipoma *(Figures 2C and 2D)*. The patient presented good evolution with no data of respiratory compromise. He was discharged due to improvement, with tomographic follow-up one month after the procedure without evidence of recurrence, with adequate patency of the tracheal lumen.

DISCUSSION

Most primary tracheal tumors in adults are malignant and benign tumors are rare. Primary benign tumors of the trachea include mainly leiomyoma, papilloma, fibroma, hemangioma, chondroma, and mixed salivary gland tumors; whereas lipoma is very rare.[1-4]

Airway lipomas affect the main bronchi and less frequently the trachea, as in our case. They usually originate in the submucosal fat of the tracheobronchial tree, are usually pedunculated, may extend between cartilage rings into peritracheal tissues, and recur after resection.[1]

Benign tracheal tumors tend to grow slowly and are asymptomatic in the early stages. They are difficult to diagnose during this period; moreover, they are misdiagnosed after respiratory symptoms such as bronchial asthma or pulmonary infections appear. Symptoms of airway obstruction appear when the degree of tracheal blockage increases from 50 to 75% or when the luminal diameter is less than 8 mm. In our case, the patient presented dyspnea.[1-3,5] He had a clinical history of six months of evolution with respiratory symptoms and dyspnea on exertion. The clinical picture is compatible with lesions or tumors occupying the tracheal lumen as in this case.

In patients with gradually worsening dyspnea it is suggested to consider the possibility of a tracheal tumor, it is necessary to perform a timely examination; including thoracic computed tomography (CT) and bronchoscopy can provide an accurate diagnosis. In fact, the sign of this disease is mainly inspiratory dyspnea, and it is evidently different from expiratory dyspnea caused by bronchial asthma and pulmonary infectious diseases. A careful physical examination may be helpful in the differential diagnosis.

Commonly, it is difficult to find a lesion on a conventional chest radiography because the trachea is covered by the mediastinum, almost always seen as normal, as in this case *(Figure 1)*.[1-3] Studies such as CT and flexible bronchoscopy are valuable for diagnosis, which were performed in our case.[1-3]

CT of the neck and chest showed a soft tissue tumor endotracheally and in the anterior wall of the tracheal wall. Resection was adequately performed without complications, especially since pathologic biopsy reported a benign tracheal lipoma. Endoscopic treatment by loop resection or cryotherapy is recommended as the first approach.

Interventional treatment through bronchoscopy should only be applied to benign tracheal tumors with a narrow base, originating from submucosal, nodular or polypoid

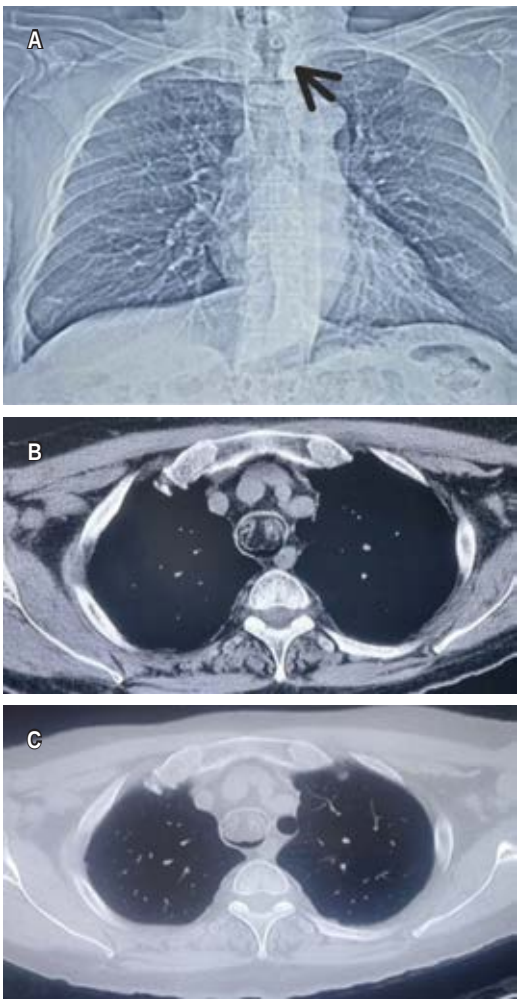

Figure 1: A) Chest X-ray, showing tracheal stenosis (arrow). **B)** Mediastinal window, showing a 2 × 3 cm mass arising from the anterior wall of the middle portion of the trachea located six rings above the carina. **C)** Pulmonary window.

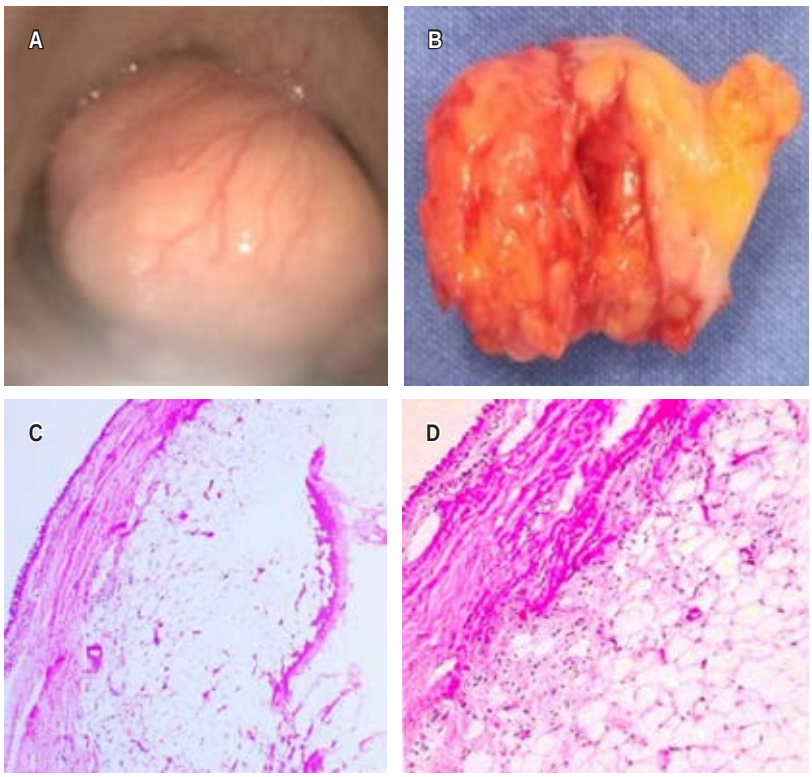

Figure 2:

A) Bronchoscopy, showing a mobile pedunculated lesion, with smooth surface, implanted in the anterior wall of the trachea. **B)** Lipoma of classic histology of 30 mm of major axis. **C)** Panoramic view of submucosal tumor with adipose differentiation. **D)** Benign neoplasm composed of mature adipocytes.

tissues protruding into the tracheal lumen, where the base is connected to the tracheal wall by a pedicle of irregular length, where the tissue surface and irrigation is smaller and, therefore, the risk of bleeding decreases. In our case, the decision was made to resect it by this technique.

Tracheal resection with reconstruction should be considered when the histopathological study provides evidence of malignant margins or the radiological image shows tumor extension through the tracheal wall and endoscopic treatment fails.[1-3,5]

CONCLUSIONS

Most tumors of the tracheobronchial tree are malignant. Benign tumors are rare and lipoma is extremely rare as in our case. Tracheal lipoma is histologically benign and may cause airway obstruction. Primary tracheal tumors should be suspected in patients with recurrent dyspnea symptoms and respiratory symptomatology. Cervical and thoracic CT scans should be considered; flexible bronchoscopy should be timely, as it can provide an accurate diagnosis.

Interventional treatments through fibrobronchoscopy are mainly suitable for benign tracheal tumors with narrow margins. However, if bronchoscopic treatment is not possible, surgical resection should be considered to decrease the mortality risk of this pathology.[1-3,5]

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Conflict of interests: the authors declare that they have no conflict of interests.

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022
Abstracts of free works
doi: 10.35366/112958

Abstracts of free works of the I International Congress of Sleeping Medicine

Resúmenes de trabajos libres del I Congreso Internacional de Medicina del Dormir

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How to cite: Santana-Miranda R, Hurtado-Alvarado G, Barrera-Medina A, Reséndiz-García MC, Jiménez-Correa U, et al. Abstracts of free works of the I International Congress of Sleeping Medicine. Neumol Cir Torax. 2022; 81 (4):263-268. https://dx.doi.org/10.35366/112958

Effect of sleep recovery on memory in fruit flies *Drosophila melanogaster* subjected to sleep deprivation+

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+Winning abstract in the basic/translational research category.

Introduction: sleep is considered a vital and complex phenomenon. There is research that studies the role that sleep plays in learning and memory processes. Studies in the fruit fly, *Drosophila melanogaster*, have shown how lack of sleep affects the acquisition and consolidation of information. However, as far as memory is concerned, it is currently under investigation. **Objective:** to analyze the effect of sleep recovery on memory in *Drosophila melanogaster* by means of a learning task. **Material and methods:** 100 flies of the *Drosophila melanogaster* species of the wild type strain were used; they were divided into two groups: control group (50), and experimental group (50), both groups were submitted to the same learning protocol. Flies were trained individually for six consecutive days, and consisted of food localization using green and red visual cues. At the end of the training days, the experimental group was subjected to sleep deprivation for six hours by mechanical stimulation with the aid of a rotating arm in the second half of the night. On the night of the seventh and eighth days, the gnats slept freely, and on the ninth day they again performed the behavioral test in order to record hits and misses. **Results:** the flies subjected to sleep deprivation initially made significant errors in performing the learned task. However, after the sleep recovery period, a decrease in the error rate was observed, as well as an increase in the hit rate, suggesting a recovery of memory processes. However, the values do not return to the values previously recorded before sleep deprivation, but there is a difference compared to the first day of learning. **Conclusion:** sleep is actively involved in the processes of information consolidation and retrieval in *Drosophila melanogaster*.

Sleep disturbance and symptoms of chronic fatigue in patients with a history of severe COVID-19 infection++

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++Winning abstract in the category social-economic impact research.

Introduction: a wide range of symptoms have been reported in individuals with a history of COVID-19 infection such as insomnia, OSAHS daytime sleepiness and chronic fatigue. **Objective:** to describe and compare sleep disturbances and chronic fatigue in patients with a history of hospitalization for severe COVID-19. **Material and methods:** design: comparative, impact, cross-sectional and prolective study. Population: adults of both sexes with a history of hospitalization for COVID-19. Subjects: 50. Variables: age, sex, days of hospital stay, endotracheal intubation, insomnia, daytime sleepiness, OSAHS, chronic fatigue. **Results:** the age of the patients was 52.8 ± 15.7 years, 56% women. The frequency of insomnia, daytime sleepiness and OSAS was 92, 28 and 35%, respectively. The mean score on the chronic fatigue scale of 22.8 ± 4.7 points. Age > 54 years was associated with greater severity of insomnia ($p = 0.05$) and endotracheal intubation with greater suspicion of OSAS ($p = 0.02$). Prolonged hospital stay contributed to a higher score in the assessment of chronic fatigue and insomnia severity ($p < 0.001$). **Conclusions:** a higher frequency of sleep disturbances was reported compared to patients without a history of severe COVID-19 infection. Age, prolonged hospital stay and endotracheal intubation played an important role in the presentation of sleep disturbances and chronic fatigue.

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Perinatal factors associated with infantile central apnea-hypopnea syndrome+++

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+++Winning abstract in the clinical research category.

Introduction: infantile central apnea-hypopnea syndrome (CAHS) considers infants ≥ 37 weeks of gestation; the reported frequency is 0.5 to 5.4%; its presence is a risk factor for neurodevelopmental alterations. There are several biological and environmental risk factors associated with the presence of central component respiratory events. **Objective:** to describe perinatal factors associated with the presence of infant central component apnea in infants referred by the *Hospital General de México* to the *Clínica de Trastornos del Sueño*-UNAM (CTS-UNAM). **Material and methods:** observational, cross-sectional, descriptive, retrospective study registered at the Ethics Committee of the General Hospital of Mexico: a sample of 41 CTS-UNAM files with informed consent was analyzed. Variables: childhood central apnea and perinatal factors. Inclusion criteria: patients from one to 23 months of age (term newborns), with a diagnosis of infantile central apnea by nap type polysomnography, with an average age at registration of six months in a follow-up and early intervention program for SAHCI. Descriptive statistics were performed, with mean and standard deviation for quantitative variables; percentages and frequencies for categorical variables. **Results:** 46.3% female; mean age of six months, with abnormal neurological examination in 34.1% of the cases and intrapartum complications and gastroesophageal reflux disease in 36.6% each. The degree of severity of SAHCI was recorded as severe (53.7%), moderate (31.7%) and mild (14.6%). **Conclusions:** the perinatal risk factors most frequently associated with SAHCI were: intrapartum complications, gastroesophageal reflux and abnormal neurological examination. SAHCI is diagnosed late and with considerable intensity in 85% of cases. Prospective studies of neurodevelopmental follow-up and polysomnography in the infant population at low and high risk of developmental abnormalities are required.

Evaluation of the relationship between peripheral temperature and electroencephalographic activity during sleep

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Introduction: peripheral temperature (Tp) presents a circadian rhythm that is synchronized with the wake-sleep cycle. The circadian phase of greatest heat loss coincides with the presence of sleep; moreover, Tp presents differences between NREM and REM sleep. As the spectral power density (SPD) of the electroencephalogram (EEG) in NREM and REM sleep varies circadian, a direct contribution of temperature to this variation has been proposed. **Objective:** to evaluate the relationship between Tp and EEG PED during NREM and REM sleep. **Material and methods:** 15 healthy volunteers (eight women) aged 24.7 ± 4.3 years participated. Two PSG recordings were performed on consecutive nights. The first was an adaptation recording. Tp was recorded using iButton DS192H thermosensors placed on the anterior of the right and left wrists. Tp was obtained from the average of the temperatures of both wrists. With the fast Fourier transform, the PED of the delta, theta, alpha and beta bands of EEG leads C4 and C3 were calculated. The relationship between Tp and DPE was analyzed by Spearman correlations in NREM (N2 and N3 phases) and REM sleep. **Results:** only in the theta-C4 band of NREM sleep was there a significant negative correlation (rho = -0.6) between Tp and DPE. **Conclusions:** in REM sleep there was no relationship between Tp and DPE and in NREM sleep there was a moderate relationship only in one band. Thus, Tp would be independent of EEG DPE, which is consistent with previous studies showing that temperature is not a determining factor in the circadian variation of EEG DPE.

Chronic rapid eye movement sleep deprivation and restriction of rapid eye movement sleep reduces memory and learning in Wistar rats

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Introduction: the sleep-wake cycle is a fundamental physiological process for humans and various animal species, as it regulates metabolic, immunological and cognitive processes, among others. Some studies have shown that sleep is involved in the consolidation and retrieval of certain types of memory. However, the differential effect of selective REM sleep deprivation (PSMOR), chronic REM sleep restriction (RSMOR) and the recovery period on declarative memory is still largely unknown. **Objective:** to evaluate the effect of PSMOR and RSMOR on learning and episodic memory, as well as during the recovery period of PSMOR through the novel object recognition test (NOR test). **Material and methods:** 20 male Wistar rats were used and randomly placed in the following groups (n = 6) 1. control, 2. PSMOR × 72 hours, 3. PSMOR × 72 hours + eight days of recovery, 4. RSMOR × 11 days. PSMOR and RSMOR were performed using the multi-platform technique. After the sleep deprivation, restriction and recovery periods, the animals were evaluated with the behavioral NOR test. **Results:** sleep deficit produced a decrease in NOR test performance. The PSMOR × 72-hour condition caused the greatest alterations affecting performance on the NOR task, and the animals' eight-day sleep recovery was insufficient to adequately restore the adverse effects of the sleep loss generated by PSMOR. **Conclusions:** we suggest that differential sleep loss has an impact on correct learning and produces deficits in declarative memory.

Contents

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Symptoms of insomnia, sleepiness and sleep quality in Mexico City merchants

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Introduction: sleep disorders represent a worldwide public health problem that affects the functioning of people who suffer from them and increases the risk of developing physical and mental health problems as well as the risk of suffering occupational accidents. Street vendors are a vulnerable population in Mexico because they do not have health systems that allow adequate follow-up. **Objectives:** to determine the frequency of insomnia symptoms, sleepiness and sleep quality in street vendors in Mexico City. **Material and methods:** a cross-sectional descriptive study was carried out that included 310 merchants in the northern area of Mexico City. Participants answered the insomnia severity index (ISI), Pittsburgh sleep quality index (IPSQ) and Epworth sleepiness scale. **Results:** the participants were 224 (72.3%) women and 86 (27.7%) men in an age range of 16 to 77 years (34.4 ± 11.75). It was observed that, according to the ISI, 27.7% presented absence of insomnia, while 42.3% presented subclinical insomnia, 28.4% moderate clinical insomnia and only 1.6% severe clinical insomnia; while in the ESE, 77.1% presented normal somnolence, 9.4% marginal somnolence and 13.5% excessive somnolence; finally, the IPSQ showed that 55.5% presented good sleep quality, which contrasted with 44.5% who presented poor sleep quality. **Conclusions:** most of the traders did not present scores that would allow determining that there is a sleep disorder; however, the data shows a high predisposition to develop them due to the poor quality of sleep and the level of insomnia obtained in the tests.

Association of fear of COVID-19 and sleep quality in adults

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Introduction: COVID-19 emerged at the end of 2019 as a new pathogen that rapidly became a leading cause of morbidity and mortality. In this context, it was expected that individually, increased stress, as well as anxiety, depressive and sleep disorders would be perceived. **Objective:** to determine if there is an association between fear of COVID-19 and decreased sleep quality in a sample of Mexican adults. **Material and methods:** an online survey was applied that included sociodemographic data, Pittsburgh sleep quality index (PSQI) and the fear of COVID-19 scale (FCV-19S). Sleep quality was compared between genders and a bivariate correlation was performed considering: age, gender, history of mental health and substance use disorder, and PSQI and FCV-19S scores. A $p < 0.05$ was considered significant. **Results:** 502 surveys were evaluated (78% women). Women obtained higher scores on both the PSQI (8.3 ± 3.5 versus 6.9 ± 3.2, t = -3.8, $p < 0.001$), and the FCV-19S (17.3 ± 6 versus 14.6 ± 5.5, t = -4.4, $p < 0.001$). Most of the subjects evaluated reported decreased quality (women 83%, men 78%, $\chi^2 = 1.8$, $p = 0.1$). PSQI score correlated significantly with gender (r = 0.17), FCV-19S score (r = 0.31) and history of mental health disorder (r = 0.22) or substance use (r = 0.1). **Conclusions:** sleep disturbance is highly frequent in the Mexican population and, in addition, it was related to fear of COVID, mental health disorders and substance use. In the context of the pandemic, it is even more important to explore and diagnose sleep disorders.

Sleep quality and quality of life in Mexican adolescents

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Introduction: sleep disorders are relevant because they increase the risk of suffering psychiatric diseases at any time of life. In adolescence, sleep disorders and poor sleep quality are associated with the development of comorbidities that affect the normal development of those who suffer from them and have consequences in adulthood. **Objective:** to establish the association between quality of life and sleep quality in a sample of adolescents. **Material and methods:** anthropometry and determination of body mass index (BMIz) Z-score were performed in a population of high school students, the Pittsburgh quality of sleep index (PQSI) and the quality of life questionnaire (SF-36) were applied. From the sleep rating, the information was grouped and comparisons were made with Student's t-test; and finally, a correlation was performed. A $p < 0.05$ was considered significant. **Results:** 125 adolescents were evaluated, 37 (30%) reported poor sleep quality. No statistically significant associations were found between PSQI and weight, gender and BMIz. In 6/8 dimensions of the SF-36 the group with decreased sleep quality obtained lower scores. We found statistically significant correlations between poor sleep quality and physical function (r = -0.2), physical role (r = -0.3), emotional role (r = -0.3), vitality (r = -0.4), mental health (r = -0.4), bodily pain (r = -0.3) and general health (r = -0.3). **Conclusions:** a close association was observed between poor sleep quality and decreased quality of life. Although other psychiatric symptoms were not evaluated, alterations in quality of life could indicate an environment that facilitates its development. Poor sleep quality is associated with decreased quality of life in a group of adolescents.

Sleep disturbances and depression in children during quarantine by COVID-19

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Introduction: pandemic conditions of confinement associated with COVID-19 have affected children, who have been prone to develop sleep and mood disorders (anxiety and depression). **Objective:** to detect sleep disturbances and depression by means of instruments designed for children. **Material and methods:** the questionnaires sleep disturbances in school children (EASE) and childhood depression

(CDI) were applied to children between 6 and 12 years of age, who were contacted via internet by the acceptance of informed consent from their parents and assent from the children. Groups with and without depression were compared according to the CDI score and tests of association and risk (odds ratio [OR]) were performed with the χ^2 test with alpha significance less than 0.05. **Results:** 240 children aged 9.93 ± 1.8 years (111, 46.3% girls) who answered the CDI participated and two groups were formed, with depression 136 (56.7%) and without depression 104 (43.3%). There was an association with the EASE dimensions and positive for depression and the risk of presenting a sleep disturbance given having depression (OR), difficulty falling asleep 59.6% p = 0.0001, OR = 3.4; nightmares 24%, p = 0. 0001, OR = 8.17, nocturnal awakenings, not significant p = 0.104; daytime sleepiness 9.6%, p = 0.012, OR = 4.35; tiredness and difficulty waking up, 47.1%, p = 0.0001, OR = 5.34 and sleepwalking, not significant p = 0.65. **Conclusions:** the pandemic conditions have affected the mood of children; 43% presents depression, which have been positively associated with sleep disorders with greater risk to fall asleep, nightmares, daytime sleepiness and tiredness with difficulties to wake up.

Sleep disturbances and neuropsychiatric manifestations in patients recovered from COVID-19 and their relatives

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Introduction: almost two years after the declaration of the COVID-19 pandemic, the specialized literature for the acute respiratory management of this entity is extensive. However, despite the similarities between SARS-CoV-2 and other coronaviruses, The lack of knowledge of the pathophysiology and its interaction with the environment makes its sequelae unpredictable. Considering the high prevalence of neuropsychiatric symptoms in the recovered and general population, early identification of these symptoms would allow limiting the impact of the still unpublished chronic effects of this virus on quality of life and functionality. **Objective:** to compare the severity of insomnia and depression symptoms among people recovered from COVID-19 and their relatives during two moments of the pandemic. **Material and methods:** the insomnia severity index and the patient health questionnaire were applied to persons recovered from COVID-19 in a period of less than three months, as well as to family members. They were sent and answered electronically between September 2020 and November 2021. A multivariate analysis was performed between the scores of both instruments as an independent measure with intergroup factors, differences between waves and history of COVID-19. **Results:** a total of 318 participants (first wave, n = 175) were divided into COVID (n = 185) and non-COVID (n = 133) groups. Overall means of 11.54 were obtained for the PHQ-9 (COVID, M = 12.81; non-COVID, M = 9.78) and 12.30 for the ISI (COVID, M = 13.67; non-COVID, M = 10.38). Positive associations were found between wave type and ISI score (s = 0.003), between wave type and PHQ-9 score (s = 0.0015), and between group type and PHQ-9 score (s = 0.003). **Conclusions:** an increase in insomnia and depression symptoms was observed in participants during the third wave compared to the first wave and was associated with having undergone COVID-19.

Impact of prolonged respiratory events on obstructive sleep apnea

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Introduction: it has been considered that the apnea hypopnea index (AHI) should not be the only parameter to evaluate the severity of obstructive sleep apnea. In this study we evaluate the impact of presenting prolonged events. **Objective:** to compare differences between variables of patients with events shorter and longer than 20 seconds. **Material and methods:** cross-sectional, analytical, where patients with AHI > 30/h were included by means of respiratory polygraphy (PR) scored manually, counting the total number of events and calculating measures of central tendency. Patients were grouped into two groups according to the average duration of total events (less than and greater than 20 seconds). Statistical analysis was performed in STATA v9.2. **Results:** 37 patients were included, 56.76% men, with mean age of 51 years, mean BMI (body mass index) of 41.68 kg/m^2 and AHI of 77/h, with no difference between groups. The group with events greater than 20 seconds had higher $PaCO_2$ (40.5 versus 35.1 mmHg), more obstructive apneas (431 versus 242), fewer hypopneas (133 versus 311), lower average saturation (81 versus 86%), more time saturating below 80% (39 versus 16%) and the drop in saturation on watch was calculated to the average in the PR and was higher in patients with prolonged events (10.7 versus 7%); all with a p < 0.05. There were no differences in demographic variables, comorbidities, spirometry and chest radiography. **Conclusions:** despite presenting the same AHI, patients with prolonged events have a greater impact on oxygenation and ventilation.

First acute myocardial infarction and its association with sleep apnea: preliminary analysis

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Introduction: sleep is a vital state associated with the maintenance of health. The most common sleep breathing disorder is sleep apnea (SA). The obstructive form (OSA) affects nearly 1 billion adults worldwide. It has been documented that OSA can induce intermittent hypoxemia, sympathetic stimulation, intrathoracic pressure changes, and inflammatory disorders; these mechanisms are related to the onset and progression of cardiovascular disease.

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Objective: to evaluate the prevalence, severity and association of SA and first acute myocardial infarction (AMI). **Material and methods:** 24 patients with AMI were evaluated: cardiac markers, sleep quality, degree of daytime sleepiness, severity of apnea and level of nocturnal hypoxemia. Apnea was classified into two groups: no apnea and mild AS (up to 14.9 ev/h) and moderate and severe AS (> 15 ev/h). **Results:** 70.8% of patients sleep < 7 h/night, 46% presented abnormal sleepiness. Of the 24 patients, 13 had no or mild AS (mean = 8.1) and 11 had moderate or severe AS (mean = 27.5) (p = 0.0001). Troponin (TnT) (1,430 versus 10,584 pg/mL; p = 0.037) and creatine kinase (CK) (3,496 versus 951 U/L; p = 0.05) levels were higher in patients with moderate/severe AS. Regarding nocturnal hypoxemia, SpO_2%, percentage of time with saturation < 90% and desaturation index (ODI) was higher in moderate/severe apnea (72% versus 80.9%; p = 0.001; 36.3% versus 57.6%; p = 0.097 and 22.4 versus 41.86 ev/h; p = 0.004, respectively). **Conclusion:** moderate/severe AS is associated with higher levels of myocardial damage markers and greater nocturnal hypoxemia.

Prevalence of poor sleep quality and hypersomnia in patients with Parkinson's disease: experience in a tertiary center

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Introduction: sleep disorders are common in Parkinson's disease (PD) and occur in two thirds of patients, being among the non-motor symptoms that most severely affect their quality of life. **Objective:** to provide sleep screening to all patients diagnosed with PD. **Material and methods:** all patients with a previous diagnosis of PD were evaluated within the neurology consultation for sleep disorders using the clinical tools: Pittsburgh sleep quality index (PSQI), Epworth scale, STOP-BANG questionnaire and patient health questionnaire (PHQ-9). A complete clinical history was taken, focusing on sleep habits and risk factors. Patients with any sleep disorder were evaluated and continued their treatment according to their results. **Results:** between August 2021 and July 2022, a total of 47 patients with a diagnosis of PD who attended the neurology office were screened for sleep disorders. They were identified by PSQI 74.4% with poor sleep quality and 46.8% of patients had hypersomnia, identified by the Epworth scale. **Conclusion:** with this initiative, we present our experience and results incorporating routine screening for these disorders in a clinical setting outside a sleep clinic.

Effects of sleep extension on attention during the course of the day

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Introduction: sleep extension consists of sleeping 10 hours or more, which tends to improve cognitive processes such as attention. **Objective:** to analyze the effects of sleep extension on attention during the course of the day. **Material and methods:** six university students participated (three males, three females; age: 18.16 ± 1.47 years), who went through three control nights (slept from 12:00-08:00 hours) and three nights of sleep extension. Participants were recorded on a 29-hour constant routine protocol, in which illumination (< 5 lux), ambient temperature (24 ± 1 °C), posture, and food intake were held constant. In this protocol, attention was recorded by means of a continuous performance task. During sleep extension, three participants extended their sleep by going to bed earlier (3.30 ± 0.91 hours earlier) and the other three participants awakened later (1.44 ± 0.10 hours later). **Results:** in the first four hours of recording, no significant differences were found in the percentage of correct responses among all participants with sleep extension (93.83%) compared to eight-hour sleepers (88.83%), but significant differences were found in reaction times (extension: 363.47 m, 8 h: 407.45 m, U = 22.00, p < 0.05). In the last four hours of the recording, after 24 h without sleep, all participants with sleep extension had a higher percentage of correct responses on the attention task compared to 8-h sleepers (extension: 74.25%, 8 h: 55.80%, U = 18.00, p < 0.02). However, no significant differences in reaction time were found between the sleep extension group (363 ms) compared to eight-hour sleepers (407.45 ms). **Conclusion:** sleep extension improves attention, even when people have been exposed to sleep deprivation for 24 hours.

Prevalence of epileptiform activity in patients with sleep parasomnias without rapid eye movements

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Introduction: parasomnias are undesirable behaviors that occur at sleep onset, during sleep or upon awakening from sleep. They are classified according to the stage of sleep during which they occur: non-rapid eye movement (NMOR) sleep parasomnias, rapid eye movement (REM) sleep parasomnias, and other parasomnias. The NMOR sleep parasomnias include arousal disorders (confusional awakenings, sleepwalking and night terrors). They are caused by abnormal activation in one area of the brain, while the rest of the brain remains in sleep. Predisposing and precipitating factors include maturational factors, epileptiform activity and sleep breathing disorders. The prevalence of epileptiform activity in healthy patients is 1.5% and in

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patients with NMOR sleep parasomnias between 9.8-25% have been reported. One possible explanation is that patients with epilepsy have been reported to have been previously diagnosed as NMOR sleep parasomnias. **Objective:** to determine the prevalence of epileptiform activity in patients with NMOR sleep parasomnias. **Material and methods:** an exploratory, observational, retrospective study was conducted on patients with NMOR sleep parasomnias with polysomnographic recording with 10-20 montage and video in the period 2010-2020 who presented at least one episode of parasomnias during the recording. **Results:** a 38.5% prevalence of epileptiform activity was observed in patients with NMOR sleep parasomnias. **Conclusions:** in patients with NMOR sleep parasomnias the prevalence of epileptiform activity is higher than that reported in the healthy population.

Polysomnographic variables in infants with bronchopulmonary dysplasia at an altitude of 2,240 meters above sea level

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Introduction: bronchopulmonary dysplasia (BPD) is a chronic lung disease as a consequence of multiple factors added to the immaturity of the airway; it causes a decrease in lung growth, as well as in pulmonary vessels, leading to a limitation in respiratory function that could favor the presence of sleep disorders due to a decrease in cortical stimuli and muscle activity, less central and peripheral sensitivity that physiologically lead to a decrease in SpO_2 and an increase in $PaCO_2$. **Objectives:** to describe polysomnographic variables in children with BPD at an altitude of 2,240 meters above sea level. **Material and methods:** exploratory, observational, retrospective study in children with BPD with nap type polysomnography from January 2015 to July 2021 at the Sleep Disorders Clinic of the UNAM; polysomnographic variables were analyzed and grouped based on severity of dysplasia, prematurity, sleep stages and CO2 levels; statistical analysis was performed with SPSS 26 software. **Results:** 195 children, 51.7% male, mean age 42 days, 42.3% with moderate BPD. Mean awakening index 22.5 ev/h and apnea/hypopnea index 51.7 ev/h, NMOR sleep 64% and MOR 24%, minimum SpO2 67% ($p = 0.010$) and CO_2 39 mmHg ($p = 0.333$). We observed differences in mild vs moderate BPD on arousal index ($p = 0.028$) and minimum SpO_2 ($p = 0.044$), in mild vs. severe on arousal index ($p = 0.082$) and in moderate vs. severe on minimum SpO_2 ($p = 0.004$); children with elevated CO_2 levels presented a higher apnea/hypopnea index ($p = 0.000$), higher sleep efficiency ($p = 0.004$) and higher number of central apneas ($p = 0.001$) and average SpO_2 ($p = 0.022$). **Conclusions:** children with BPD presented a higher rate of awakenings, increased light sleep, decreased deep sleep and REM; higher number of central apneas and desaturations. None presented hypoventilation. Children with elevated CO_2 levels presented greater sleep efficiency, respiratory events and hypoxemia; there were no differences in sleep macrostructure or arousal response in NMOR and REM sleep. BPD may favor the appearance of respiratory disorders during sleep that predispose to alterations in neurocognitive development. Integration into a neurodevelopmental and early intervention program is suggested.

Effects of sleep deprivation on sustained attention and its relationship to brain electrical activity

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Introduction: sustained attention is the ability to respond efficiently to environmental stimuli over an extended period of time; overall stability and performance over time on task are indicators of sustained attention. Attention can be affected by sleep deprivation. It is of interest to us to know how these changes in sustained attention are related to the electrical activity of the brain during task performance. **Objective:** to know the effects of sleep deprivation on sustained attention and its relationship with brain activity. **Material and methods:** 12 people without sleep disorders were deprived of sleep for 28 hours, remained awake in the laboratory and answered a visual continuous performance task while their brain electrical activity was recorded at the beginning of the session (12 hours, baseline) and at 16 hours the following day. **Results:** it was observed that with sleep deprivation variability in correct responses ($T = 0.0$, $p < 0.01$) and reaction time variability ($T = 2.0$, $p < 0.01$) increased, while performance worsened with time on task ($T = 8.0$, $p < 0.05$). Furthermore, in brain activity increased theta power (4-8 Hz, $T = 0.0$, $p < 0.01$) and decreased fast beta (22-32 Hz, $T = 5.0$, $p < 0.01$). We found a positive correlation between variability of correct responses and reaction time with delta ($R = 0.75$, $p < 0.01$ $R = 0.68$, $p < 0.05$) and theta ($R = 0.66$, $p < 0.05$; $R = 0.84$, $p < 0.001$) bands and a negative correlation of performance with time on task with those frequencies (delta $R = -0.76$, $p < 0.01$; theta $R = -0.62$, $p < 0.05$). **Conclusions:** sleep deprivation caused a decrease in sustained attention. It was found that the higher the power of delta and theta the more sustained attention decreased when people were sleep deprived.

NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 4 / October-December 2022

Letter to the editor

doi: 10.35366/112959

Giant pulmonary cryptococcoma in immunocompetent patient

Criptococoma pulmonar gigante en paciente inmunocompetente

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Dear editor

The invasive infections by *Cryptococcus neoformans* or *Cryptococcus gattii* more frequently involve the lungs and the central nervous system (CNS) with a high mortality rate; besides, the muscles, skeletal, skin and soft tissues, abdominal viscera, eyes, and prostate of both previous healthy and immunosuppressed individuals may be affected.[1-5] More often, *C. gattii* causes mass lesions in CNS, while *C. neoformans* does it in lungs.[2] Risk factors include HIV/AIDS, solid organ transplant, immunomodulatory agents, liver cirrhosis, chronic renal disease, diabetes mellitus, malignancy, and autoimmune disease.[2]

We read the case study by Mestre-Orozco L *et al.* of a 23-year-old man who had antecedent of close contact with reservoirs of *Cryptococcus* and developed headache, and convulsions four days after the second COVID-19 vaccine and underwent amphotericin B plus fluconazole without complete improvement.[3] The chest imaging evaluation showed a cryptococcoma (10 × 10 cm) in the lung left lower lobe that was operated on. The authors emphasized the lack of previous immunosuppression in the present case, which can raise the hypothesis of the role played by the vaccination anti-SARS-CoV-2. They also stressed the abrupt CNS manifestations shortly after the second dose of vaccine, and the voluminous dimension of the pulmonary lesion, which evolved undetected until then.[3]

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How to cite: Modesto-dos Santos V, Modesto-dos Santos LA. Giant pulmonary cryptococcoma in immunocompetent patient. Neumol Cir Torax. 2022; 81 (4):269-270. https://dx.doi.org/10.35366/112959

In this setting, the aim is commenting on other occurrences of cryptococcosis with cryptococcoma among immunosuppressed as well as in immunocompetent individuals. O'Hern JA *et al.* reviewed data of 45 patients with infections by *C. gattii* (35 confirmed and 10 probable), with median age of 41 (5-60) years and median follow-up of five years.[4] They were treated by 166-715 days; 44% had both pulmonary and CNS lesions, 20% died up to one year after diagnosis, while 11% of survivors evolved with major sequels. Cryptococcomas measuring 6 (2.2-10) cm underwent surgery and 90% were cured; four cases of brain lesions developed immune reconstitution inflammatory syndrome (IRIS), characterized by intracranial hypertension and a cryptococcal antigen over than 1:512 and a schedule of corticosteroids from 63 days to over six months was utilized with success.[4] The authors highlighted that morbidity associated with *C. gattii* infection remains high, although early diagnosis and combined surgical and medical management can eradicate the disease, differing from the outcomes following therapy of *C. neoformans* infection.[4] Tucker M *et al.* also reported the development of IRIS in an immunocompetent male patient with rapidly enlarging cryptococcoma by *C. neoformans* that compressed vascular structures in spite of the four weeks of amphotericin B plus eight weeks of fluconazole.[5] The critical consequences of vascular encroachment were responsive to prednisone, and authors stressed that this was the first cryptococcal-IRIS in an immunocompetent host.[5] Finally, Brazilian authors described the findings of complete necropsy study of a 32-year-old man who died due to the acquired immunodeficiency syndrome (AIDS) and systemic mycobacteriosis, and presented with an unsuspected restrained prostatic cryptococcoma.[1] The prostatic lesion measured 2 cm in diameter with numerous forms of *C. neoformans*; worthy of note, this agent was not found in any other site, contrasting with mycobacteria miliary dissemination detected in the lungs, spleen, liver, adrenals, and lymph nodes.[1] The authors highlighted the

isolated prostatic focus of cryptococcal infection coexistent with the scattered dissemination of mycobacteriosis in a severely immunosuppressed host, and commenting the major role of prostate foci for recurrent cryptococcal infections; prostatic cryptococcosis is usually asymptomatic and may be detected in necropsy study.[1]

In conclusion, the aim of the herein commented articles has been to enhance the awareness of health care workers about less focused aspects of the development of cryptococcomas either among immunosuppressed or in immunocompetent individuals.

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