2 - 2024

e-ISSN 2594-1526

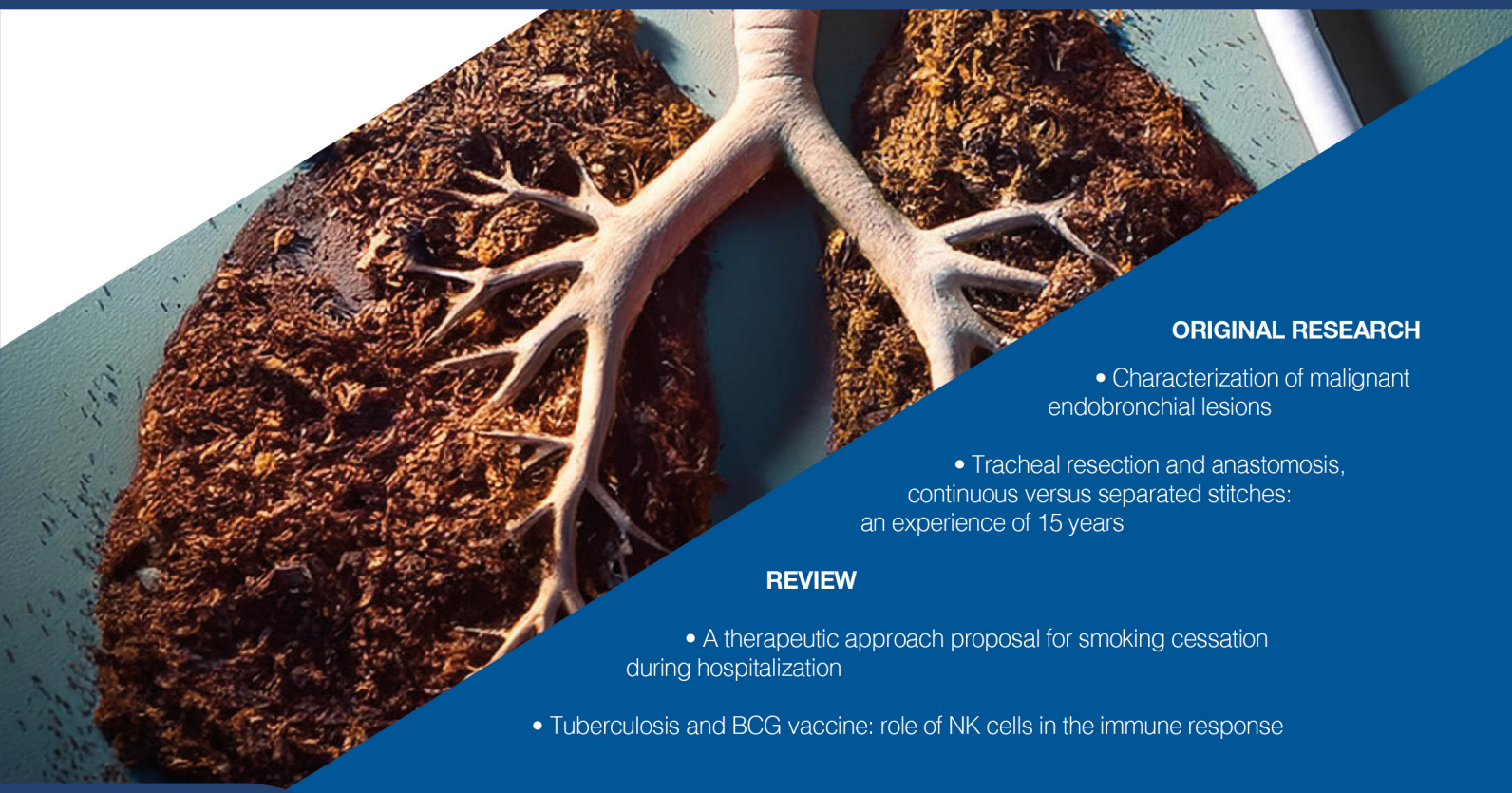
VOL. 83 NO. 2 APRIL-JUNE, 2024

NCT

Neumología y Cirugía de Tórax

Founded in 1939

TREATMENT OF SMOKING DURING HOSPITALIZATION



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Founded in 1939 as Revista Mexicana de Tuberculosis y Enfermedades del Aparato Respiratorio (Mexican Journal of Tuberculosis and Respiratory Diseases).

e-ISSN 2594-1526
Volume 83 / Number 2 / April-June 2024

Revista oficial de:
Sociedad Mexicana de Neumología y Cirugía de Tórax
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas

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Pneumology and Thoracic Surgery
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NCT Pneumology and Thoracic Surgery, Vol. 83, No. 2, April-June - 2024. It is published quarterly by the Sociedad Mexicana de Neumología y Cirugía de Tórax, A.C., calle Montecito No. 38 - interior: 32nd floor, office 26, colonia Nápoles, alcaldía Benito Juárez, C.P. 03810, Mexico City, Mexico. Tel. 55-8589-8532. http://www.medigraphic.com/neumologia, martin@medigraphic.com Editor in charge: Dr. Juan Carlos Vázquez García. Reservation of Exclusive Use Rights: species diffusion via computer network No. 04-2022-111709231200-203, e-ISSN 2594-1526, granted by the Instituto Nacional del Derecho de Autor. Art, design and formation by Graphimedic, S.A. de C.V., emyc@medigraphic.com calle Coquimbo 936, colonia Lindavista Norte, alcaldía Gustavo A. Madero, C.P. 07300, Mexico City, Mexico, phones: 55-8589-8527 to 31. Responsible for the last update of this number for its electronic format, Internet Department, Graphimedic, S.A. de C.V., Ing. Luis Rosales Jiménez, date of last modification, December 12, 2024.

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Neumología y Cirugía de Tórax
Vol. 83 - No. 2 / April-June 2024

Editorial
doi: 10.35366/119280

Treatment of smoking during hospitalization. An opportunity not to be missed

Tratamiento del tabaquismo durante la hospitalización. Una oportunidad que no debe ser desaprovechada

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In this issue of Neumología y Cirugía de Tórax Bedolla-Tinoco et al. present a comprehensive review of interventions targeting hospitalized patients who smoke.[1] The authors highlight the hospitalization period as a particularly opportune moment to initiate smoking cessation strategies for several compelling reasons.

First, patients are often in a state of vulnerability during hospitalization, which may enhance their motivation to quit smoking. Additionally, the smoke-free hospital environment, coupled with enforced abstinence due to illness, creates a unique context in which patients may be more receptive to health-promoting interventions. This moment offers not only an immediate chance to support smoking cessation but also an opportunity to shift the prevailing paradigm of care.

From a health systems perspective, there is a pressing need to move beyond a purely restorative approach and embrace preventive strategies—particularly those focused on secondary and tertiary prevention. Smoking cessation during hospitalization represents a high-impact intervention with the potential for significant health benefits both in the short and long term.

The initial studies of this approach were conducted in patients with ischemic cardiovascular disease admitted for an acute event at the Ottawa Heart Institute. All patients were provided with a systematic intervention, regardless of their degree of motivation.The intervention consisted in asking about tobacco use, providing brief advice, nicotine replacement therapy with patches to active smokers and follow-up by telephone advice after discharge. The vast majority accepted the intervention (91%) and the reported abstinence rate was 44% at six months.[2] This «Ottawa model» by Pipe A et al was considered as a standard of care in all institutions for this Canadian province.[3] In 2014, Rigotti et al published a similar experience at Massachusetts General Hospital.[4]

Currently, US hospital quality recommendations (NHQM) adopted the recommendations of the Joint Commission and Medicare, promoting the implementation the current evidence of smoking cessation intervention in clinical practice. The requirement is for systematic documentation of tobacco use on admission, provision of smoking cessation counseling and medication during hospitalization and at discharge.

Systematic reviews and meta-analyses have evidenced a significant and consistent effect of interventions during hospitalization to achieve medium-term abstinence.[5]

However, health impact outcomes in terms of morbidity and mortality from tobacco-related diseases, which are the ultimate goal of smoking cessation interventions, have notbeen measured. Based on the available evidence,

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How to cite: Zabert GE. Treatment of smoking during hospitalization. An opportunity not to be missed. Neumol Cir Torax. 2024; 83 (2):121-122. https://dx.doi.org/10.35366/119280

Jiménez Ruiz et al. published a guideline on the treatment of smoking in hospitalized patients.[6]

In Latin America, there are reports that show the scarce intervention in patients with respiratory pathologies related to smoking, such as chronic obstructive pulmonary disease (COPD) and lung cancer.[7] Among the barriers to implement smoking cessation intervention systematically in hospitals, some were related to health systems, such as lack of adequate resources to record tobacco use in all hospitalized patients, limited training of physicians in cessation counseling techniques, limited availability of effective cessation medications in hospital pharmacies and lack of standard of care protocols. While other reported factors were related to patients (denial of consumption at the time of hospitalization, refusal of intervention or pharmacological treatment, personal preferences regarding nicotine use, among others) and their relatives (e.g. skepticism about the effectiveness of the intervention, consumption environment influenced by social or cultural aspects).[8]

Finally, Torres Esteche et al. presented Hospital Maciel's experience, that evidenced the feasibility and the impact of implementing a similar aproach to the Ottawa model in a public hospital in Uruguay.[9]

Bedolla-Tinoco et al., propose a management algorithm and recommendations based on updated published evidence adapted to Mexico with the expectation of becoming an input to be implemented in all inpatient settings. Their initiative is very timely and worthy of attention by health authorities as a standard of quality care.[1]

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NCT
Neumología y Cirugía de Tórax
Vol. 83 - No. 2 / April-June 2024

Original

doi: 10.35366/119281

Characterization of malignant endobronchial lesions

Caracterización de lesiones endobronquiales malignas

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ABSTRACT. Introduction: bronchoscopy is an invaluable technique for visualizing the upper and lower airways, used for diagnostic and therapeutic purposes. It helps diagnose inflammatory, infectious, tumoral, and hemorrhagic processes. Endobronchial lesions, especially neoplastic ones, are significant findings detected during bronchoscopy, often requiring histopathological evaluation for definitive diagnosis. **Objectives:** the main objective of this study was to characterize suspicious endobronchial lesions for malignancy and correlate them with histopathological findings. **Material and methods:** a retrospective analysis was conducted on patients with suspected lung metastasis or lung cancer undergoing bronchoscopy at the General Hospital of Mexico from 2018 to 2023. Demographic data, bronchoscopic images, and pathology results were reviewed. **Results:** a total of 122 patients were included (52 women, 70 men; mean age 62 years). Radiographic findings indicated parenchymal opacities, hilar enlargement, atelectasis, and pleural effusion. Bronchoscopy revealed endobronchial tumors, mucosal infiltration, extrinsic compression, and normal mucosa. Histopathological analysis confirmed various neoplasms, with squamous cell carcinoma and adenocarcinoma being the most common. **Conclusions:** endobronchial lesions, including tumors and mucosal infiltration, are often diagnosed late, highlighting the importance of bronchoscopy in early detection and histopathological confirmation. Adenocarcinoma predominates among identified neoplasms, underscoring the role of bronchoscopy in providing accurate diagnoses without the need for invasive surgical procedures, thus improving patient management and quality of life.

Keywords: bronchoscopy, squamous cell carcinoma of the lung, lung adenocarcinoma, endobronchial tumor, bronchoscopic findings.

RESUMEN. Introducción: la broncoscopia es una técnica invaluable para visualizar las vías respiratorias superiores e inferiores y es utilizada con fines diagnósticos y terapéuticos. Ayuda a diagnosticar procesos inflamatorios, infecciosos, tumorales y hemorrágicos. Las lesiones endobronquiales, especialmente las neoplásicas, son hallazgos significativos detectados durante la broncoscopia que a menudo requieren evaluación histopatológica para un diagnóstico definitivo. **Objetivos:** caracterizar las lesiones endobronquiales sospechosas de malignidad y correlacionarlas con los hallazgos histopatológicos. **Material y métodos:** se realizó un análisis retrospectivo de pacientes con sospecha de metástasis pulmonar o cáncer de pulmón sometidos a broncoscopia en el Hospital General de México de 2018 a 2023. Se revisaron datos demográficos, imágenes broncoscópicas y resultados de patología. **Resultados:** se incluyeron 122 pacientes (52 mujeres, 70 hombres; edad media 62 años). Los hallazgos radiográficos indicaron opacidades parenquimatosas, agrandamiento hiliar, atelectasia y derrame pleural. La broncoscopia reveló tumores endobronquiales, infiltración mucosa, compresión extrínseca y mucosa normal. El análisis histopatológico confirmó diversas neoplasias, siendo el carcinoma escamocelular y el adenocarcinoma los más comunes. **Conclusiones:** las lesiones endobronquiales, incluidos los tumores y la infiltración mucosa, con frecuencia se diagnostican tardíamente, lo que subraya la importancia de la broncoscopia en la detección temprana y la confirmación histopatológica. El adenocarcinoma predomina entre las neoplasias identificadas, lo que destaca el papel de la broncoscopia en proporcionar diagnósticos precisos sin necesidad de procedimientos quirúrgicos invasivos, mejorando así el manejo del paciente y la calidad de vida.

Palabras clave: broncoscopia, carcinoma de células escamosas de pulmón, adenocarcinoma de pulmón, tumor endobronquial, hallazgos broncoscópicos.

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Received: V-04-2024; accepted: XI-27-2024.

How to cite: Rabadan-Armenta SJ, García-Torres ME, Hernández-Hernández MA. Characterization of malignant endobronchial lesions. Neumol Cir Torax. 2024; 83 (2):123-128. https://dx.doi.org/10.35366/119281

INTRODUCTION

Bronchoscopy is a visualization technique of the upper and lower airways that is used for diagnostic or therapeutic purposes. This technique is useful for diagnosing inflammatory, infectious, tumor and hemorrhagic processes.[1]

The most common neoplastic lesions in the bronchi are secondary to bronchogenic carcinoma, representing only 1% of extrathoracic tumors.[2] The incidence varies according to the literature and depends on the evolutionary stage of the primary disease, the group of patients studied and the follow-up program.[3] The reported prevalence of visible endobronchial metastases in the main or lobar bronchi is 2%.[4]

For the clinical study of these patients, minimally invasive diagnostic methods such as chest radiography and computed tomography (CT) of the chest are commonly initiated. These methods may provide indirect or suggestive data of airway compromise. Bronchoscopy is the chosen study for the identification and evaluation of lesions in the central airway. Based on the radiological findings, it is determined which patients are candidates for fibrobronchoscopy for tissue sampling and subsequent histopathological analysis.

Flexible bronchoscopy is an invasive procedure that allows direct visualization of the airway and sample collection by bronchoalveolar lavage, bronchial brushing or biopsy. At the General Hospital of Mexico, Mexico City, flexible bronchoscopy has a crucial role in the diagnosis of tumors with suspected airway malignancy.

The main objective of this study is the characterization of endobronchial lesions with suspected malignancy and their correlation with histopathologic findings.

MATERIAL AND METHODS

Retrospective analysis of cases of patients with suspected malignant lung lesion or lung cancer brought to the Bronchoscopy area of the General Hospital of Mexico from 2018 to 2023. Demographic data, imaging studies, bronchoscopic images and pathology findings were reviewed.

The diagnostic suspicion of lung cancer and pulmonary metastasis was established based on anamnesis, clinical evaluation, and chest X-ray and CT findings. First of all, flexible bronchoscopy was used to obtain the sample, as well as surgical biopsy in patients in whom no diagnosis was obtained by flexible bronchoscopic biopsy and/or no lesion was evident to perform bronchoscopic sampling.

The histological diagnosis was confirmed by biopsy of the identified lesion, in addition to bronchoalveolar brushing and lavage. Endobronchial metastasis was defined as single or multiple lesions visible through bronchoscopy, compromising the trachea, tubes or segmental bronchi, and with histology equal to the primary extrathoracic malignancy.

The main bronchoscopic findings and the number of bronchi affected were correlated with the malignant lesion confirmed by histopathology and the number of metastases in the patient. The presence of mucosal infiltration, endobronchial tumor, hypervascularization, irregular and hypervascularized edematous mucosa were considered as suspicious findings of malignancy. Other variables such as extrinsic compression were also evaluated.

Statistical analysis: was performed using Microsoft Excel and IBM Statistical Package for the Social Sciences (SPSS), version 20.0.

Characteristics of the equipment and procedures applied: the EB-1970K Pentax *video*bronchoscope, with a 2.8 mm working channel was used. Cook alligator bronchoscopy forceps and a protected brush were used for post-biopsy cytology. In total, 3 to 5 biopsies were performed during bronchoscopies that were conducted with narrow band imaging (NBI).

RESULTS

Demographic characteristics

A total of 122 patients were included, including 52 women (42.6%) and 70 men (57.4%), the mean age was 62 years with values ranging from 46 to 82 years.

Imaging studies

Chest radiography was the initial diagnostic imaging method used, the radiological features found were single parenchymal opacity in 43 (35.2%) patients; multiple parenchymal opacities in 21 (17.2%); pulmonary cavity in nine (7.4%); enlargement of the pulmonary hilum in 17 (13.9%); atelectasis in 12 (9.8%); unilateral pleural effusion in six (4.9%); bilateral pleural effusion in five (4.1%); no alterations were identified in the chest X-ray in nine (7.4%) cases.

Chest CT with contrast was performed on 48 patients before the study with the following findings: 32 (66.7%) patients with tumor lesion; six (12.5%) patients with obstructive pneumonia; 18 (37.5%) with atelectasis; parenchymal tumors were located in the right lung in 28 (58.3%) patients and left lung in 20 (41.7%). Hilar and prebronchial lymphadenopathy was found in 33 patients (68.8%), three with pleural effusion (6.3%).

Bronchoscopic study

Bronchoscopy was performed in all 122 patients due to chest X-ray and/or computed tomography findings. Of these, 100 patients underwent biopsy, brushing and bronchoalveolar lavage for cytological study.

Table 1: Bronchoscopic findings and correlation with diagnostic methods (N = 122).

Bronchoscopic appearance	Biopsy n (%)	Brushing n (%)	Bronchioloalveolar lavage n (%)
Endobronchial tumor (n = 64)	63 (98.4)	5 (7.8)	1 (1.6)
Mucosal infiltrative lesions with increased vascularization (n = 21)	17 (81)	1 (4.8)	0 (0)
Extrinsic compression of the bronchial wall (n = 15)	2 (13.3)	0 (0)	0 (0)

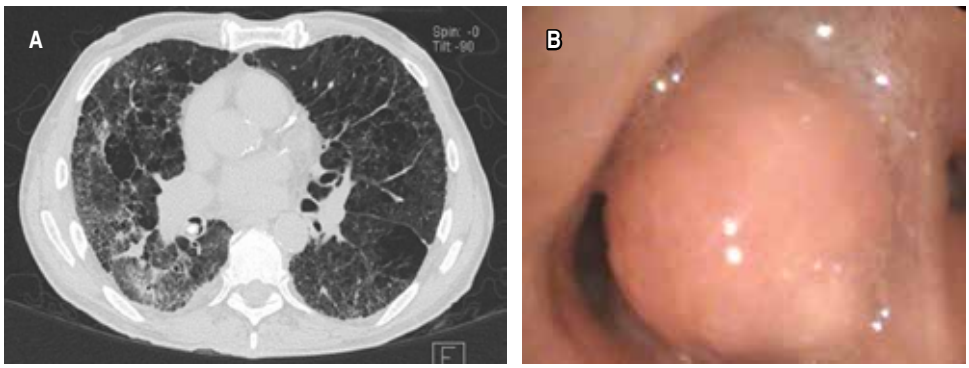

Figure 1:

Endobronchial tumor. **A)** 75-year-old patient with chest CT scan showing intrabronchial lesion. **B)** Bronchoscopy with endobronchial tumor of polypoid appearance in the right lower lobe; biopsy with result of pulmonary adenocarcinoma.

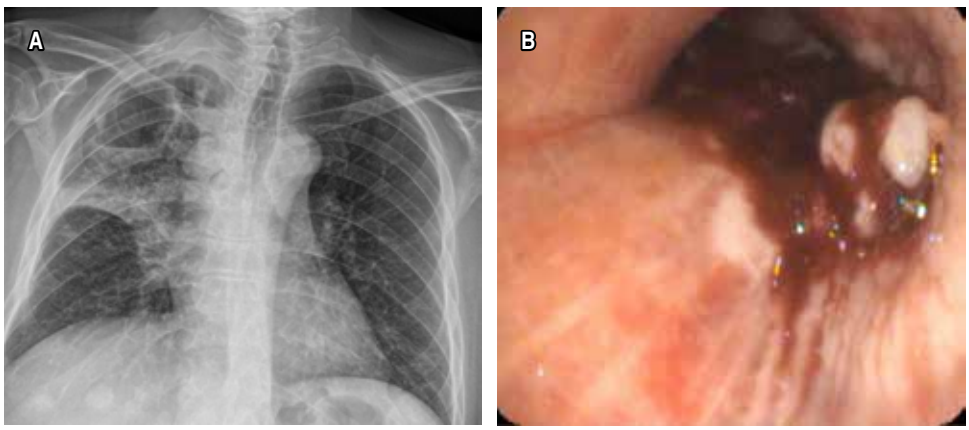

Figure 2:

Pearly endobronchial tumor.
A) 51-year-old patient with chest X-ray showing right apical cavity.
B) Bronchoscopy with bleeding tumor; biopsy with renal clear cell result.

The bronchoscopic features of the lesions observed were as follows *(Table 1)*:

Sixty-four endobronchial tumors were identified, the most frequent location was in the right bronchial tree, with 39 (60.9%) patients. Of these, 19 (29.6%) were found between segments 6 to 10 right, 12 (18.7%) in the middle lobe and eight (12.5%) in segments 1 to 3. In the left bronchial tree, 25 cases (39%) were observed. Of these, six (9.3%) were found between left segments 6 to 10, 10 (15.6%) in the lingula and nine (14%) in segments 1 to 3 *(Figures 1 and 2)*.

Mucosal infiltrative lesions with increased vascularization were observed in 21 patients.

Extrinsic compression of the bronchial wall was identified in 15 patients.

Bronchoscopically normal appearance of the bronchial tree mucosa was found in 14 subjects.

Pale and atrophic mucosa was found in 34 patients.

Erythematous and edematous mucosa was identified in 22 cases.

Abundant bronchial secretions were reported in 15 patients, while moderate bronchial secretions were observed in 22.

Combinations of these lesions were found especially in mucosal characteristics.

Biopsies were taken, as well as brushing and cytological lavage of the following lesions:

Of the 64 endobronchial tumors, biopsies were performed, as well as bronchioloalveolar brushing and lavage.

The histopathological result of the biopsy was positive in 98.4% of the cases (63 patients), brushing showed a diagnosis in 7.8% (five patients) and bronchioloalveolar lavage only reported cells compatible with malignancy in 1.6% (one patient) *(Table 2)*.

Mucosal infiltrative lesions with increased vascularization were observed in 21 patients and biopsies were taken, as well as bronchioloalveolar brushing and lavage.

Histopathological analysis of the biopsy was positive in 81% (17 patients), brushing was diagnostic in 4.8% (one case) and bronchioloalveolar lavage did not report cells compatible with malignancy in any patient.

Finally, extrinsic compression of the bronchial wall was identified in 15 patients and biopsies were obtained, as well as bronchioloalveolar brushing and lavage.

Biopsy was positive in 13.3% (two patients), brushing was not diagnostic in any patient and bronchioloalveolar lavage did not report cells compatible with malignancy in any patient.

Histopathology

The results obtained from the samples collected by bronchoscopy were as follows:

Of the 63 endobronchial tumor samples, 24 (38.1%) corresponded to squamous cell carcinoma, 19 (30.2%) to adenocarcinoma, eight (12.7%) to small cell lung cancer, five (7.9%) to infiltrating ductal carcinoma, four (6.3%) to germinal tumor and three (4.8%) to clear cell renal carcinoma.

As for mucosal infiltrative lesions with increased vascularization, of the 17 patients, 13 (76.5%) corresponded to adenocarcinoma and six (35.3%) to squamous cell carcinoma. Two patients with extrinsic compression presented pulmonary adenocarcinoma.

In total, by histopathology of bronchoscopy samples, 30 (23.8%) cases were diagnosed with squamous cell carcinoma, 34 (27.0%) with pulmonary adenocarcinoma, eight (6.3%) with small cell lung cancer, five (4.0%) with infiltrating ductal carcinoma, four (3.2%) with germinal tumor and three (2.4%) with clear cell renal carcinoma.

DISCUSSION

Lung cancer remains one of the leading causes of death worldwide, with high mortality rates because most cases are diagnosed in advanced stages. Like other malignant neoplasms, lung cancer can present endobronchial metastasis, complicating its diagnosis and treatment even more. In this context, chest X-rays and CT scans are key tools for the initial identification of lung lesions. In our study, chest radiographs revealed pathological features in most patients, with alterations such as parenchymal opacities, hilar enlargement and pleural effusion, which coincided with reports in the literature, where radiography continues to be useful in the initial detection of neoplastic pathologies.[5]

Contrast-enhanced computed tomography was also crucial in the evaluation of suspicious lung lesions, providing more precise anatomical details. Tumor lesions were identified in 66.7% of patients and hilar and prebronchial lymphadenopathy was observed in 68.8%, which highlights the importance of this technique in the evaluation prior to more invasive procedures such as bronchoscopy.[5]

Table 2: Chest radiographic and computed tomography findings.

Radiological finding	Chest X-ray N = 122 n (%)	Chest tomography N = 48 n (%)
Single parenchymal opacity	43 (35.2)	—
Multiple parenchymal opacities	21 (17.2)	—
Lung cavity	9 (7.4)	—
Enlargement of the pulmonary hilum	17 (13.9)	—
Atelectasia	12 (9.8)	18 (37.5)
Unilateral pleural effusion	6 (4.9)	3 (6.3)
Bilateral pleural effusion	5 (4.1)	—
No alterations	9 (7.4)	—
Tumor lesion	—	32 (66.7)
Obstructive pneumonia	—	6 (12.5)
Hilar and prebronchial lymphadenopathy	—	33 (68.8)

As for endobronchial neoplasms, despite their rarity, they represent a considerable diagnostic and therapeutic challenge. In our study, different histological subtypes were documented, with a predominance of squamous cell carcinoma (38.1%) and adenocarcinoma (30.2%). These findings differ from those reported in the literature, where carcinoid tumors and mucoepidermoid carcinoma are usually the most common.[1,2] In addition, we identified rare secondary tumors, such as infiltrating ductal carcinoma and clear cell renal carcinoma, highlighting the complexity of endobronchial metastases, the prevalence of which is low but clinically significant.[3,4]

It is relevant to mention that endobronchial metastases are usually a late sign of the disease, which coincides with what was found in this study, since bronchoscopy allowed the diagnosis of the primary tumor in all cases, but already at an advanced stage. This finding underscores the need for more effective tools for early detection of these lesions.[6]

Regarding the diagnostic tools available today, it is essential to highlight the importance of advanced technologies in bronchoscopy, such as narrow band imaging (NBI), bronchial autofluorescence (BAF) and high-magnification bronchoscopy. These modalities allow detailed visualization of mucosal and vascular lesions, facilitating the detection of suspicious high-grade lesions. NBI, for example, uses blue and green light to highlight the vascularization and structure of the mucosa, improving the identification of areas of dysplasia and neoplasia at early stages.[7,8]

Also, newer technologies, such as optical coherence tomography (OCT) and confocal laser endomicroscopy (CLE), are emerging as promising tools in the real-time evaluation of endobronchial lesions. OCT, which provides near-histological images, has proven useful for tumor characterization and assessment of airway remodeling,[9] while CLE allows in vivo imaging of the tumor microenvironment in great detail, which could improve early diagnosis of cancers and assessment of response to treatment.[10]

In our study, bronchoscopy with biopsy was the most effective diagnostic method, with a positive yield in 98.4% of cases, which is in agreement with the literature, where bronchoscopic biopsy is considered the gold standard for the evaluation of intraluminal lesions.[11] However, it is important to consider the low sensitivity of other techniques, such as bronchial brushing and bronchioloalveolar lavage, which highlights the need for a combination of diagnostic methods to optimize results.[12]

In a recent prospective study, brushing performed before biopsy with endobronchial forceps significantly increased diagnostic yield compared to brushing after biopsy. The overall diagnostic yield of brushing for detecting malignancy in visible endobronchial lesions is about 60 to 90%.[13] The diagnostic yield of endobronchial biopsy for visible endobronchial tumors is at least 70%.[14] Bronchioalveolar lavage (BAL), commonly used as an adjunct to other bronchoscopic sampling modalities for the diagnosis of malignant neoplasms, has a diagnostic yield of less than 50% in most studies, but this percentage is higher than 80% in lymphangitic carcinomatosis.[15]

Finally, although there are no well-established guidelines for the management of endobronchial tumors, treatment should be individualized, considering the location of the primary tumor, the patient's characteristics and the general state of the disease. Since in many cases these lesions represent a late sign of systemic metastasis, a multidisciplinary approach integrating bronchoscopic findings with other imaging modalities and histological studies is essential to guide therapeutic decisions.[11]

As for complications associated with transbronchial biopsy (TBLB), the most common include pneumothorax and bleeding.[16] The rate of pneumothorax varies between 1 and 5% in the general population, but is higher in the presence of risk factors such as surrounding emphysema or the use of mechanical ventilation.[17] However, no cases of pneumothorax were documented in our study, which could be attributed to careful patient selection and the experience of the medical team.

CONCLUSIONS

Endobronchial lesions in this study remain a late diagnosed condition. Bronchoscopy is still the most important invasive method of diagnosis. One of the important advantages is that it allows the visualization of lesions, in addition to taking a biopsy. Among the most common lesions are endobronchial tumors and mucosal infiltration. Adenocarcinoma is the most frequent form found in our patients. Bronchoscopy has allowed us to give a correct histopathological diagnosis without the complications of surgical interventions, less severe post-surgical complications and better recovery.

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

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NCT
Neumología y Cirugía de Tórax
Vol. 83 - No. 2 / April-June 2024

Original

doi: 10.35366/119282

Tracheal resection and anastomosis, continuous versus separated stitches: an experience of 15 years

Resección traqueal y anastomosis, puntos continuos versus separados: una experiencia de 15 años

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ABSTRACT. Introduction: prolonged ventilation and advances in medical care have resulted in an increase in the number of laryngotracheal injuries related to orotracheal intubation. Other etiologies such as tumors, blunt trauma and the performance of tracheostomies generate obstructive airway problems. **Material and methods:** a series of cases was carried out on all patients in whom tracheal resection and anastomosis were performed at the Bajío High Specialty Regional Hospital during the years 2007 to 2022. The data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 25 program. **Results:** a total of 37 patients were collected. The main surgical indication was post-intubation stenosis, of which grade III was the most frequent. Only one patient presented re-stenosis requiring a T-cannula. No recurrent paralysis was detected. **Discussion:** the distribution by sex and average age is similar to other studies already published. No patient had a history of chronic obstructive pulmonary disease. In the patients evaluated, it was not necessary to perform supralaryngeal tracheal release maneuvers. **Conclusions:** tracheoplasty is a procedure with a low number of complications and is effective.

Keywords: tracheal resection, tracheal anastomosis, tracheal stenosis, tracheoplasty, tracheal tumor.

RESUMEN. Introducción: la ventilación prolongada y los avances en el cuidado médico ha resultado en un incremento en el número de lesiones laringotraqueales relacionadas a la intubación orotraqueal. Otras etiologías como tumores, trauma contuso y la realización de traqueotomías generan problemas obstructivos de la vía aérea. **Material y métodos:** se realizó una serie de casos de todos los pacientes en los que se efectuó resección traqueal y anastomosis en el Hospital Regional de Alta Especialidad del Bajío durante los años 2007 a 2022. Los datos se analizaron con el programa *Statistical Package for the Social Sciences* (SPSS) versión 25. **Resultados:** se recopilaron un total de 37 pacientes. La principal indicación quirúrgica fue estenosis posintubación de entre las cuales el grado III fue la más frecuente. Sólo un paciente presentó reestenosis con necesidad de cánula en T. No se detectó ninguna parálisis recurrencial. **Discusión:** la distribución por sexo y la edad promedio es similar a otros estudios ya publicados. Ningún paciente tuvo antecedente de enfermedad pulmonar obstructiva crónica. En los pacientes evaluados no fue necesaria la realización de maniobras de liberación traqueal supralaríngeas. **Conclusiones:** la traqueoplastía es un procedimiento con bajo número de complicaciones y efectivo.

Palabras clave: resección traqueal, anastomosis traqueal, estenosis traqueal, traqueoplastía, tumor traqueal.

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Received: IV-27-2024; accepted: XI-25-2024.

How to cite: Acuña-Pinzón CL, Martínez-Zamorano M, Acuña-Pinzón AF, Condoy-Nieves JF, Narváez-Fernández S. Tracheal resection and anastomosis, continuous versus separated stitches: an experience of 15 years. Neumol Cir Torax. 2024; 83 (2):129-133. https://dx.doi.org/10.35366/119282

INTRODUCTION

Tracheal resection and anastomosis is a surgical procedure, in which part of the trachea is removed to subsequently restore its continuity by using a tension-free anastomosis between the residual rings, mostly in order to resolve the tracheal obstruction that in many cases is due to stenosis.[1] Prolonged ventilation and advances in critical care, cardiopulmonary surgery and neurosurgery have resulted in an increase in the number of laryngotracheal injuries related to tracheal intubation. The COVID-19 pandemic has resulted in an increased number of mechanically ventilated patients which, associated with tracheal mucosal changes secondary to the viral infection, increases the incidence of post-intubation stenosis.[2] Blunt tracheal trauma and placement of a tracheostomy tube can lead to granulation tissue and subsequent airway obstruction.[3]

Table 1: Demographic and surgical data of the patients studied.

Variable	n (%)
Age (years)*	32.27 ± 14.47
Gender	
Female	9 (24.3)
Male	28 (75.7)
Comorbidity	
Systemic arterial hypertension	3 (8.1)
Diabetes *mellitus*	1 (2.7)
Cause of stenosis	
Prolonged intubation	34 (91.9)
Trauma	2 (5.4)
Tracheal tumor	1 (2.7)
Initial management	
Tracheostomy	14 (37.8)
Dilatations	6 (16.2)
Tracheoplasty	17 (45.9)
Stenosis grade (Myer-Cotton)	
I	13 (35.1)
II	2 (5.4)
III	15 (40.5)
IV	6 (16.2)
Resected rings	
2	3 (8.1)
3	13 (35.1)
4	14 (37.8)
5	7 (18.9)
Type of anastomosis	
End-to-end	34 (91.9)
Cricotracheal	3 (8.1)
Type of stitches	
Continuous	15 (40.5)
Detatched	22 (59.5)
Bleeding (mL)*	115.4 ± 108.28
Complications	1 (2.7)

* Value expressed in mean ± standard deviation.

MATERIAL AND METHODS

Patients. Data were obtained for patients who underwent tracheal resection with tracheoplasty at the Hospital Regional de Alta Especialidad del Bajío during the period from 2007 to 2022. All patients presented an obstructive pattern of respiratory function and none reported alterations in swallowing. In regard to the surgical technique, the one described by Grillo and collaborators[4] was used, with some modifications according to the consideration of the treating surgeon. The obtained surgical pieces were analyzed in order to classify the stenosis grade by using the Myer-Cotton classification.

Variables. General information regarding sex, age, cause of stenosis, degree of stenosis (Myer-Cotton classification in surgical pieces), number of resected rings and concomitant diseases was included.

Statistics. The obtained data were compiled in an Excel spreadsheet table (Microsoft) and then analyzed statistically with the SPSS version 25 program. Quantitative variables were described by central tendency measures. The χ^2 test was used to describe associations between qualitative variables and Student's t-test between quantitative variables. A p value < 0.05 was considered significant in all tests.

RESULTS

A total of 37 patients was compiled, of whom 24.3% were female and 75.7% were male. The mean age was 32.27 years. The cause of tracheal stenosis was prolonged intubation in 91.9% of cases, tracheal trauma in 5.4% and tracheal tumor in 2.7%. In regard to concomitant diseases, 8.1% of the patients had diabetes and 2.7% had arterial hypertension.

Myer-Cotton classification divides our patients in 35.1% grade 1, 5.4% grade II, 40.5% grade III and 16.2% grade IV.

As part of the initial management, 37.8% of the patients were tracheostomized and 16.2% underwent dilatation. All patients underwent resection with end-to-end anastomosis by the Thoracic Surgery Service of the Hospital Regional de Alta Especialidad del Bajío. Cricotracheal anastomosis was performed in 8.1% and tracheotracheal anastomosis in 91.9%. The anastomosis was performed with synthetic, absorbable, multifilament suture (polyglactin 910) in all cases, using continuous suture in 40.5% of patients and separate stitches in 59.5%. Regarding the number of resected rings, the mean was 3.6 rings. The average surgical bleeding was 115 mL. No drainage was left in any of the cases.

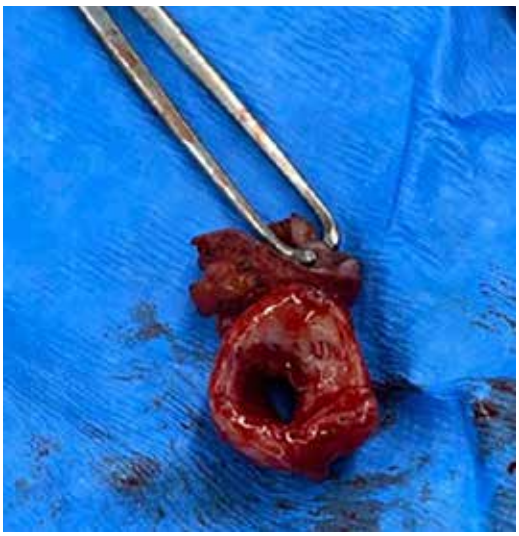

Figure 1: Surgical piece of tracheal resection. The clear decrease in the tracheal lumen can be seen.

Regarding the final results, the problem that indicated surgery was resolved in 97.2% of the patients. Only one subject presented restenosis and required management with a continuous T-cannula due to the patient's rejection of other treatment methods. No recurrent paralysis or complications related to the surgical wound (seromas, hematomas, infections) were detected. There was no relationship between suture type and restenosis (p = 0.403). Patient demographic and surgical data are summarized in *Table 1*.

DISCUSSION

Tracheal resection was reported in adults for the first time by Conley in 1953 and subsequently by Gerwat and Bryce in 1974 in children.[5]

The male preponderance in this type of procedure has been previously reported in studies of patients with post-intubation tracheal stenosis;[3,6-11] However, in studies in which patients with tracheal tumors are included, the distribution by sex is similar[12] or even inverted[13,14] due to the higher female prevalence in thyroid tumors.[12,14]

The mean age of the patients was similar to that published in other studies;[3,6,8] although the type of patient analyzed in these studies must be taken into consideration. Post-intubation tracheal stenosis was the main indication in our hospital. One patient underwent tracheal resection due to tracheal tumor with histopathologic report of a 1.5 × 1 cm well-differentiated neuroendocrine neoplasm with tumor-free proximal and distal borders. Patients with resections secondary to neoplasms on average are older.[12]

Despite the scarce presence of comorbidities in patients treated at our institution, the absence of chronic obstructive pulmonary disease, which is the most frequent respiratory disease in most studies, is notable.[7,15]

The technical difficulty varies depending on the site and severity of the stenosis. Grades III and IV according to the Myer-Cotton classification were the most frequent in the literature.[6-8,15,16] In our study, most of the patients had grade III stenosis. It is notable that the second group in terms of frequency is grade I cases. On reviewing the clinical records of these patients, we found multiple endoscopic dilatations and/or use of tracheostomy with failure of decannulation. These variations with the literature may be due to the fact that for this study the patients were classified considering the surgical piece obtained *(Figure 1)* and not the pre-surgical bronchoscopic/tomographic findings *(Figure 2)*.

The surgical approach in all patients was the transcervical incision as it allows resection of lesions as low as the T1 level. No patient presented lesions below this level or close to the carina, therefore other approaches such as sternotomy or thoracotomy were not necessary.

The performance of suprahyoid tracheal release maneuvers[17] has been described and their performance carries a risk of post-surgical dysphagia.[8] In our series, these mobilization maneuvers were not necessary and tension-free anastomosis was achieved in all cases.

The number of resected rings is in agreement with some of the studies consulted.[2,6,11,18] Regarding the suture technique, there are only two studies that explored this question. The observational study and review by Ziaian B and associates[19] concluded that patients treated with continuous suturing had a shorter operative time, but no change in the final outcome beyond a small reduction in the percentage of restenosis. The study developed by Kutlu[20]

Figure 2: Three-dimensional reconstruction of computed axial tomography. It shows concentric tracheal stenosis.

evaluated patients who underwent sleeve bronchoplasty using continuous stitches, concluding that there is no difference in outcomes compared to other similar studies using interrupted sutures. In our study there were no statistically significant differences in the final outcome (complications), so we consider that this is a topic that requires much more study and it is surprising how limited the scientific evidence on the effectiveness and safety of the different suturing techniques is, considering the wide acceptance of separate stitches.

No patient had postsurgical tracheostomy. The «guardian» suture from the chin to the sternum was used in only 15 cases without finding tracheal dehiscence or increased postoperative complications in patients in whom it was not used.

Our series had a cut-off point in 2022, at which time there was no evidence of an increase in the number of patients with tracheal stenosis undergoing tracheoplasty. Although a history of COVID-19 infection has been described as a risk factor for restenosis,[2] the only patient who presented this complication in our series underwent surgery in 2014.

Among patients with tracheal stenosis, there were no major complications, which is consistent with the literature consulted and confirms that tracheoplasty is a safe and effective procedure for the treatment of this pathology.[21-23]

CONCLUSIONS

Despite the technical complexity of the procedure, tracheoplasty continues to be a procedure with a low number of complications and effective in clinical practice for the treatment of patients with benign or malignant tracheal stenosis. The present study does not demonstrate a benefit in the placement of the «guardian» suture or in the technique used to perform the anastomosis (continuous versus interrupted).

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

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NCT
Neumología y Cirugía de Tórax
Vol. 83 - No. 2 / April-June 2024

Review

doi: 10.35366/119283

A therapeutic approach proposal for smoking cessation during hospitalization

Propuesta de abordaje terapéutico para el abandono del tabaco en pacientes hospitalizados

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ABSTRACT. Smoking is a major public health issue stemming from nicotine addiction and the multi-organ damage caused by the toxic substances released during tobacco combustion. It has been described that during hospitalization, patients are more receptive to initiating smoking cessation treatment, taking advantage of the enforced abstinence due to the smoking ban in hospitals, with even greater effectiveness compared to standard treatment. Quitting smoking in hospitalized patients reduces the risk of infections, surgical wound bleeding, hospital stay length in patients diagnosed with pneumonia, the number of exacerbations in COPD patients, as well as acute coronary events. This review aims to formulate a management algorithm and provide recommendations based on the most up-to-date evidence regarding the treatment of tobacco addiction in the inpatient setting in our country. The initial evaluation involves assessing smoking consumption, level of motivation, nicotine dependence, and withdrawal symptoms. For patients with more than 6 months of abstinence, management is limited to verifying continued abstinence and preventing relapse. In contrast, those with less than 6 months of abstinence should be evaluated for withdrawal symptoms and receive both pharmacological treatment and brief counseling. Follow-up after discharge presents the main challenge, as many patients may experience immediate relapse or fail to return for further care. Therefore, healthcare services must have an established plan in place.

Keywords: smoking cessation treatment, hospitalization, cessation, nicotine withdrawal syndrome.

RESUMEN. El tabaquismo es un problema primordial de salud pública derivado de la adicción a la nicotina y del daño multiorgánico causado por los tóxicos de la combustión del tabaco. Se ha descrito que durante una hospitalización los pacientes son más receptivos para iniciar tratamiento en el cese del tabaquismo aprovechando la abstinencia obligada por la prohibición de fumar en los hospitales; incluso con efectividad mayor al tratamiento habitual. Dejar de fumar en pacientes hospitalizados genera disminución del riesgo de infección, de sangrado de heridas quirúrgicas, de la estancia hospitalaria en pacientes con diagnóstico de neumonía, en el número de exacerbaciones de pacientes con enfermedad pulmonar obstructiva crónica, así como de eventos coronarios agudos. La presente revisión tiene el objetivo de formular un algoritmo de manejo y recomendaciones basadas con la evidencia más actualizada sobre el tratamiento de la adicción al tabaco en el contexto intrahospitalario en nuestro país. La evaluación inicial consiste en la cuantificación de consumo, grado de motivación, dependencia de nicotina y síndrome de abstinencia; al contar con más de seis meses de abstinencia, el manejo se limita a la comprobación del mismo y el control de recaídas; mientras que aquellos con abstinencia menor a seis meses deberán valorarse datos del síndrome de abstinencia y recibir, tanto tratamiento farmacológico como consejo breve. El seguimiento posterior al egreso es el principal desafío, ya que muchos de los pacientes pueden tener recaídas inmediatas o bien no acudir para recibir atención, por lo que los servicios de salud deben contar con un plan establecido.

Palabras clave: tratamiento tabaquismo, hospitalización, cesación, síndrome de abstinencia a nicotina.

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Received: IX-08-2024; accepted: X-22-2024.

How to cite: Bedolla-Tinoco A, Ortíz-González YG, García-Peña LE, Thirión-Romero I, Robles-Hernández R, Hernández-Pérez A et al. A therapeutic approach proposal for smoking cessation during hospitalization. Neumol Cir Torax. 2024; 83 (2):134-142. https://dx.doi.org/10.35366/119283

Abbreviation:
TAPS = the tobacco, alcohol, prescription medication and other substances use tool.

INTRODUCTION

It is well known that the tobacco consumption is one of the main health problems worldwide, it is associated with approximately 8 million death every year.[1] In Mexico, according to the Global Adult Tobacco Survey (GATS) 2023, 15.6% of the population actively consumes tobacco, which reflects the public health problem we face.[2] In addition, there are economic damages because of the decrease in the labor productivity and the increase in health care costs because of the increase in hospitalizations and complications of chronic-degenerative diseases.[3,4]

In a survey made of 81 patients hospitalized at the National Institute for Respiratory Diseases Ismael Cosío Villegas (INER), it was found that 78.2% of smokers presented symptoms associated with withdrawal syndrome. The main symptoms were tension (44.4%), hypersomnia (41.9%), depression (40.7%), anxiety (38.2%). The average time in the hospital for smokers was 9.9 ± 4 days; among the main diagnoses of smokers were the chronic obstructive pulmonary disease (COPD), asthma and lung cancer with 22.2%, 13.6 and 12.3% respectively.[5] As it is shown in this report, withdrawal symptoms are frequent and show the opportunity area to achieve effective interventions in the health care system.

Quitting smoking in preparation for hospitalization is known to have multiple benefits. For example, it decreases the post surgical complication rate, it improves wound healing and tissue proliferation, and in patients hospitalized for other diseases attenuates inflammation mechanisms; resulting in fewer complications and reduced hospital stay.[6-8]

The objective of this document is to propose recommendations based on evidence and an algorithm on the tobacco treatment in the in-hospital context, space and time conducive to smoking cessation.

Inpatient intervention

Among the main objectives in hospitalized smokers are: 1) taking advantage of the hospital stay as an ideal time for intervention; 2) individualizing treatment, taking into account the intensity of the withdrawal symptoms, comorbidities and patient preference for ease of use, cost and accessibility; 3) give a follow up plan and treatment after hospital discharge; 4) promoting the training of all health personnel to give brief advice and make referrals to clinics to stop smoking; 5) decreasing the direct and indirect complications of tobacco use.

We divided the intervention in hospitalized smokers into two parts: a diagnostic and a therapeutic one.

Diagnostic evaluation

In general, evaluation is based on analyzing the history and patterns of tobacco consumption. It includes the quantification of their consumption, analysis of the degree of motivation to quit smoking, the degree of physical and psychological dependence on nicotine, exploring of previous attempts to quit and if they were accompanied by pharmacological treatment, as well as the measurement of exhale carbon dioxide (CO) or measurement of continine *(Table 1)*.

Therapeutic intervention includes pharmacological and no pharmacological as a whole.[9] In *Figure 1*, we present a proposal algorithm for the evaluation and treatment of tobacco consumption in the in-hospital context.

Quantification of cumulative tobacco consumption

The packet-year index is calculated, establishing the average number of cigarettes consumed per day in the years that they have smoked multiplied by the number of years divided by 20 (cigarettes per packet); as well as the number of daily cigarettes consumed before admission, since they

Table 1: Recommendations for the evaluation of active smokers.

Interrogate every inpatient about nicotine use. If the consumption is through tobacco, it must calculate: cigarettes per day on average, years of smoking, pack-years and date of last cigarette consumed
Assess motivation to quit smoking (Richmond test)
Find out the number of previous successful attempts (> 24 hours)
Evaluate physical and psychological dependence on nicotine (Fagerström test and TAPDS)
Evaluate abstinence syndrome and craving at baseline. (Craving to Nicotine Questionnaire [CCN] or the smoking urges [QSU])
Conduct questionnaires to assess symptoms of anxiety and depression
Measure exhaled CO and/or cotinine on admission
Interrogate history of epilepsy, comorbidities, medications, other drug use, pregnancy, and allergies to plan pharmacological intervention

TAPS = evaluation of psychological dependence on tobacco.

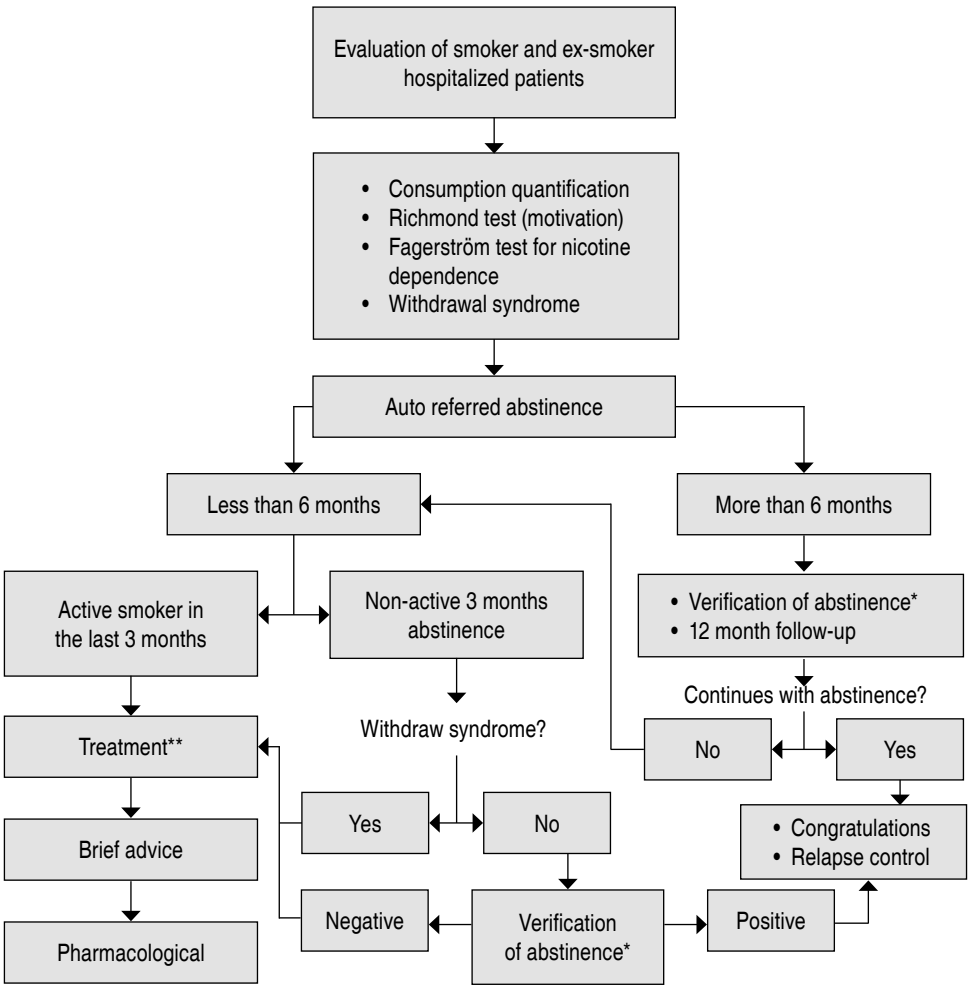

Figure 1:

Smoking management algorithm in hospitalized patients.
All patients with abstinence less than six months are recommended for follow-up.
* The abstinence test will be carried out with an exhaled carbon monoxide or cotinine test. In case of unavailability, it will be self-referred.
‡ For treatment evaluation *(Table 3)*.

allow to guide the nicotine replacement treatment.[10] The patients can be categorized as:[9,11,12]

1. Active smoker if their last consumption is less than three months.
2. Non-active smoker if their last consumption is more than three months, but less than six months.
3. Ex-smoker if their last consumption is more than six months.
4. Non-smoker if there is no consumption or if the total consumption has been less than 100 cigarettes.

In addition, it is important to question about passive exposure to tobacco in places such as home or work, to assess relapse and general health risks.

Degree of motivation analysis

A strong association with abstinence success has not been demonstrated; however, some tests could be considered to predict the adherence to treatment.[13] Motivation can be measured by visual analog scales, the Richmond test, the Smoking Abstinence Questionnaire (SAQ), and the Henri Mondor Paris or Khimji Watt test.[14] The Richmond test is the most widely used and classifies the degree of motivation as: 0-5 weak motivation, 6-8 medium motivation and > 9 strong motivation.

Analysis of the degree of physical and psychological dependence on nicotine

The Dependence Nicotine Questionnaire of Fagerström is the world standard for the assessment of physical dependence on nicotine,[15] it has six items that asses the amount of consumption, compulsion and dependence. Reagents from 0 to 1 and the multiple choice items from 0 to 3 are scored. These are added together for a total score of 0 to 10. The higher it is, the more intense the physical dependence on nicotine. The scores obtained allow to classify the dependence into five levels: very low (0 to 2 points); low (3

to 4 points); moderate (5 points); high (6 to 7 points); and very high (8 to 10 points). Measuring dependence has been used primarily for dose selection in drug therapy.[16]

Currently, it is recognized that tobacco dependence it is a multidimensional behavioral phenomenon that involves psychological, social and physical components, such as the number of cigarettes consumed. Therefore, the characterization of the patient is relevant for the diagnosis, and according to the consumption pattern in Mexico, which is mostly as occasional consumption, it is suggested to integrate evaluations such as the psychological dependence on tobacco assessment scale (TAPS).[17] Others can be mentioned, such as the Heavy Smoking Index (HSI) or the Nicotine Dependence Syndrome Scale (NDSS) that predict the craving to smoke, the withdrawal syndrome and cessation success.[15]

Craving and withdrawal syndrome

The absence or decrease in the intensity of craving and withdrawal syndrome have been used as secondary treatment goals as well as smoking cessation; currently they are also used for the decision of the type and dose of pharmaceutical treatment, mainly nicotine replacement therapy in its various presentations. The evaluation can be done using various questionnaires, such as the nicotine craving questionnaire (CCN),[18] or the Questionnaire on Smoking Urges (QSU) that allow to discriminate stable and the high intensity aspects of the need to smoke.[19] It is recommended to select a short questionnaire that contains the desire to quit smoking and the withdrawal symptoms referred to by the Diagnostic and Statistical Manual of Mental Disorders (DSM), including cravings.[20]

Analysis of previous attempts of cessation

The number of attempts will be investigated, how long he remained smoke-free in those attempts, the treatments that were used and above all, the withdrawal syndrome, since these can predict the success of abstinence or the relapse.[21] Abstinence for at least 24 hours has predicted the following cessation, that is why this cut-off point is taken into account to define previous attempts.[22,23]

Table 2: Summary of recommendations on the non-pharmacological treatment in active smokers.

Brief advice training for all the hospital member health personnel
Provide brief advice explaining the risks of this and benefits of its abandonment
Continue counseling and/or refer for cognitive-behavioral treatment post-hospital discharge

Biochemical verification of smoking cessation

Different tools can be used such as the measurement of nicotine and cotinine in saliva, urine or blood and/or exhaled carbon monoxide (CO); the latter being the simplest, innocuous, cheapest and very useful to corroborate abstinence.[11,24-26] Levels of CO are expressed in ppm (1-6 = non-smoker, 7-10 = light smoker, 11-20 = smoker, > 20 = heavy smoker).[9]

Treatment

The interventions that can be performed are similar to those of outpatient treatment, which consists of non-pharmacological and pharmacological measures. Psychological counseling can be used in its various forms after hospital discharge,[11,27,28] and brief advice is essential during hospitalization. The effectiveness of therapeutic interventions in patients with respiratory diagnoses is less clear, in part because there are few studies in this subgroup.[29]

Non-pharmacological treatment

Types of hospital non-pharmacological interventions include brief advice and self-help materials. In the outpatient context, the greater the intensity of the behavioral intervention, the greater the effectiveness, but in the hospital context it is necessary to limit and systematize it in a brief and accessible way. Rigotti et al. showed that brief counseling initiated during a hospitalization and continued with non-pharmacological measures for at least one month after discharge increased smoking cessation rates (OR 1.37; 95% CI, 1.27-1.48).[30] The short advice to quit smoking is the most recommended type of advice, as well as being simple it can be given by any health worker. It includes three steps:

1. «Asking» about tobacco use,
2. «Advise» that the best method to quit smoking is with a combination of medication and behavioral support, and
3. «Act» guiding to establish a plan with the available means. It is critical to clearly explain the benefits of quitting, highlight the risks, and congratulate the decision to quit.[27,28,30]

Training on how to give brief advice should be implemented through educational programs for health personnel, including advice on treatment to quit smoking, as they have shown a 41% increase in counseling and the prescription of treatments at discharge up to 31%[29] *(Table 2)*.

Table 3: Pharmacological recommendations for active smokers.

Nicotine replacement therapy (NRT)	NRT administration during in-hospital stay in active smokers and/or with high to moderate dependence or withdrawal symptoms regardless the degree of dependency
	Consider combination of immediate and long acting NRT if existing high dependence and/or withdrawal syndrome
	High nicotine dependence and/or consumption of < 10 cigarettes/day consider: PN 21 mg for six weeks, 14 mg for four weeks, 7 mg for two weeks
	Low to moderate dependence and/or consumption < 10 cigarettes/day consider: PN of 14 mg for six weeks and 7 mg for four weeks
	Low dependence on nicotine and consumption < 10 cigarettes/day, and/or intolerance to patch consider: Immediate-acting NRT (chewing gum, spray, inhaler or dragees) individual with dosing ad lib/for necessary reason
	Immediate-acting NRT (gum or tablet): 4 mg if they smoke their first cigarette in the first 30 minutes after waking up; 2 mg if you smoke your first cigarette after waking up. It is recommended Ad lib schema or according to the manufacturer
	NRT prescribing considerations: not recommended in uncontrolled HBP. For oral presentations not recommended if there are oral or pharyngeal lesions, history of radiation therapy to the head and neck, peptic ulcer or UGIB risk.
Oral therapy	Start treatment based on varenicline, cytisine or bupropion in hospitalized active smokers patients with a high degree of dependence, prolongue use or multiple unsuccessful abandonment attempts
	Consider varenicline, cytisine and/or bupropion, in combination with NRT
	Varenicline, its dosage will be with tablets: 0.5 mg every 24 hours day 1 to 3, 0.5 mg every 12 hours day 3 to 7 and 1 mg twice daily to complete 12 weeks
	In patients with an anxiety and/or depression profile, it is recommended to use NRT of immediate and/or prolonged action in combination with bupropion
	Bupropion dosage: 150 mg starting dose the first 3 to 7 days increasing the dose at 150 mg twice daily for 12 weeks
	Events to consider in the prescription of bupropion: contraindicate consumption of alcohol, avoid if renal failure, uncontrolled HBP or hepatic exists, evaluate drug interactions and reconsider another option if epilepsy, CVE, AVM, TBI, any cancer with suspected brain metastasis or brain neoplasia
	If cytisine is indicated you may consider two schemes: • From 1st to 3rd day one tablet every 2 hours 6 tablets. From 4th to 12th day one tablet every 2.5 hours 5 tablets. From 13th to 16th day one tablet every 3 hours 4 tablets. From 17th to 20th day one tablet every 5 hours. From 21st to 25th day one tablet every 24 hours. • Reduced schedule: 2 tablets (3 mg) every 8 hours for 25 days Tablets: 1.5 mg
	If there is poor adherence to treatment due to adverse effects, it is possible to reduce the dose of each medication as follows: • Varenicline 0.5 mg twice daily • Bupropion 150 mg once daily

AVM = arteriovenous malformation. CVE = cerebrovascular event. HBP = high blood pressure. NP = nicotine patches. TBI = traumatic brain injury. UGIB = upper gastrointestinal bleeding.

Non-pharmacological measures at discharge

Some measures such as personal contacts between the healthcare professional and the patient, sending SMS, email, proactive telephone contact, etc.,[31-34] have shown their usefulness in increasing the effectiveness of the interventions offered during the hospital period.

Pharmacological treatment

The four first-line smoking cessation drugs are: bupropion, varenicline, cytisine, and nicotine replacement therapy.[35]

Drug therapy during the hospital stay can attenuate withdrawal symptoms and increase withdrawal success. The characteristics of each of the pharmacological alternatives are described below:

1. Nicotine replacement therapy (NRT)

The use of any presentation is recommended (chewing gum, tablets, mouth spray or patches). It is useful to help manage withdrawal symptoms acutely.[26] In the in-hospital context they increase effectiveness by 54% compared to counseling alone[36] *(Table 3)*.

Adverse effects and drug interactions: the mostcommonly reported include singulum, gastrointestinal symptoms, headache, jaw and orodental pain. Few interactions have been reported with other drugs, including adenosine (tachycardia), cimetidine (increased nicotine concentration), and memantine (increased toxicity to nicotine).[37] There are few contraindications for these types of drugs such as nicotine hypersensitivity, and lactating women. Traditionally, its prescription was contraindicated in patients with coronary heart disease (CHD), however, there is evidence demonstrating efficacy and safety in this type of patient.[38]

Choice of NRT scheme: it is currently based on three characteristics: 1) the degree of the patient's nicotine dependence, 2) the number of daily cigarettes consumed, 3) the latency time between awakening and the first cigarette smoked. The nicotine patch is the simplest presentation to use; despite not acting as quickly to decrease acute withdrawal, it is an excellent maintenance therapy.[39] For patients with moderate to high dependence, long-acting NRT (patches) plus immediate-acting NRT (gum, tablets, etc.) have been recommended in patients who smoke > 10 cigarettes a day. For patients with low dependence the NRT can be used with either 2 mg ad lib chewing gum or patches in their dosages of 14 or 21 mg/day depending on cigarette consumption.[40,41]

Duration of treatment: in most studies a total duration of 10-12 weeks is established. The American Thoracic Society (ATS) Clinical Practice Guideline recommends an extended regimen of at least 12 weeks.[42]

2. Varenicline

It is currently the most effective medication for smoking cessation, recommending its use over nicotine and bupropion patches.[42] The treatment is effective regardless of nicotine dependence and can be combined with other drugs to increase success[41] *(Table 3)*.

Adverse effects and interactions: the main symptoms are nausea (24-29%), but the dose can be adjusted to 50% to reduce these symptoms without affecting their effectiveness; others are constipation (5-8%), less frequent insomnia, vivid dreams and headache (< 5%). It requires dose adjustments in liver or kidney failure.[43] Varenicline is safe in patients with a history of acute coronary syndrome (ACS).[41] It has previously been associated with increased anxiety, depression, and even suicidal ideation; however, this was ruled out by a meta-analysis in 2018 [ABT1].[44,45] It has few interactions with other drugs,[43] being ideal in patients with polypharmacy.

Contraindications: hypersensitivity to varenicline, and caution during lactation.[43]

Disadvantages: its main drawback in hospitalized patients lies in the need to use it for a week before it reaches its efficacy 10 so it must be combined with a fast-acting nicotine replacement treatment. In addition, it is the most expensive pharmacological treatment related to smoking cessation. It was recently reincorporated by the FDA, still unavailable in our country, considerably hindering access to medicines, although it is likely to be reincorporated into the therapeutic armamentarium.

3. Bupropion

Its recommendation for use in the in-hospital context is unclear, as its effectiveness in achieving abstinence is lower compared to NRT or varenicline.[46]

Adverse effects: Among the most common are tachycardia (11%), weight loss (14-19%), xerostomia (17-26%), headache (25-34%) and insomnia (11-20%). Serious adverse effects that have been reported are complete atrioventricular block, hypertension (2-6%), decreased seizure threshold, and psychiatric disturbances such as hostile behavior (6%), requires adjustment in renal failure and not recommended in hepatic failure.[47] No association with suicidal ideation has been demonstrated.[45]

Contraindications: use of alcohol, benzodiazepines, barbiturates, linezolid, methylene blue, anticoagulants, or antiepileptic drugs; concomitant use of monoamine oxidase inhibitors or within 14 days of discontinuation; current or previous diagnosis of bulimia or anorexia nervosa; hypersensitivity to bupropion; or history of uncontrolled seizures and liver failure.[47,48]

Disadvantages: it requires a period of 7 to 14 days to reach therapeutic concentrations, so in the hospital context it must be combined with nicotine substitutes and can be associated with important interactions with other drugs.[47] It requires a meticulous assessment of drug interactions.

4. Cytisine

Cytisine is an alkaloid purified from the seeds of Cytisus laburnum and has been used for decades to quit smoking in regions such as Eastern Europe.[49] Cytisine, like varenicline, competes with great affinity for nicotinic cholinergic receptors in the brain.[50] It has been shown to be as effective as varenicline,[51] being the best cost-effective therapy for the treatment of smoking, especially in the absence of varenicline on the market. One of its great advantages has been its low cost, especially in Eastern European countries,[49,52] although at the time it is marketed in the United States, procedures already started, it could raise the cost substantially and gets closer to varenicline.

Adverse effects: mainly abnormal dreams (16.6%), nausea (10.9%), sleep disturbance (18.6%) and headache (9.2%).[51]

Disadvantages: its main limitation are the treatment schemes that suggest an initial consumption every two

hours; however, it has been found that fixed doses of every eight hours or every six hours seem to be equally effective.[53] This drug is not available in Mexico.

Interventions in hospitalized ex-smokers

Cessation less than six months

The following measures are recommended:

1. Avoid relapses: the greatest risk is during the first six months of abstinence, so it is advisable to offer follow-up.[9]
2. Reinforce and recognize achievements.[9,12]
3. Offer of Support: The ex-smoker should be offered assistance in initiating and maintaining abstinence during their hospital stay.[9]
4. Assessment of abstinence syndrome and corroboration of abstinence: if the patient has been abstinent for less than three months, it is still possible for the patient to develop abstinence syndrome.[54]
5. Assess symptoms of depression and refer if they are present to the psychiatrist.[54]
6. Advice from a nutritionist since he can present weight gain.[55]

Cessation greater than six months

In this group of patients, they will simply recognize their achievements, reinforce their maintenance and offer help in case of relapse.[9]

Follow-up on hospital discharge

Perhaps this is the main challenge, since many of the patients may have immediate relapses, or do not come to receive care upon discharge. Health services must have a follow-up plan at discharge. Pharmacotherapy is not consistently covered by health systems and toll-free smoking cessation hotlines are poorly linked to health care systems.[32] A referral to a smoking cessation clinic is recommended for follow-up days after discharge.[56]

CONCLUSIONS

Scientific evidence is consistent regarding increases in smoking cessation rates when implementing cessation interventions in hospitalized patients, accompanied by timely monitoring of discharge. It is necessary to document and characterize consumption at each clinical visit, train health personnel to provide brief counseling and pharmacological treatment. In addition, it is essential to promote policies for the health system at the national level to support and provide smoking cessation treatments and counseling during a hospitalization.

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

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NCT
Neumología y Cirugía de Tórax
Vol. 83 - No. 2 / April-June 2024

Review
doi: 10.35366/119284

Tuberculosis and BCG vaccine: role of NK cells in the immune response

Tuberculosis y vacuna BCG: papel de las células NK en la respuesta inmune

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ABSTRACT. The innate immune is the first line of defense of the immune system and is characterized by the rapid response against infectious agents through the recognition of molecular patterns. Within the cells of innate immunity are natural killer cells, which show cytotoxic activity against infected or transformed cells. They have activation, inhibition and natural cytotoxicity receptors that allow their activation, causing the release of perforins, granzymes B and granulysins contained in their cytoplasmic granules which participate in the elimination of target cells. Furthermore, natural killer cells are a source of cytokines such as IFN-γ, TNF-α, IL-10, IL-2 and GM-CSF. They are important source of IFN-γ which promotes the activation of bactericidal mechanisms in macrophages in defense against intracellular pathogens such as *Mycobacterium tuberculosis*, which causes tuberculosis. Tuberculosis is an infectious disease that represents a global health problem, and the only preventive measure is the BCG vaccine, which is generally applied at birth. Natural killer cells have been reported to participate in immunity against tuberculosis, as well as in the protection conferred by BCG. The objective of this review is to highlight the most important findings on the role of natural killer cells in tuberculosis and in response to BCG vaccination in humans and animals, which may open a broader panorama to propose new preventive measures or therapies against tuberculosis, infections or cancer.

Keywords: NK cells, tuberculosis, BCG vaccine, innate immunity, trained immunity.

RESUMEN. La inmunidad innata es la primera línea de defensa del sistema inmune y se caracteriza por la respuesta rápida contra agentes infecciosos a través del reconocimiento de los patrones moleculares. Dentro de las células de la inmunidad innata se encuentran las células asesinas naturales, las cuales, muestran actividad citotóxica contra células infectadas o transformadas. Tienen receptores de activación, inhibición y de citotoxicidad natural que permiten su activación causando la liberación de perforinas, granzimas B y granulisinas contenidas en sus gránulos citoplasmáticos que participan en la eliminación de las células blanco. Además, las células asesinas naturales son fuente de citocinas como IFN-γ, TNF-α, IL-10, IL-2 y GM-CSF. Son fuente importante de IFN-γ, el cual, promueve la activación de los mecanismos bactericidas de los macrófagos en la defensa contra patógenos intracelulares como *Mycobacterium tuberculosis* causante de la tuberculosis. La tuberculosis es una enfermedad infectocontagiosa que representa un problema de salud a nivel mundial y la única medida preventiva es la vacuna BCG que generalmente se aplica al nacimiento. Se ha reportado que las células asesinas naturales participan en la inmunidad contra la tuberculosis, así como en la protección conferida por BCG. El objetivo de esta revisión es destacar los hallazgos más importantes sobre el papel de las células asesinas naturales en la tuberculosis y en respuesta a la vacunación con BCG en humanos y animales, lo que puede abrir un panorama más amplio para proponer nuevas medidas preventivas o terapias contra la tuberculosis, infecciones o cáncer.

Palabras clave: células NK, tuberculosis, vacuna BCG, inmunidad innata, inmunidad entrenada.

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Received: VI-04-2024; accepted: VII-04-2024

How to cite: Rojas-Valles EU, Antonio-Pablo RC, Herrera-Barrios MT. Tuberculosis and BCG vaccine: role of NK cells in the immune response. Neumol Cir Torax. 2024; 83 (2):143-152. https://dx.doi.org/10.35366/119284

Abbreviations:

Ag = antigens
BCG = bacillus Calmette-Guérin
DC = dendritic cell
GM-CSF = granulocyte macrophage-colony stimulating factor
HLA = human leucocyte antigens
IFN-γ = Interferon-gamma
IL = Interleukin
KIR = killer inhibitory receptor
LTBI = latent tuberculosis infection
M. bovis = *Mycobacterium* bovis
MHC = major histocompatibility complex
M. tuberculosis = *Mycobacterium tuberculosis*
NK = natural killer cells
PRR = pattern recognition receptor
PTB = pulmonary tuberculosis
TLR = toll-like receptors
TNF-α = tumor necrosis factor-alpha
WHO = World Health Organization

INTRODUCTION

All living organisms have an immune system that protects them from pathogens that can cause disease. This system involves various cell lineages with specific functions in host defense. NK cells are involved in defense in tuberculosis and it is important to know their role in infection and as part of the response to a vaccine such as BCG.

Tuberculosis

Tuberculosis is an infectious disease caused by *M. tuberculosis*, posing a global public health problem. It is the second leading cause of death from a single infectious agent after COVID-19; it has been estimated that a quarter of the world's population is infected.[1] In 2022, the WHO reported 10.3 million new cases and 1.3 million deaths from tuberculosis.[1]

It is transmitted by the airborne route, when a person with PTB expels the mycobacteria through coughing or sneezing; these remain suspended in the environment and are inhaled by other people and the fate of the infection will be determined by the immunity of the person and the virulence of the *Mycobacterium*. When *M. tuberculosis* reaches the pulmonary alveoli it is phagocytized mainly by resident macrophages, initiating cytokine production and migration of monocytes to the site of infection, where they will differentiate into macrophages. However, *M. tuberculosis* is also phagocytosed by DCs, which migrate to thoracic lymph nodes to present mycobacterial antigens to naïve T-cells, leading to the proliferation and differentiation of antigen-specific CD4+ or CD8+ T-cells. These cells migrate to the site of infection, surrounding infected and uninfected cells in the lung, forming part of the multicellular structure called granuloma. It has been speculated that the granuloma prevents and contains the spread of *M. tuberculosis* to extrapulmonary sites, but it has also been considered a niche that mycobacteria exploit to persist in the host.[2]

Most infected individuals (90-95%) control the infection and have LTBI, characterized by no signs or symptoms of TB and no contagiousness, but produce interferon gamma (IFN-γ) in response to mycobacterial Ag (IGRA positive). However, 5-10% develop active TBP within two years, associated with factors that reduce the immune response such as: malnutrition, HIV infection, compromised immune system, smoking, alcoholism and diabetes mellitus.[3-6]

Innate immunity

In the lung, cells of innate immunity represent the first line of defense when *M. tuberculosis* reaches the pulmonary alveoli. Macrophages, DCs, neutrophils and NK cells interact with the *Mycobacterium* to try to control infection and prevent disease.[7] However, *M. tuberculosis* can infect cells and replicate to persist in the host using its evasion mechanisms, such as: 1) altering phagosome-lysosome biogenesis, 2) producing components (PtpA, 1-TbAd and MarP) to neutralize and tolerate the acidic environment of the phagosome, 3) causing phagosomal membrane rupture to escape to the cytosol and gain access to nutrients using the ESX-1 secretion system, 4) causing plasma membrane rupture to infect nearby cells, and 5) inhibiting inflammasome activation, pyroptosis and autophagy.[8]

M. tuberculosis recognition

Cells of innate immunity recognize pathogen-associated molecular patterns of *M. tuberculosis* through their PRRs, such as: C-type lectins (mannoses receptors, DC-SIGN, dectin-1, dectin-2 and Mincle); NOD-type receptors; complement receptors (CR3); collectins (surfactant proteins A and D, mannose-bound lectin); scavenger receptors (MARCO, SR-A1, CD36, SR-B1); Fc receptors (FcgR); glycophosphatidyl-inositol-anchored membrane receptors (CD14); and Toll-like receptors (TLR-2, TLR-4 and TLR-9).[9]

Particularly, different PRRs of innate immunity cells that recognize *M. tuberculosis* Ag have been described *(Table 1A)*, allowing phagocytosis and/or host defense through cytokine production (IL-1ß, IL-6, TNF-α), autophagy and inflammasome activation.[9]

Mycobacterial antigens modifying the immune response

M. tuberculosis has components that promote or inhibit host defense mechanisms such as phagocytosis, autophagy, apoptosis, and inflammasome *(Table 1B)*.[10]

BCG vaccine

In 1908 Léon Charles Albert Calmette and Jean-Marie Camille Guérin initiated the attenuation of *M. bovis* isolated in 1902 from a tuberculous cow and generated the live-attenuated vaccine against tuberculosis.[11,12] They made 231 serial passages of *M. bovis* over 13 years, until in 1921 they obtained the *M. bovis* BCG (Bacillus Calmette and Guérin) strain, which conferred protection against tuberculosis in guinea pigs.[11-13]

In 1921, the BCG vaccine was administered for the first time in a child exposed to tuberculosis bacilli, demonstrating that after two years of constant exposure he did not present lesions and signs of tuberculosis.[11,14] Therefore, from 1924 onwards, this vaccine was distributed to 20 countries for its application by WHO recommendation.[12,15]

Genomic studies have shown that the BCG strain lacks the difference region-1 (RD-1) present in *M. tuberculosis* and *M. bovis*.[13] In this region are genes encoding proteins involved in the secretion system (Rv3876, Rv3877 and Rv3878) and virulence factors important in the pathogenesis of the disease (Rv3871, PE35, PPE68, Rv2879c, CFP-10 and ESAT-6).[11,13,16-20]

Innate immunity to BCG

BCG vaccine is applied intradermally causing a local immune reaction *(Figure 1A)*, which is initiated by the recognition of the bacilli by macrophages and DCs, which increase the expression of MHC class I and class II molecules, co-stimulatory molecules (CD40, CD80, CD83 and CD86) and the chemokine receptor 7 (CCR7); favoring migration to lymph nodes and the processing and presentation of Ag to T-cells.[12,21] On the other hand, macrophages recognize, phagocytize and degrade BCG by activating different PRRs such as TLR-2, TLR-4 and TLR-9; which stimulates the expression and secretion of proinflammatory cytokines (IL-6, IL-12, TNF-α and MCP-1), favoring a TH1 response involving CD4+ T-cells and, in addition, the activation of CD8+ T-cells.[12] This response is characterized by the production of IFN-γ, a crucial cytokine in the protection against intracellular pathogens such as *M. tuberculosis*, because it activates the bactericidal mechanisms of macrophages *(Figure 1B)*.[12]

This vaccine also induces non-specific trained immunity *(Figure 1C)*, based on epigenetic reprogramming in monocytes,

Table 1: Receptors of innate immunity cells and effect of *M. tuberculosis* components.

A) Receptors of innate immunity cells and their mycobacterial ligands.		
Cell	**Receptor**	***M. tuberculosis* antigens**
Macrophage	TLRs MR CD91, calreticulin	LM, LAM, ManLAM, PIM, Hsp60/65, DNA y RNA LAM ManLAM, MBL
DC	TLRs DC-SIGN	LM, LAM, ManLAM, PIM, Hsp60/65, DNA, RNA ManLAM
NK	NKp44 NKp46 NKp30 NKG2D TLR-2	MA, mAPG, AG *M. bovis* BCG *M. bovis* BCG PG
B) Effect of *M. tuberculosis* antigens on defense mechanisms.		
Defense mechanism	**Favored antigen**	**Inhibited antigen**
Phagocytosis	PPE57	PIMs, ManLAM, PKG, PtpA, EIS
Autophagy	ESAT-6, c-di-AMP	EIS, SapM, LrpG, PDIM
Apoptosis	LpqH, PE _PGRS3 3, ESAT- 6, OppD, PstS1, Rv0183, Rv0901, PE9/PE10, Mce4A	PtpA, NuoG, PknE, SecA2, SodA, SigH, MPT64, Rv3354
Inflammasome	EsxA, Mtb DNA	Zmp1

AG = arabinogalactan. c-di-AMP = cyclic di-adenosine monophosphate. DC = dendritic cells. EIS = enhanced intracellular survival. ESAT-6 = early secreted antigenic target of 6 kDa. LAM = lipoarabinomannan. LM = lipomannan. LrpG = leucine-responsive regulatory protein G. MA = mycolic acids. ManLAM = monosylated lipoarabinomannan. mAPG = mycolyl-arabinogalactan-peptidoglycan. MBL = mannose-binding lectin. Mce4A = mammalian cell entry complex 4A. MPT64 = *M. tuberculosis* Protein 64. NK = natural killers. NuoG = subunit of NADH dehydrogenase type I. OppD = oligopeptide permease D. PDIM = phthiocerol dimycocerosates. PE9/PE10 = protein proline-glutamate 9/10. PG = peptidoglycan. PIM = phosphatidyl inositol mannoside. PKG = protein kinase G. PknE = protein kinase E. PPE57 = protein proline-proline-glutamate 57. PstS1 = phosphate-specific transport substrate binding protein-1. PtpA = protein tyrosine phosphatase. MR = mannose receptor. SapM = secretory acid phosphatase. SigH = Sigma factor H. TLR = toll-like receptors. Zmp1 = zinc metalloprotease.

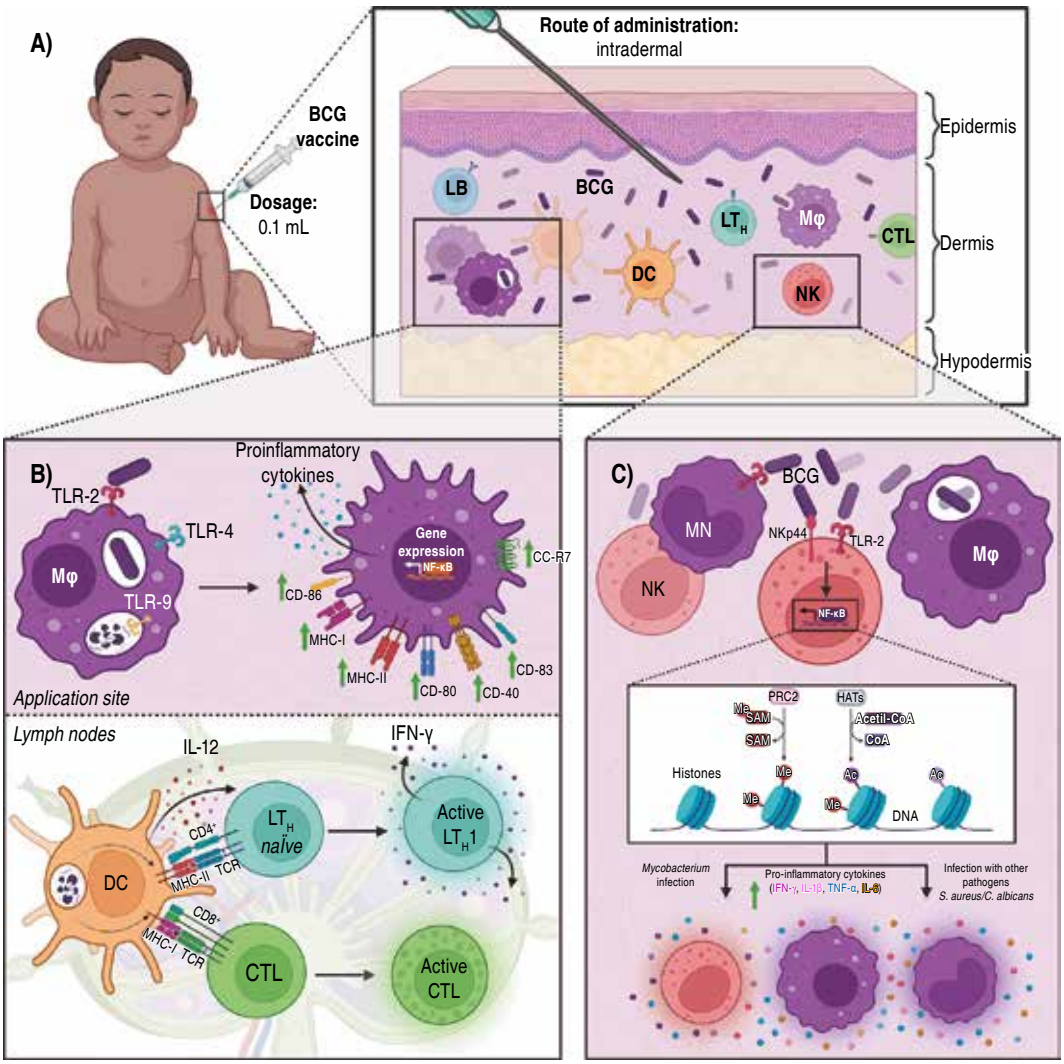

Figure 1: Immunity generated towards BCG vaccine. **A)** BCG vaccine is administered intradermally and immune system cells interact with mycobacteria. **B)** M- recognize BCG components through their TLR-2, TLR-4 and TLR-9 receptors and produce proinflammatory cytokines, increase the expression of MHC-I and MHC-II molecules, co-stimulatory molecules (CD86, CD80, CD83, CD40) and CCR7. On the other hand, dendritic cells (DC) migrate to lymph nodes and present BCG antigens (Ag) coupled to MHC molecules, LTH and CTL, favoring the production of IL-12 and IFN-γ. **C)** NK cells, M• and monocytes recognize BCG and generate trained immunity by epigenetic modifications involving the enzymes: PRC2 (with methyltransferase activity on histone H3, using S-adenosyl methionine [SAM-Me] as substrate) and HAT (with acetyltransferase activity on histones, using acetyl-CoA as substrate). Allowing rapid production of proinflammatory cytokines upon reinfection with *Mycobacterium*, or unrelated pathogens (*S. aureus* or *C. albicans*).
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Ag = antigens. BCG = *M. bovis* BCG vaccine. CCR-7 = chemokine receptor 7. DC = dendritic cell. CTL = cytotoxic T lymphocytes. LTH = helper T lymphocytes. MHC = major histocompatibility complex. M• = macrophages. NK = natural killer cells. TLR = toll-like receptors.

macrophages and NK cells. So the cells respond rapidly and strongly to secondary *Mycobacterium* infections and even to different pathogens.[12,15] This epigenetic reprogramming takes place in histones by methylation, acetylation, deamination and proline isomerization at the promoter sites of genes coding for proinflammatory cytokines.[12] Thus NK cells produce proinflammatory cytokines (IFN-γ, IL-1β, IL-6 and TNF-α) in response to BCG-related and non-BCG-related pathogens after two to 12 post-vaccination weeks.[15]

While it has been suggested that NK cells are crucial in cross-protection against other BCG-induced pathogens, their importance in response to BCG vaccination has not been described. Thus, we will describe recent reports below.

NK cells

They belong to the lymphoid lineage and have cytotoxic activity against infected (virus, bacteria or parasites) or tumor

cells.[22,23] They were first described in the 1970's, and their importance in innate immunity is currently recognized.[24] They are classified within the innate lymphoid cells, although under certain circumstances they show adaptive and memory characteristics. They are part of the first line of defense involved in the recognition and elimination of infected or transformed cells; in addition, they produce IFN-γ, IL-6, TNF-α and chemokines such as MIP-1α, MIP-1ß and IL-8.[25-27] They are mainly located in the blood (5-20% of circulating lymphocytes in humans) and lymph nodes, as well as in the skin, intestine, liver and lungs.[22,28]

Origin and morphology

They originate in the bone marrow from a pluripotential hematopoietic stem cell (CD34+), which will give rise to a lymphoid progenitor. The process of differentiation and maturation begins when the lymphoid progenitor derives into a T/NK biopotential that mediated by IL-12, IL-7 and IL-15 and the transcription factors eomesodermin (EOMES), E4BP4, Id2, BLIMP and T-bet will guide the development into an immature NK cell to a mature NK cell. These cells express specific surface markers (CD56+ and CD16+) *(Figure 2A)* that allow them to be differentiated from T (CD3+) and B (CD19+) cells. Two subpopulations have been described according to their maturation: CD56brightCD16- (90% in peripheral blood) and CD56dimCD16+, the latter showing greater cytotoxicity.[29-32]

NK cells are granular cells (10 to 15 mm) with little rough endoplasmic reticulum, mitochondria and free ribosomes. They are characterized by cytoplasmic granules containing cytolytic enzymes such as perforins, granzyme B, granulysins, proteoglycans and TNF-α *(Figure 2B)*.[30,33]

NK cell receptors

These cells on the membrane have receptors that allow them to interact with other cells and thus identify infected or tumor cells *(Figure 2C)*. They possess: a) C lectin-like receptors: NKG2D/CD94, which recognize human leukocyte Ag E5 (HLA-E5); b) KIR (Killer Inhibitory Receptor) activation and inhibition receptors that function by detecting the increase or decrease of HLA-I6 molecules; c) natural cytotoxicity receptors, specific to NK cells that include activating receptors such as NKp30, NKp44 and NKp46; and d) the CD16 receptor (IgG low affinity Fc receptor, FcgIII) that participates in recognition of opsonized cells.[22,31] Some of the activating and inhibitory receptors, as well as their ligands, are described in *Table 2*.[22,34-38]

Functions

They are innate effector cells that participate in the response against pathogens, infected or tumor cells, in addition to favoring an adaptive immune response.[26,31,39] Their cytotoxic activation occurs upon contact with infected or tumor cells that

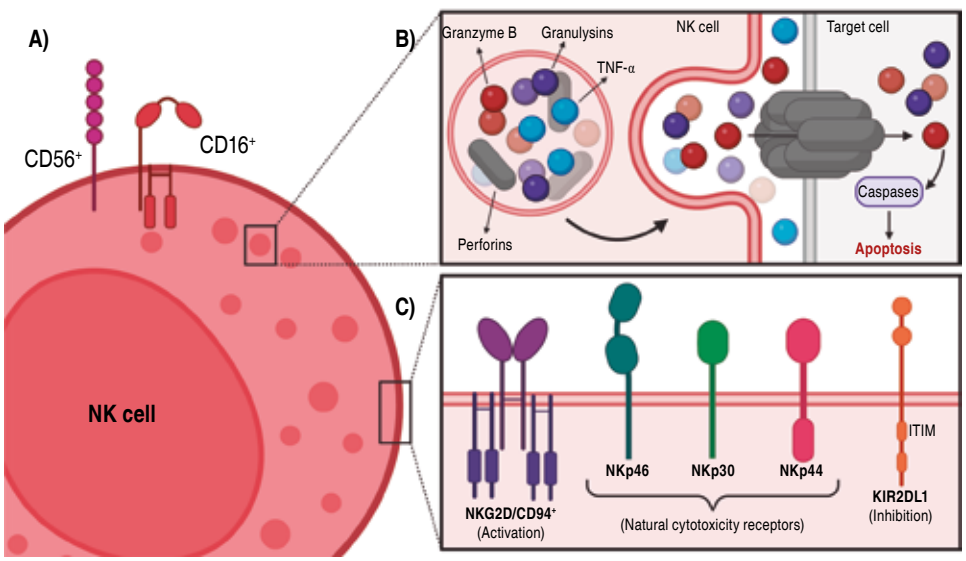

Figure 2: Immunobiology of NK cells. **A)** NK cells express CD56+CD16+ allowing their identification. **B)** They have a high content of cytoplasmic granules with cytolytic enzymes (perforin, granulysin and granzyme, as well as TNF-α. Perforins favor the formation of pores in the membrane, allowing the entry of granulysins and granzyme, which will activate the caspases pathway and initiate cell death by apoptosis. **C)** NK cells have inhibitory, activation and natural cytotoxicity receptors, involved in the recognition of components of infected or tumor cells in order to carry out the activation or inhibition of the secretion of the contents of their granules.
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Table 2: Receptors for activation and inhibition of NK cells.

Activation receptors	Linking	Reference
NKG2C	HLA-E	34, 35
NKG2D	MIC (a and b) and ULBP (1-6)	34-36
NKG2E	HLA-E	34, 35
KIR2-DS1	HLA-C2 (lysine in position 80)	34, 37
KIR2-DS2	HLA-C2 with viral peptide	34, 37
KIR3-D	HLA-F	34, 35
NKp30	B7-H6, HCMV-pp65, BAG6, heparan sulfate	22, 34
NKp44	MLL5, viral hemagglutinin, PCNA, PDGF-DD	22, 34
NKp46	Complement factor P, viral hemagglutinin, heparan sulfate	22, 34
NKp80	AICL	38
CD16	IgG antibody complex section	34, 35
CD94	HLA-E	34, 35
DNAM-1	CD155 and CD112	34, 38
Inhibitory receptors		
KIR2DL1	HLA-C2 (lysine in position 80)	34
KIR2DL2/3	HLA-C1 (asparagine in position 80) and HLA-C2 (lysine in position 80)	34
KIR3DL1	HLA-A, HLA-Bw4	34
KIR3DL2	HLA-Aw3, HLA-Aw11	34
NKG2A	Inhibitory peptide in HLA-E	34
NKRP1A	LLT1	34
KLRG1	Cadherins	34
PD1	PDL1-L2	38

AICL = activating inducing ligand. BAG6 = scythe protein. HCMV = human cytomegalovirus. HLA = human leukocyte antigen. LLT1 = lectin-like transcript. MIC = class I chain-related protein. MLL5 = mixed lineage leukemia 5. PCNA= proliferating cell nuclear antigen. PDGF-DD = platelet-derived growth factor-DD. PDL1 = programmed death-ligand 1. ULBP= UL16-binding proteins.

lack MHC-I, or MHC-I is altered. They can also be activated with IL-2, favoring their action against tumors. This cytotoxic activity can be inhibited by recognition of MHC-I in target cells, which prevents cell lysis.[35,40,41] Another of their functions is the production of cytokines (IFN-γ, IL-10, TNF-α, GM-CSF) after their activation and subsequent stimulation with IL-12.[35]

Due to the cytokine profile they produce they can be classified into: NK1, secreting IFN-γ, IL-10, TNF-α and GM-CSF; and NK2, secreting IL-5, IL-13, TNF-α and GM-CSF. IFN-γ production is the most important impact on the host immune system since it promotes the bactericidal mechanisms of macrophages, such as phagocytosis and IL-12 production, promoting IFN-γ production and the development of the TH1 response; it also modulates the immune response of T cells and DC.[26,31,35]

Role of NK cells in tuberculosis

NK cells have cytolytic capacity acting at the initial stage of infection without MHC restriction. It has been described that NK cell protection against virus, bacterial and parasitic infections is based on cell recognition and cytolytic effect, production of IFN-γ, IL-12, IL-22, TNF-α and GM-CSF, and secretion of cytolytic proteins (perforin, granzymes and granulysins). They carry out lysis of human monocytes and macrophages infected with *M. tuberculosis* through interaction with their natural membrane cytotoxicity receptors NKp36 and NKG2D.[42] There are components of *M. tuberculosis* that are recognized by receptors present on NK cells *(Figure 3)*, such is the case of mycolyl-arabinogalactan-peptidoglycan (mAPG), mycolic acids (MA) and arabinogalactan (AG) that are ligands of the NKp44 receptor; while peptidoglycan binds only to TLR-2. During TBP and meningeal tuberculosis in humans, peripheral blood NK cells are activated by showing increased CD69+ activation marker, but show a significant reduction of NKp36 and NKG2D receptors in LTBI and PTB compared to healthy individuals, which may affect the recognition and control of *M. tuberculosis* *(Figure 3)*.[43] These cells can inhibit the growth of *M. tuberculosis* H37Rv in infected human macrophages through the production of IL-22, which promotes phagolysosomal fusion, or by degranulation of their cytolytic proteins (perforins, granzymes and granulysins) *(Figure 3)*, through the MAPS kinase pathway (ERK, JNK, p38) mediated by NKG2D receptors.[44,45]

NK cell response in BCG vaccination

The NK cell response stimulated by BCG vaccination is considered to be of great interest, as it may elicit cross-

immunity against different types of infections and various cancers. This has led to research using animal models and, in addition, the response of these cells has been evaluated in humans following BCG vaccination.

Animal model response

After immunization of mice with BCG, there is an activation of NK cells as producers of IFN-γ, which favors the bactericidal capacity of macrophages.[46] In addition, post-vaccination there is migration of neutrophils to the site of infection to subsequently produce IL-12 and TNF-α that will serve to stimulate the migration, survival and action of NK cells as a source of IFN-γ. This favors the increase of NK cells at the site of infection and in the lymph nodes, reaching the maximum peak of cells in the lung and spleen at seven days, together with IFN-γ production at five days.[47,48] BCG-generated immunity is partly due to NK cells, as they promote TH1 cell activation. Some of the characteristics of BCG-treated NK cells are increased granzyme B expression, IFN-γ, CD107 and CD11b levels, and cytotoxicity against mouse melanoma-like tumor cells (B16F10).[46] Other studies have highlighted the importance of NK cells in protection, as they have reported that SCID (severe combined immunodeficient, lacking T and B-cells) and NSG (NOD/SCID/IL2RG, lacking T, B and NK cells) mice were vaccinated with BCG or saline (control) and subsequently challenged with *Candida* albicans. They observed that 100% of vaccinated SCID mice survived compared to 30% of the control group; while NSG mice gradually died. This result supports the importance of the presence of NK cells in the protection conferred by BCG to other infections.[49]

Human response

As already mentioned, these cells are an important source of cytokines, since cord blood from newborns exposed to BCG favors the production of IFN-γ, IL-10, IL-12, IL-13 and IL-15; demonstrating that only NK cells are the source of IFN-γ, while monocytes produce IL-10 and IL-12.[50] On the other hand, it has been demonstrated that NK cells purified from peripheral blood of healthy volunteers cultured with *M. bovis* BCG, show an activated state (increased CD69+CD25+), and are able to produce elevated levels of IFN-γ and TNF-α, in addition to showing cytotoxic activity and capacity to destroy immature DCs through a mechanism involving TLR-2.[51]

In South Africa, a study in the BCG-vaccinated newborn population showed increased IFN-γ-secreting NK cells at five and nine weeks post-vaccination compared to the unvaccinated.[52] In addition, vaccinated children showed increased secretion of IL-12, IFN-γ, IL-6, IL-1β and TNF-α in plasma, suggesting protection against cytokine-mediated

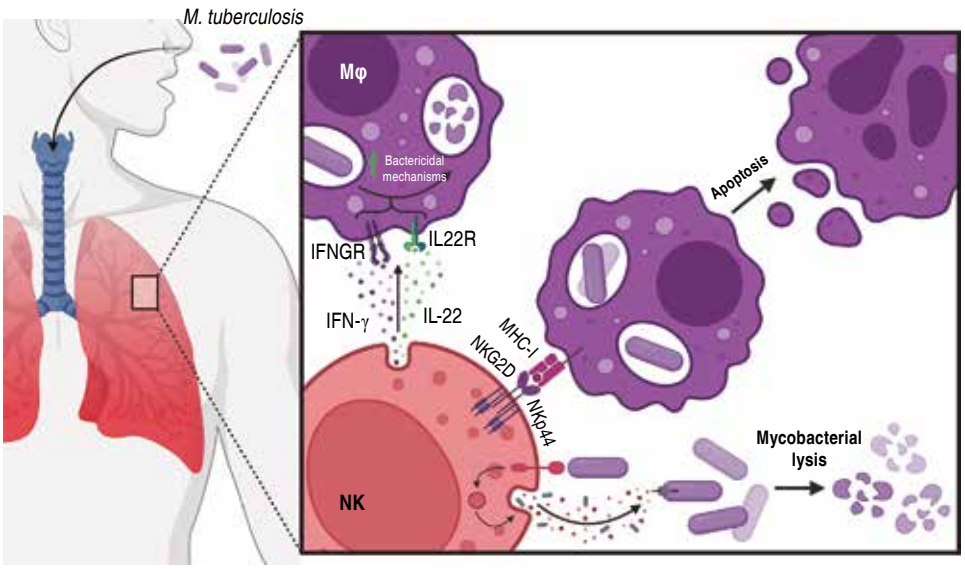

Figure 3: Role of NK cells in tuberculosis. They participate in the defense against *M. tuberculosis* by producing IFN-γ and IL-22, activating the bactericidal mechanisms of macrophages and promoting mycobacterial killing. In addition, they recognize MHC-I components through their natural activation receptors (NKG2D) to secrete the contents of their granules and promote apoptosis of cells infected with mycobacteria. Finally, they recognize mycobacterial components through their natural cytotoxicity receptors, such as NKp44 which recognizes *Mycobacterium* wall components (mycolic acids, arabinogalactan and mycolyl-arabinogalactan-peptidoglycan), thereby promoting the release of their granule components on mycobacteria and promoting lysis.
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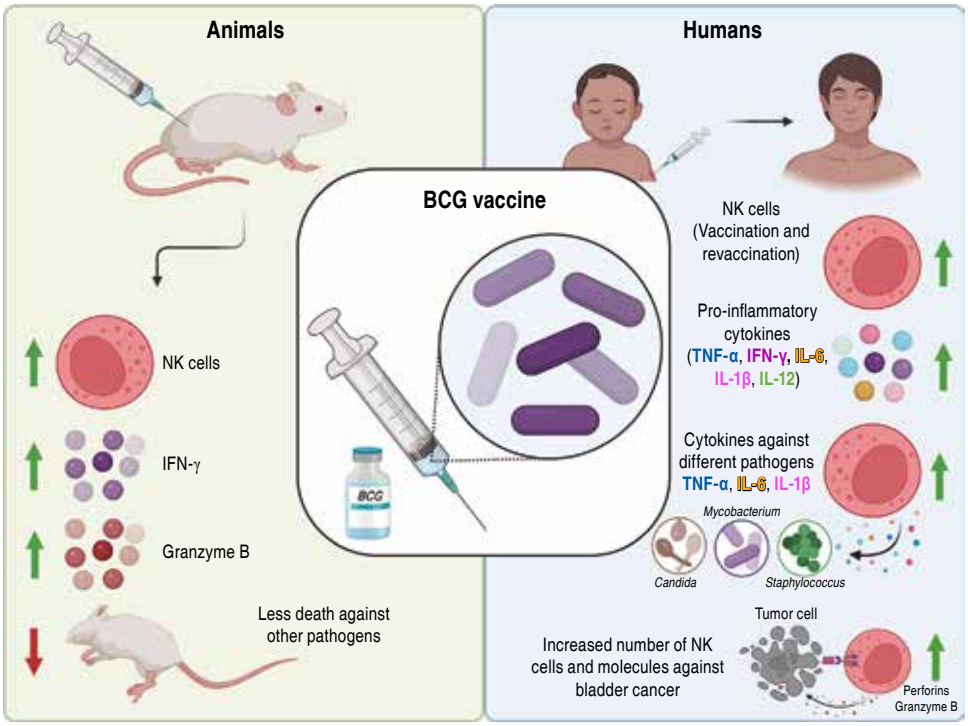

Figure 4: NK cell involvement in response to vaccination in animals and humans. BCG-vaccinated mice show increased NK cells, increased IFN-γ and granzyme production, and increased survival when infected with other non-*Mycobacterium* pathogens. Similarly, increased NK cells were observed in children and adults vaccinated with BCG associated with increased secretion of proinflammatory cytokines and increased response against unrelated pathogens. It has even been observed that BCG-stimulated human NK cells show increased cytolytic activity against cancer cells, which favors the development of anti-tumor therapies. Created with BioRender.com, NA26TGYQMU.

mycobacterial infections.[52] Until a few years ago, it was believed that innate cells had no memory; however, revaccination with BCG in adults increased the number of CD56brightCD16- and CD56dimCD16+ NK cells, which persisted in peripheral blood for more than one year.[53]

Trained immunity has been studied in CD56+ NK cells from healthy volunteers isolated from blood before vaccination, two weeks and three months post BCG vaccination. CD56+ NK cells stimulated with sonicated *M. tuberculosis* H37Rv, *C. albicans* and inactivated *Staphylococcus aureus* were able to produce elevated amounts of proinflammatory cytokines (IL-1β, IL-6, TNF-α) compared to the basal condition. This demonstrated that NK cells have immunological memory by having an increased proinflammatory response and recognition capacity to other mycobacteria and other non-BCG microorganisms.[49] Other studies have reported that peripheral blood mononuclear cells from healthy volunteers stimulated with BCG induce activation and proliferation of CD56bright NK cells.[54] In addition, co-culture of CD56bright NK cells with BCG showed elevated levels of perforins, granzyme B and IFN-γ, as well as efficient degranulation against bladder cancer cells.[54] BCG-treated bladder cancer patients have shown increased CD56bright NK cells, suggesting that BCG-induced NK cell activation may be an important component of the immune response against bladder cancer.[54]

CONCLUSIONS

Tuberculosis is a disease that affects the world's population and the BCG vaccine is the preventive measure. However, this vaccine has been shown to favor immunity trained on innate cells such as NK cells. Considering together the findings we have described above *(Figure 4)*, BCG-activated NK cells play an important role in the development of trained immunity against infections by other mycobacteria or unrelated pathogens and as antitumor therapy against bladder cancer. Thus, new lines of research can be generated to propose new drugs or therapies against various infections or cancers by mediating NK cell activation.

Acknowledgments: to Edwin Uriel Rojas-Valles and Roberto Carlos Antonio-Pablo for their valuable contributions in the preparation of the manuscript.

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

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NCT
Neumología y Cirugía de Tórax
Vol. 83 - No. 2 / April-June 2024

Procedures and recommendations

doi: 10.35366/119285

Whole-body plethysmography: updated recommendations and procedure

Pletismografía corporal: actualización en las recomendaciones y procedimiento

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ABSTRACT. Body plethysmography (BP) is a lung function test that measures lung mechanics, through the measurement of functional residual capacity (FRC_{pleth}), and specific airway resistance (sRaw). It is particularly useful for confirming pulmonary restriction as well as quantifying pulmonary hyperinflation. The objective of this document is to provide an update on the procedure and recommendations for body plethysmography according to the latest international standards -American Thoracic Society (ATS) and European Respiratory Society (ERS) 2021 y 2023- as well as to issue practical recommendations for its interpretation.

Keywords: body plethysmography, lung function, lung volumen.

RESUMEN. La pletismografía corporal es una prueba de función pulmonar que mide la mecánica pulmonar a través de la medición de la capacidad residual funcional (FRC_{pleth}) y la resistencia específica de la vía aérea (sRaw). Su uso es de gran utilidad para la confirmación de restricción pulmonar, así como para la cuantificación de la hiperinflación pulmonar. El objetivo de este documento es actualizar el procedimiento y las recomendaciones de la pletismografía corporal de acuerdo con los estándares internacionales vigentes de la Sociedad Americana del Tórax y la Sociedad Europea Respiratoria, 2021 y 2023, así como emitir recomendaciones prácticas para su interpretación.

Palabras clave: pletismografía corporal, función pulmonar, volúmenes pulmonares.

Abbreviations:

ATS = *American Thoracic Society*
ERS = *European Respiratory Society*
ERV = Expiratory reserve volume
EVC = Expiratory vital capacity
FEV_1 = Forced expiratory volume in the first second
FRC = Functional residual capacity
FRCpleth = Functional residual capacity by plethysmography
FVC = Forced vital capacity
GLI = Global lung initiative
IC = Inspiratory capacity
ITGV = Intrathoracic gas volume
LLN = Lower limit of normality
ULN = Upper limit of normality
p5 = percentil 5
p95 = percentil 95
BP = Body plethysmography
PRISm = Preserved ratio impaired spirometry
Raw = Airway resistance
RV = Residual volume
sRaw = Specific airway resistance
SVC = Slow vital capacity
TLC = Total lung capacity
VC = Vital capacity
TV = Tidal volume

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Received: V-03-2024; accepted: X-16-2024.

How to cite: Alvarado-Amador I, Centeno-Saenz GI, Silva-Cerón M, Riego-Ramírez D, Castillo-Ayala A, Gochicoa-Rangel L et al. Whole-body plethysmography: updated recommendations and procedure. Neumol Cir Torax. 2024; 83 (2):153-165. https://dx.doi.org/10.35366/119285

INTRODUCTION

Body plethysmography (BP) is a pulmonary function test that measures functional residual capacity (FRC_{pleth}), also known as intrathoracic gas volume (ITGV), as well as specific airway resistance (sRaw)[1] (see supplementary material). It confirms the presence of pulmonary restriction and, in obstructive disease, quantifies pulmonary hyperinflation.[2,3]

The values obtained in BP depend on the distensibility and elasticity of the rib cage and lung parenchyma, as well as the integrity of the respiratory musculature. Distensibility is the ease with which a body stretches or deforms (change in volume observed by change in pressure), while elasticity is the opposition of a body to being stretched (ability to return to its original shape).[4]

BP measurement is based on Boyle-Mariotte's Law: «the volume of a gas is inversely proportional to the pressure to which the gas is subjected under isothermal conditions; therefore, during compression of a gas under these conditions, the product of pressure and volume remains constant».[5] The aim of this review is to update the document published in 2019 on plethysmography procedure and recommendations, in accordance with current international standards-ATS [American Thoracic Society]/ERS [European Respiratory Society] 2021 and 2023-[6,7] and provide practical recommendations for its interpretation.

DEFINITION

BP is a pulmonary mechanics test that measures lung volumes, quantifies the total amount of gas in the thorax (whether in direct communication with the airway or not),[5] and measures total lung capacity (TLC), which is subdivided into four volumes and four capacities shown in *Figure 1* and their definitions are summarized in *Table 1*.[7,8]

The cardinal measurement of BP is FRC, which requires that the end-expiratory air volume at tidal volume (TV) remain stable. According to the ATS 2019 spirometry standard, this stability is defined as the presence of at least three breaths at TV with a difference between maximum and minimum end-expiratory lung volume within 15% of TV.[9]

FRC_{pleth} includes ventilated and non ventilated lung compartments, and its results may be higher than those obtained by dilution or gas washout methods in the presence of severe obstruction, bullae, or emphysema. Although theoretically FRC_{pleth} may be increased by abdominal gas, the amount of abdominal gas is small (~100 mL) and larger volumes appear to have no effect on FRC measurement.[10] In cases of severe obstruction FRC_{pleth} may be overestimated when the respiratory rate (RR) during the gasping maneuver is > 1 Hz (60 breaths/min) because mouth pressure underestimates the absolute change in alveolar pressure.[7,11]

After measuring FRC, an inspiratory capacity (IC) maneuver is required to measure TLC, followed by a slow expiratory vital capacity (EVC) maneuver until the residual

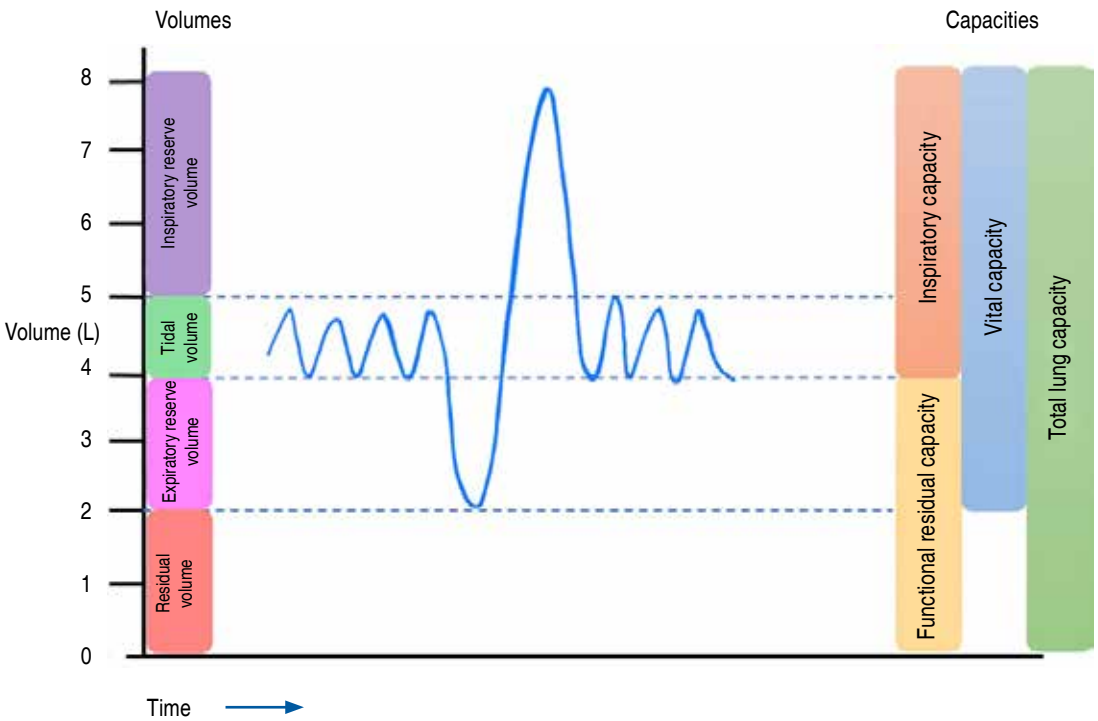

Figure 1:

Static lung volumes and capacities based on a volume-time spirogram.

Table 1: Lung volumes and capacities.

Lung volumes	
Tidal volume (TV)	It is the volume of gas inhaled or exhaled during the normal respiratory cycle
Inspiratory reserve volume (IRV)	It is the maximum volume of gas that can be inhaled from the tidal volume at the end of inspiration.
Expiratory reserve volume (ERV)	This is the maximum volume of gas that can be exhaled from the tidal volume at the end of expiration, i.e. from FRC to RV
Residual volume (RV)	This is the volume of gas that remains in the lung after a maximum exhalation
Lung capacities	
Vital capacity (VC)	It is the maximum change in volume that can be exhaled or inhaled between the positions of full inspiration (TLC) and full expiration (RV). It corresponds to the sum of the displaceable volumes (VT, IRV and ERV)
Inspiratory capacity (IC)	It is the maximum volume of gas that can be inhaled from the FRC to the TLC. It is the sum of IRV and VT
Functional residual capacity (FRC)	It is the volume of gas present in the lung at the end of passive expiration, of a normal respiratory cycle. It is the sum of ERV and VR
Total lung capacity (TLC)	It is the total volume of the lung at maximum inspiration. It is the sum of all the RV, ERV, VT and IRV volumes, and can also be calculated by the sum of the IC and the FRC or the RV with the VC

volume (RV) is reached, without removing the mouthpiece.[7] It is important to emphasize the slow EVC maneuver, since a forced maneuver can cause premature closure of the dependent airway and generate overestimation of the RV *(Figures 2 and 3)*.[7]

To perform the calculation of TLC and RV it is required to report the pulmonary subdivisions, for this purpose it is important to measure vital capacity (VC) and one of its subdivisions, such as IC (inspiratory capacity) or expiratory reserve volume (ERV); the repeatability of both HF and ERV will be determined in part by the repeatability of FRC.[7]

Linked (associated) spirometry is ideal; unlinked spirometry is not a recommended option for plethysmography.[7]

INDICATIONS FOR BP

Indications are detailed in *Table 2*.[1,12] We recommend measuring lung volumes in individuals with abnormal spirometry results (decreased forced vital capacity [FVC], e.g., probable mixed pattern, PRISm).[6]

CONTRAINDICATIONS TO BP

They are similar to the rest of the contraindications for the other respiratory function tests *(Table 3)*.[6,13] Some risks during the performance of BP are: hypoxemia in subjects in need of supplemental oxygen, anxiety, distress, claustrophobia and dyspnea.

EQUIPMENT AND CONSUMABLES FOR BP

The plethysmograph is an airtight chamber with a volume ranging from 700 to 1,200 L (larger volumes are used for obese, very tall, or wheelchair-bound patients). Its airtight design allows it to maintain a constant volume. As a result, changes in thoracic volume, which occur during the compression or decompression of pulmonary gas during respiratory maneuvers, can be calculated by measuring the changes in cabin pressure.[7]

The plethysmograph requires: software and hardware conforming to ISO 26782, mouth pressure transducer (≥ ± 50 cmH_2O; minimum 8 Hz response) and flow sensor meeting the standards presented for spirometry. It should measure changes in cabin pressure accurately within ± 0.2 cmH_2O. Changes in temperature can cause a pressure change of up to 1 cmH_2O, requiring a wider working range of the transducer.[7,14]

A time constant of 10 s (range 5-25 s) is ideal for controlled leakage (minimizing slowly occurring pressure changes). Temperature changes inside the cabinet are common and can be detected from the volume-pressure graph *(Figure 4)* during occlusion, which shows a systematic difference in slope between compression and expansion.[7,14]

Manufacturers should specify the response frequency of their systems and how to verify it. The response frequency should be a minimum of five times the frequency of the signal being measured, in this case, for a maximum acceptable breath-hold of 1.5 Hz (90 breaths/minute) this means a minimum acceptable response frequency of 8 Hz.[7,14]

It is crucial that the equipment be networked to transmit results to electronic records and to facilitate access to clinical information, as well as to collect data for research.

Other necessary consumables are listed in *Table 4*.

PERSONAL PROTECTION

Hand washing (40-60 seconds) or use of alcohol gel (20-30 seconds) before and after the test is required for both the

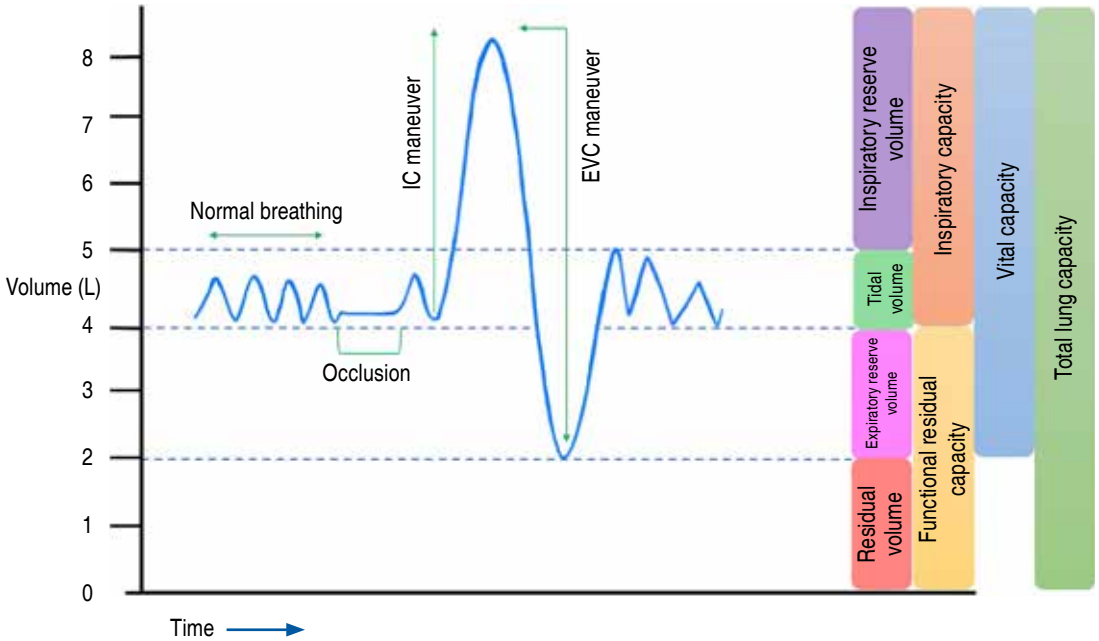

Figure 2: Body plethysmography (BP) maneuver for lung volumes. Volume-time graph showing the sequence of quiet breathing until a stable level of FRC (functional residual capacity) is reached at the end of expiration, then the shutter is closed (for a short period, approximately 2 to 3 s) to measure the intrathoracic gas volume. The shutter is then opened and the patient performs an IC (inspiratory capacity) maneuver followed by an EVC (slow expiratory vital capacity) maneuver. As a variation it is also allowed for the subject to take one breath after the shutter and then IC followed by an EVC maneuver. In this maneuver all lung volumes are calculated, the patient must remain connected to the mouthpiece with a tight lip seal throughout the measurement and specifically while the shutter is closed.

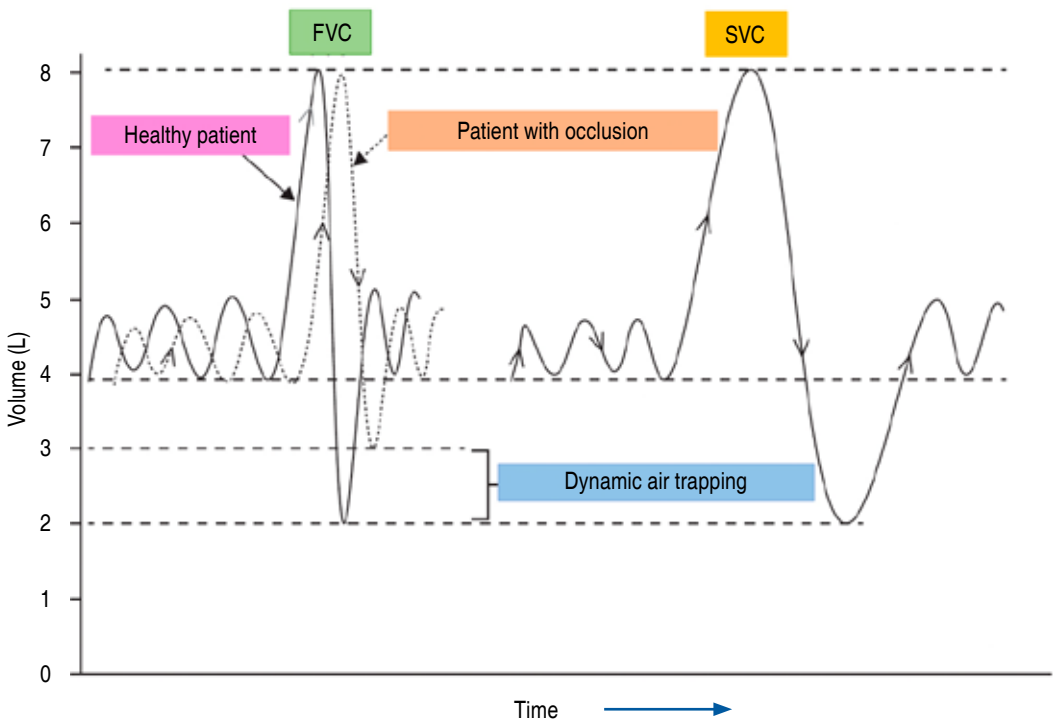

Figure 3:

Vital capacity (VC) maneuver in a healthy subject and in a subject with obstruction. In a healthy subject, the expiratory vital capacity maneuver performed in a forced (FVC) or slow (SVC) manner is expected to give the same result. However, in a subject with an obstructive ventilatory defect, there is a potential for dynamic air trapping and overestimation of residual volume with a forced maneuver.

Table 2: Indications for body plethysmography.

Confirmation and quantification of pulmonary restriction
Confirmation and quantification of pulmonary hyperinflation and air trapping, especially in patients with dyspnea disproportionate to the degree of obstruction by FEV_1
Preoperative evaluation of volume reduction surgery
Monitoring and surveillance of disease for clinical or research purposes
Patients with any of the following functional patterns by spirometry: suggestive of restriction, PRISm, probable mixed
Dyspnea or exercise intolerance

FEV_1 = forced expiratory volume in the first second. PRISm = *preserved ratio impaired spirometry*.

Table 3: Relative contraindications for body plethysmography (BP).

Recent heart attack (< 4 weeks)
Heart failure
Cardiovascular instability
Tachycardia at rest (HR > 130 bpm)
Chest or abdominal surgery < 4 weeks; eye or ear surgery < 8 weeks
Active pulmonary tuberculosis
Acute respiratory tract infections in the last two weeks
Hemoptysis
Aneurysm (of large arteries, cerebral)
Late pregnancy (third trimester) or complicated pregnancy
Poor health
Tracheostomy
Chest tube
Continuous requirement for supplemental oxygen that cannot be discontinued during the test
Subject conditions that do not allow him to be introduced into the cabin, such as claustrophobia, body paralysis, parenteral solutions or medical devices that cannot be introduced into the plethysmograph cabin

HR = heart rate. bpm = beats per minute.

operator and the subject. A surgical mask (preferably N95), short hair or hair clipped, gloves (when there is any skin lesion), and eye protection are recommended. Ensure good ventilation and the use of antimicrobial filters.[15]

INSTRUCTIONS TO THE SUBJECT BEFORE BP[13]

The main indications are described in *Table 5*.

EQUIPMENT PREPARATION BEFORE THE BP

Quality control and calibration:[14]

1. Calibration check of the body plethysmograph.
    a. Calibration verification: procedure that establishes a relationship between the volume or flow measured by the sensor and the actual flow or volume of the calibrator (syringe). Perform calibration verification of the cabinet at least once a day, so that the software will calculate the correction factors.[9,16]
    b. Perform calibration verification of the plethysmograph flow sensor for volume with a 3 L syringe at least once a day with three maneuvers at different flows in the range between 0.5 and 12 L/s (injection of 3 L in 0.5 to 6 s). Check that the volume at each flow meets the accuracy requirement of ≤ 3%, be sure to save the results (see supplementary material for detailed information).[9,16]

BP PROCEDURE[5,7,13,14]

1. The laboratory staff receives the patient, verifies their identity, and ensures that the request matches the patient's information and the study requested.

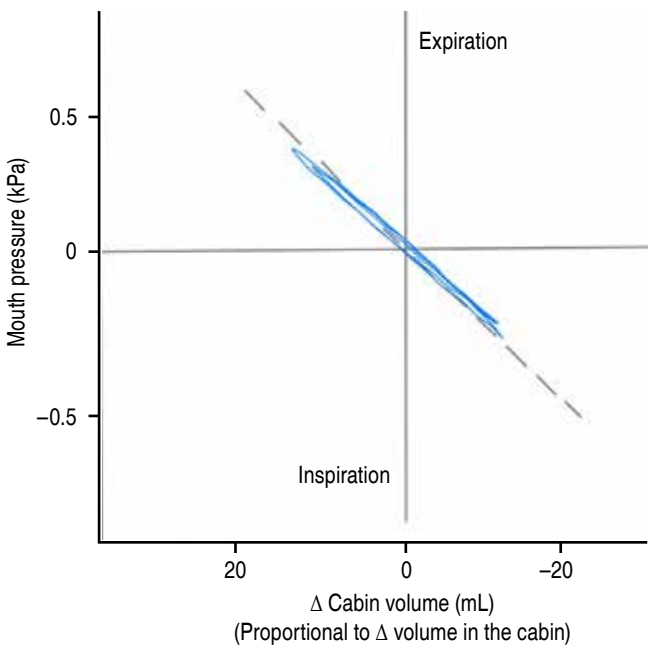

Figure 4: Gasping maneuver. A correctly performed gasping maneuver is visualized as a series of nearly overlapping straight lines, separated only by a small thermal change. The target gasping frequency is between 0.5 and 1 Hz. Δ: change in gasping frequency.

Table 4: Body plethysmography (BP) consumables.

Extra BP consumables
3-liter syringe with an accuracy of ± 0.5% of the absolute volume (15 mL), calibrated and with a valid calibration certificate
Reusable consumables: • Flow sensor • Adapters
Disposable consumables: • Disposable filter with efficiency > 99% for filtration of viruses, bacteria and mycobacteria; dead space < 100 mL and resistance less than 1.5 cmH_2O at a flow rate of 14 L/s • Mouthpieces of various sizes • Nose clip • Silicone mouthpieces
Calibrated scale and stadiometer
Anthropometric belt
Thermometer, hygrometer, barometer or local barometric pressure source, for manual adjustment of ambient conditions.

Table 5: Instructions for the subject before performing body plethysmography.

Avoid smoking and vaping two hours before
Avoid wearing restrictive chest garments, such as vests, corsets or very tight clothing
Maintain your baseline medication. Bronchodilators and inhaled steroids modify the measurement, so the decision to suspend or continue these medications should be made by the requesting physician and the technician should report the time of the last dose
Fasting is not required for the test, but a light meal is recommended four hours before
You should avoid strenuous exercise on the day of the test

2. If the patient speaks a language other than English, a family member or translator must accompany the patient to explain the procedure.
3. Check for contraindications; if there are any, notify the physician to evaluate whether the test is appropriate.
4. Explain the procedure and the risks before performing the test and offer clarifications if required. The following explanation to the patient is recommended: «Plethysmography is a test to measure the size of your lungs, it is very similar to spirometry, but to perform it you have to be inside this closed cabin for approximately 15 minutes. Don't worry about being inside the booth; you won't feel discomfort, and I will be observing and guiding you throughout the procedure.
5. Enter the patient's data into the computer: full name, date of birth, biological sex at birth, weight and height. See supplementary material for taking anthropometric values.
6. Select the appropriate reference equation for the subject.
7. Introduce the patient into the plethysmograph cabinet, seat the patient in an upright position and adjust the chair so that the feet are flat on the floor. Adjust the height of the flow sensor so that the patient can reach the nozzle without extending or flexing the neck.

Instruct and demonstrate how to perform the BP: use of mouthpiece, use teeth without biting, seal lips, use nose clip, hold cheeks without raising arms; demonstrate gasping by obstructing the back of the mouthpiece and advise that the door will remain closed during the test.

Recommendations: explain to claustrophobic patients that the door can be opened at any time during the test. Verify that thoracic expansion is not limited by the use of girdles, corsets, etcetera. In the case of the use of well-fitting dentures they are usually left in place, otherwise it is better to remove them.

BP MANEUVER[7]

1. Close the cabinet door and wait for the pressure and temperature to stabilize.
2. Set the flow sensor to zero.
3. Instruct the patient to put on the mouthpiece, nasal clamp and hold their cheeks with their hands. Holding the cheeks is particularly important in cases of airflow obstruction, where it reduces, but does not eliminate, the impact of higher gasping frequencies.
4. Instruct him to breathe quietly until a stable end-expiratory lung volume (stable FRC) is achieved, usually three to 10 breaths at stable VT. *Figure 2* exemplifies the BP maneuver.
5. Occlude the obturator at end-expiration (when the patient is at the stable FRC level) for approximately 2 to 3 s, during which time the patient performs gentle panting against the closed obturator (~ ± ± 1 kPa [~ ± 10 cmH_2O]) or at a rate between 0.5 and 1.0 Hz (30 to 60 breaths per minute) and maximum 1.5 Hz (90 breaths per minute).
6. Note: panting frequencies > 1.5 Hz may lead to an overestimation of FRC. This effect increases as the obstruction worsens. Panting frequencies:

   - Record acceptable gasping maneuvers (a series of two or three nearly overlapping straight lines, with minimal hysteresis between inspiration and expiration), on the pressure-volume graph *Figure 4*.
   - During gasping with the obturator closed, check that the maneuvers are acceptable. Verify the

automatic adjustment of the difference between ITGV and FRC_{pleth} on the spirogram trace. The gasp frequency for each maneuver should be shown on the numerical report.
- When the shut-off valve opens, IC maneuver should be performed, followed by slow EVC to RV.

7. Note: patients with severe dyspnea may have difficulty performing a IC maneuver immediately after the gasping maneuver against the closed obturator. To overcome this, instruct them to remain in the mouthpiece and breathe two or three times after the gasp maneuver, before performing the IC and EVC maneuvers *(Figure 2)*.

   - Airway resistance measurements should not be performed during the same maneuver used to measure lung volumes, as the optimal gasping frequencies differ. Additionally, prolonged time with the mouthpiece increases the risk of leaks, which may compromise the accuracy of lung volume measurements. We recommend doing the measurement of airway resistances at the end, once we have already selected acceptable and repeatable maneuvers.
   - Finish the maneuver, allow the patient to recover and repeat the process; in case of a failed maneuver, repeat the instructions and demonstrate the test again.
   - Obtain three maneuvers with acceptability criteria and assess repeatability (see section: BP assessment).
   - If you have finished the study, support the patient's exit from the cabin, save the results to generate the study report. At the end, clean and disinfect the plethysmographic booth and the patient care area.

EVALUATION OF THE BP[7]

The ERS/ATS 2023 standard for lung volumes[7] proposes the following classification based on FRC and linked spirometry.

1. Acceptable: meets all quality criteria.
2. Usable: reported and used with caution.
3. Not acceptable or rejected: consider not to report.

Criteria for acceptability

Table 6 lists the acceptability criteria for the FRC_{pleth} measurement *and Table 7* lists the acceptability criteria for the linked spirometry maneuver.

Table 6: Acceptability criteria for measurement of intrathoracic gas volume (functional residual capacity).

Tidal volume breathing before shutter closure and gasping	
Acceptable	**Before shutter closure:** • Stable end-expiratory tidal volume **During shutter closure:** • Gasping maneuvers • Superimposed straight lines without hysteresis • Parallel straight lines with minimal hysteresis • Gasping respiratory rate between 0.5 to 1 Hz or between 1.0 and 1.5 Hz with normal spirometry or mild obstruction
Usable	Any of: **Before shutter closure:** • End-expiratory tidal volume unstable, but no significant change in either direction **During shutter closure:** • Partially closed gasping maneuver • Partially overlapping straight lines • Parallel straight lines with hysteresis • Respiratory rate >1.5-2.0 Hz with normal spirometry or mild obstruction
Not acceptable or rejected	Any of: **Before shutter closure:** • Unstable end-expiratory tidal volume with significant change in either direction (e.g., increase in end-expiratory lung volume with each breath) **During shutter closure:** • Gasping maneuver with mouth opening • No straight lines • Excessive hysteresis • Force to perform the gasping maneuver exceeded the range of the oral pressure transducer • Gasping respiratory rate < 0.5 Hz, > 2 Hz with normal spirometry or mild obstruction or > 1.5 with significant obstruction

Table 7: Acceptability criteria for the linked spirometry maneuver.

Spirometry maneuver after functional residual capacity (FRC) measurement.	
Acceptable*	**Linked spirometry** • If > 6 years, SVC ≥ (FVC–150 mL) • If ≤ 6 years, SVC ≥ (FVC–100 mL) or (FVC – 10% of FVC), whichever is lower
Usable‡	**Any of:** • If > 6 years, SVC ≥ (FVC–250 mL) • If ≤ 6 years, SVC ≥ (FVC–200 mL) or (FVC – 10% of FVC), whichever is less
Not acceptable or rejected	**Any of:** • Spirometry not linked to PC • If > 6 years, SVC < (FVC–250 mL) • If ≤ 6 years, SVC < (FVC–200 mL) or (FVC – 10% of FVC), whichever is lower

FRC = functional residual capacity. FVC = forced vital capacity. SVC = slow vital capacity.
* Meets American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for within-maneuver assessment of inspiratory capacity and SVC. If forced spirometry is not performed in the same session as lung volumes, an alternative is to obtain at least three vital capacity measurements that meet ERS/ATS acceptability criteria for within-maneuver assessment and the largest of these vital capacities is a surrogate for FVC in this table.
‡ Interpret with caution.

Repeatability criteria

Obtain three acceptable FRCpleth (ITGV) values that agree within 5%. Calculate the repeatability:

[(ITGV major − ITGV minor) / ITGV average] × 100.

If you do not achieve this value, a value of 10% may be usable.

GRADING OF BP QUALITY[7]

The grading system considers the number of acceptable maneuvers for FRCpleth, SVC and repeatability. The final quality grade of the test is determined by the lowest grade obtained, for example; with ≥ 3 acceptable maneuvers for FRC and SVC with repeatability between 5 and 10%, the test is classified as C *(Table 8)*.

In grades D, E and U (usable) a report is issued, but should be interpreted with caution.

BP REPORTING[7]

Maneuvers selection

If you obtain ≥ 2 acceptable maneuvers that meet 5% FRC repeatability, these and your linked spirometry maneuvers should be used to report FRC and other lung volumes.

The value reported for FRC is the average of the technically acceptable FRC measurements used for the TLC calculation.

TLC is the average of the sum of the technically acceptable FRC values and linked CI maneuvers.

RV is the value reported for TLC minus the largest measured SVC. We recommend that all methods link spirometry maneuvers with FRC measurement to calculate TLC and/or RV.[7] For details, see supplementary material. *Table 9* shows the information that should be contained in the report.

INTERPRETATION OF THE BP

The ERS/ATS 2021 standard recommends using the lower limit of normal (LLN) and upper limit of normal (ULN) or percentile 5 (p5) and percentile 95 (p95), respectively. The predicted percentile is no longer taken as a reference.[6]

It recommends using the Global Lung Function Initiative (GLI) reference values, which integrate measurements according to sex, age range 5-80 years, from 11 countries with the limitation of being predominantly for European populations.[6]

We have analyzed GLI reference values in Mexicans living at moderate altitude (1,500-2,500 m above sea level) finding higher lung volumes and, therefore, poor adjustment of this equation to our population. It is important to analyze the fit of the different equations in each region. For interpretation purposes use biological sex at birth and not gender.

The updated algorithm for PC interpretation is shown in *Figure 5*.[6]

Start with TLC, if restrictive pattern (left side of algorithm).

Once restriction is diagnosed, assess the FRC/TLC or RV/TLC ratio. If these ratios exceed the LSN or p95, evaluate the patient's spirometry FEV1/FVC ratio. If the FEV1/FVC ratio is below LIN, it indicates a mixed pattern: restriction by plethysmography and obstruction by spirometry.

If the FEV_1/FVC ratio is not < to LIN or p5, it is a complex restriction.

If FRC/TLC or RV/TLC is not > to LSN or p95, it is a simple restriction.

On the other hand, go back to the beginning of the algorithm and check TLC, if TLC is not < to LIN or p5 (right side of the figure), proceed to see if it is > LSN or to p95, if it is not above these either, analyze the FRC/TLC or RV/TLC ratio and see if it is > ULN or p95, if it is not above, it is normal lung volumes.

If the TLC is not > ULN or at p95, but the FRC/TLC or RV/TLC ratio is > p95 it is hyperinflation or air trapping.

If from baseline the TLC is > ULN or p95 it is possible hyperinflation, proceed to look at the FRC/TLC or RV/TLC ratio, if it is not > ULN or p95 it is large lungs.

If in this same part of the algorithm, the FRC/TLC or RV/TLC is > ULN or p95 hyperinflation is confirmed.

Hyperinflation may occur with TLC, FRC and RV, or only with FRC or only with RV; in the former situation, increased TLC indicates loss of elastic retraction, so it is probably due to emphysema; whereas, in the latter situation, increased FRC or RV without increased TLC may be observed in chronic bronchitis or asthma, indicating the presence of air trapping.

CONCLUSIONS

BP represents an invaluable diagnostic tool in the classification of ventilatory disorders. In light of the updates

Table 8: Grading of body plethysmography.

Grading system for a lung volume test using BP			
Grade	**Number of FRC measurements**	**Number of SVC measurements**	**FRC repeatability**
A	≥ 3 Acceptables	≥ 3 Acceptables	Within 5%
B	≥ 2 Acceptables	≥ 2 Acceptables	Within 5%
C	≥ 2 Acceptables	≥ 2 Acceptables	Within 10%
D	1 Acceptable and ≥ 1 usable	1 Acceptable and ≥ 1 usable	Within 10%
E	1 Acceptable and 0 usable	1 Acceptable and 0 usable	NA
U	0 Acceptable and ≥ 1 usable	0 Acceptable and ≥ 1 usable	Within 10%
F	0 Acceptable 0 usable		

FRC = *functional residual capacity*. NA = not applicable. SVC = *slow vital capacity*

Table 9: Elements that the body plethysmography report must contain.

Report content
Full name of the patient
Birthdate
Identification number
Anthropometric parameters (age, sex, weight and height)
Reference equation
Absolute values of lung volumes and capacities in liters, with two decimal places and under ambient pressure and body temperature conditions (BTPS)
Absolute values, percentages of predicted; and LLN and Z-score (ERS/ATS 2021) of the three acceptable ITGV-VC maneuvers, including FRC_{pleth}, IC, ERV, VC, TLC and RV
The average value of three acceptable maneuvers for FRC_{pleth}, IC, ERV and TLC (calculation: IC + FRC)
The highest value of VC
RV = average TLC minus the highest value of VC
Spirogram graphs showing that the maneuver was performed in a linked manner and ITGV maneuvers
Optional: Last calibration date and environmental data

ATS = *American Thoracic Society*. BTPS = *body temperature, pressure, saturated* ERS = *European Respiratory Society*. ERV = *expiratory reserve volume*. FRC_{pleth} = *functional residual capacity* . IC = *inspiratory capacity*. ITGV = *intrathoracic gas volume* . LLN = lower limit of normality. RV = residual volume. TLC = *total lung capacity* . VC = *vital capacity*.

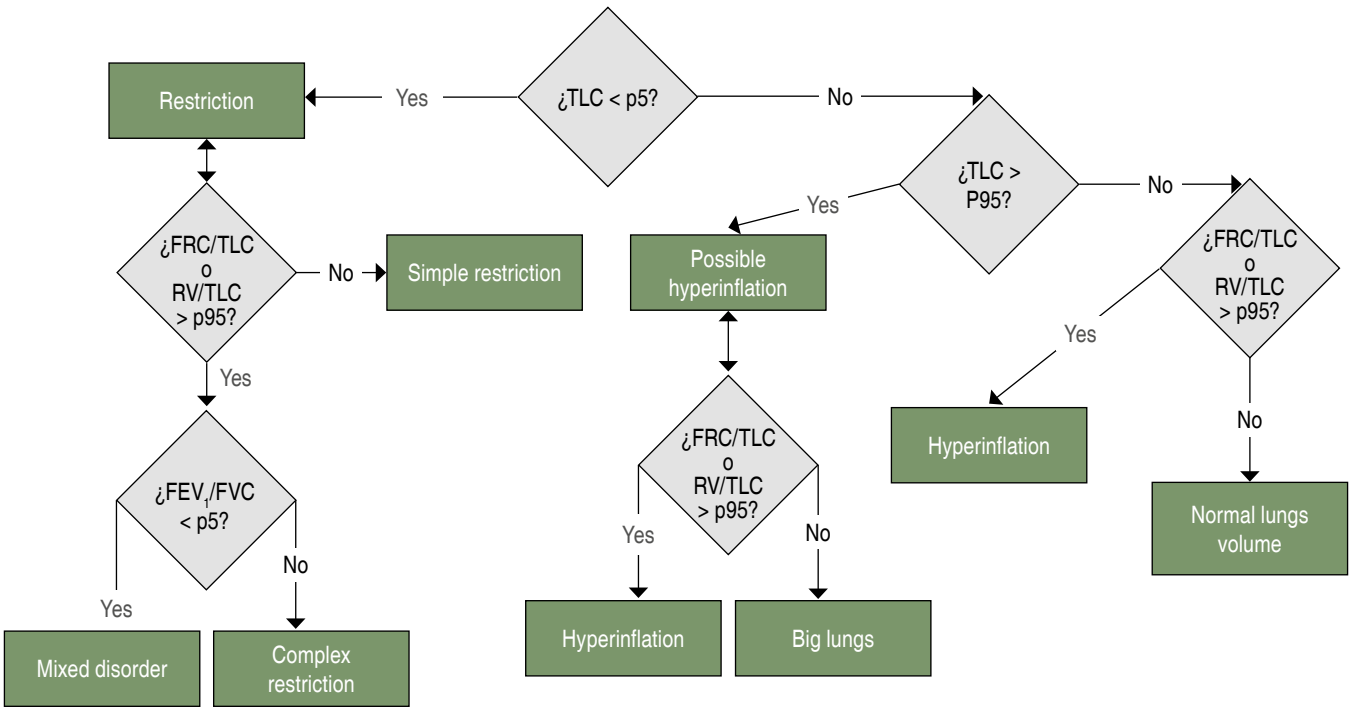

Figure 5: Algorithm for interpreting lung volumes.
FEV_1 = forced expiratory volume in the first second. FRC = functional residual capacity. FVC = forced vital capacity. p5 = 5th percentile. p95 = 95th percentile. RV = residual volume. TLC = total lung capacity.

in the technique of performance and interpretation, it is imperative that health professionals adapt and apply these innovations, in order to improve the accuracy of the measurements, deepen the understanding of their results and thus facilitate better clinical decision making. We still need to work on a reference equation that better fits the Mexican population.

Supplementary material

Specific resistance of the airway

In fluid mechanics, resistance is defined as the ratio of driving pressure (pressure difference that drives a fluid to move from one point to another) to flow. The higher the pressure required, the greater the resistance. In the respiratory setting, airway resistance (Raw) is the ratio of the pressure difference between the alveoli and the mouth (the latter is constant during free breathing) to the flow rate determined at the mouth.[5] Body plethysmography (BP) assesses airway resistance, but the primary measure recorded is specific airway resistance (sRaw), which, despite its name, is not a direct measure of resistance.[17]

Since alveolar pressure cannot be measured during free breathing, a surrogate marker of airflow resistance is used, relating flow rate to displacement volume or cabin pressure, both of which are directly measurable. This displacement volume reflects the changes in thoracic volume required to create driving pressure in the lung.[18]

The relationship between displacement volume or, equivalently, cabin pressure and flow rate, expressed in appropriate units is called «specific airway resistance, sRaw». Plotting flow vertically against displacement volume horizontally yields «closed curves» indicating sRaw *(Figure 6B)*. In healthy subjects, these curves are nearly straight, whereas in patients with respiratory pathologies they show patterns useful for differential diagnosis *(Figure 6)*. A flatter curve suggests higher sRaw. It is important to differentiate these curves as «specific resistance loops» and not simply «resistance loops», as this distinction affects data interpretation.[1,19]

The following example illustrates how sRaw is affected by lung volume and airway resistance. Consider two patients with identical lung volumes and resistances, both generating the same alveolar pressure and airflow, resulting in identical breathing loops or sRaw. However, if one lung is twice as large as the other, this patient will require twice the displacement volume to generate the same pressure, doubling his sRaw despite having the same resistance. Similarly, if the volumes are equal but the resistance of one is twice that of the other, the patient with the greater resistance

will require twice the change in alveolar pressure, resulting in a shallower loop and double the sRaw. This demonstrates that sRaw varies with lung volume and airway resistance, and that breathing loops can be similar with different resistances if the volume and resistance ratios are inverse.[1]

PREPARING THE EQUIPMENT BEFORE THE TEST

Quality control and calibration[14]

1. Daily calibration check of the body plethysmograph.
   a. Perform calibration check of the mouth pressure transducer on a daily basis.
   b. The plethysmography signal is calibrated daily using a volume signal with magnitude and frequency similar to those that will be recorded with patients.
   c. During calibration check and use, avoid rapid changes in room pressure and vibrations (examples: abrupt door closures, changes in room air currents from HVAC, and high-efficiency particulate air filter systems). Strong winds and direct sunlight may also affect measurements.[7]
   d. Ensure that the mouth occlusion shutter offers minimal resistance to opening and closing (i.e., does not jam).
   e. Follow the manufacturer's instructions for setting up the equipment.
   f. Perform monthly precision validation of the determined volume, with a lung or container model with a compression-decompression frequency of 0.5 to 1 Hz. Plethysmograph precision must be maintained at ± 50 mL or 3% of the volume of the model used (whichever is greater) based on the average of five determinations.
   g. It is convenient to have healthy biological controls, capable of achieving maneuvers with a coefficient of variation < 5% for FRC and TLC; who are tested monthly; in the event of software updates or suspicions of equipment error, measurements outside of two standard deviations of the usual merit exhaustive verification of the equipment in search of errors and corrective maintenance.
   h. Verify that the acceptability criteria are within acceptable limits (according to the manufacturer's instructions):
      h.1. QPB = quality factor (coefficient of variation) of cabin pressure.
      h.2. Tau verification (time constant (Tau) = half-life in seconds).
      h.3. KPB = calibration factor.

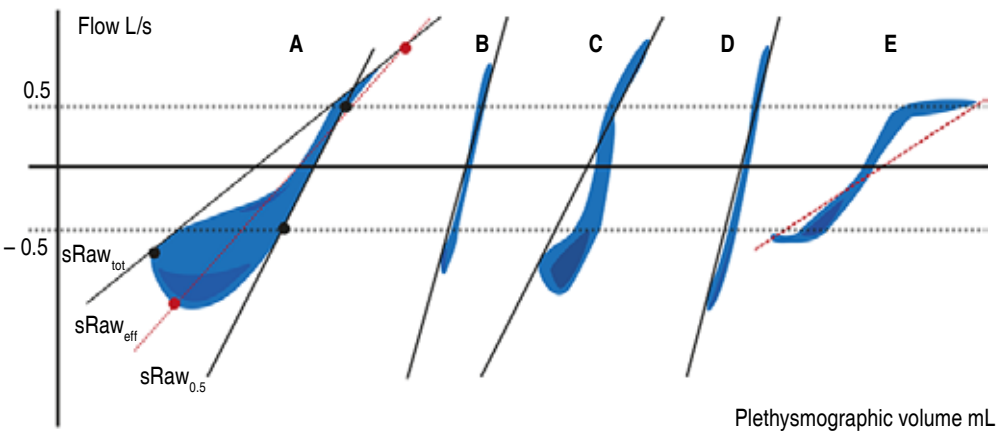

Figure 6: Plethysmographic flow-volume graph. **A)** Resistance curve in a subject with chronic obstruction where large volume changes are primarily generated during inspiration for small flow changes. The proposed calculations of the slope that best describes the curve are presented.
- sRawtot is determined as the slope of a straight line drawn between the maximum points of inspiratory and expiratory volume change. It represents a maximum value and is sensitive to changes in the small airway; however, it has a wide variability.
- sRaweff is the specific effective resistance that corresponds to a dimensional analysis of the curve, from which a representative slope is also reported. Its measurement is less variable, it is considered to be composed mainly of resistance of the central airways.
- sRaw0.5 consists of drawing a line between the points of +0.5 L/s and –0.5 L/s. Generally this portion of the graph is more linear so it has less variability and is also considered representative of the central airway. Its flow adjustment allows to eliminate artificially high values due to the presence of turbulence.

B) Normal resistance curve, healthy subjects require small volume changes to generate inspiratory and expiratory flow during tidal volume breathing, sRaw values are very similar in the three calculations. **C)** Representative curve of patients with acute obstruction. **D)** Resistance in a patient with restrictive disease, note how high flows are generated for small volume changes. **E)** sRaw of a patient with tracheal stenosis, large volume changes are required to generate low flows both in inspiration and expiration.
Adapted from: Guerrero-Zúñiga S et al. Body plethysmography: recommendations and procedure. Neumol Cir Thorax. 2019;78(Suppl 2):S113-S123.

BP PROCEDURE

Anthropometric measurements

1. Record weight in kilograms, to the nearest 0.5 kg; measure height with the individual barefoot, fully erect, heels together, and facing forward.
2. For patients who are unable to stand or who have a rib cage deformity, arm span measurement can be used to estimate standing height: measure the distance between the tips of the middle fingers (arm span).
3. For Caucasian men: height = arm span/1.03; for African-American men: height = arm span/1.06; and for women height = arm span/1.01.
4. In the case of patients who cannot be measured standing and also do not have an arm, the average span can be measured as the distance between the tip of the middle finger and the prominent cervical vertebra and multiplied by 2. And if a patient presents with significant deformity of body posture in whom it is not possible to measure the span in a linear manner, the composite span (segments) must be calculated.

BP REPORT

Selection of maneuvers

If at least two acceptable and repeatable FRC maneuvers are not obtained, all maneuvers with acceptable or usable FRC and that meet repeatability of at least 10% should be used for the calculation. If three or more maneuvers are considered (e.g., one acceptable and two usable) and FRC repeatability of at least 10% is not met, the maneuver with the largest difference in FRC from the mean FRC should be discarded along with its associated spirometry. FRC repeatability is then recalculated and additional maneuvers are similarly discarded until repeatability of at least 10% is met. The coexistence of two acceptable FRC maneuvers but not repeatable by at least 10% is rare; if it occurs, attempt to obtain another maneuver to determine which is the outlier.

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

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NCT
Neumología y Cirugía de Tórax
Vol. 83 - No. 2 / April-June 2024

Clinical case
doi: 10.35366/119286

Neuroendocrine Cell Hyperplasia of Infancy: an underrecognized disorder. Case report

Hiperplasia de células neuroendocrinas de la infancia: un trastorno poco reconocido. Reporte de un caso

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ABSTRACT. Neuroendocrine cell hyperplasia of infancy is a type of interstitial and diffuse lung disease in children. We present the clinical case of a male infant, who began showing symptoms at three months of age characterized by poor weight gain, tachypnea and wheezing; history of a hospitalization with diagnosis of bronchiolitis, but did not show clinical improvement despite treatment with systemic glucocorticoids and bronchodilators. A study approach was initiated with chest tomography, revealing ground-glass opacities primarily affecting segment 3 of the right lung, as well as the middle lobe and lingular region, concluding diagnosis of childhood neuroendocrine cell hyperplasia based on the clinical and tomographic findings. Interstitial lung disease in infants is often underrecognized, as its symptoms can easily be mistaken for other acute lung pathologies. Therefore, it is important to maintain a high index of suspicion to enable timely diagnosis.

Keywords: neuroendocrine cell hyperplasia, childhood interstitial lung disease, tachypnea.

RESUMEN. La hiperplasia de células neuroendocrinas de la infancia es una forma de enfermedad pulmonar intersticial y difusa infantil. Presentamos el caso clínico de un lactante masculino que inició sus síntomas a los tres meses de edad caracterizado por pobre ganancia pondoestatural, taquipnea y sibilancias con antecedente de una hospitalización con diagnóstico de bronquiolitis, sin presentar mejoría clínica a pesar de tratamiento con glucocorticoides sistémicos y broncodilatadores. Se inició abordaje de estudio con tomografía de tórax que evidenció vidrio deslustrado que afecta principalmente segmento 3 de pulmón derecho, así como lóbulo medio y región lingular, concluyendo diagnóstico de hiperplasia de células neuroendocrinas de la infancia con base a la clínica y los hallazgos tomográficos. La enfermedad pulmonar intersticial en lactantes es poco reconocida, ya que sus síntomas suelen confundirse fácilmente con otras patologías pulmonares agudas. Por lo tanto, es fundamental mantener un alto índice de sospecha para poder realizar diagnósticos oportunos.

Palabras clave: hiperplasia de células neuroendocrinas, enfermedad pulmonar intersticial infantil, taquipnea.

Abbreviations:

chILD = Childhood Interstitial Lung Disease.
chILDRN = Children's Interstitial and Diffuse Lung Disease Research Network.
NEHI = Neuroendocrine Cell Hyperplasia of Infancy.

INTRODUCTION

Neuroendocrine cells hyperplasia of infancy (NEHI), formerly known as persistent childhood tachypnoea, is a type of childhood interstitial lung disease (chILD). This condition is characterized by clinical signs and specific

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Received: VII-25-2024; accepted: X-23-2024.

How to cite: Piedragil-Segura A, Hernández-Ruiz J. Neuroendocrine Cell Hyperplasia of Infancy: an underrecognized disorder. Case report. Neumol Cir Torax. 2024; 83 (2):166-170. https://dx.doi.org/10.35366/119286

tomographic findings. ChILD refers to a disorder that affects the lung interstitium and distal airways, resulting in an abnormal gas exchange. These pathologies are difficult to diagnose; and children with chILD often have tachypnoea, hypoxia and crackling respiratory sounds.[1-3]

The classification scheme proposed by Children's Interstitial and Diffuse Lung Disease Research Network (chILDRN) is organized into two categories: «Specific interstitial lung diseases in children» and «Non-specific interstitial lung diseases in children» *(Table 1)*.[1,3,4]

Epidemiological data on childhood neuroendocrine cells hyperplasia are limited and the exact incidence and prevalence of this disease is unknown. However, it is considered a rare condition, probably due to the low recognition of patients with NEHI. The chILDRN established a prospective registry that included the participation of 25 centers in the United States, with a total of 683 patients diagnosed with different childhood lung diseases. Of these, 155 (23%) were diagnosed with NEHI.[5] At Vanderbilt Children's Hospital, 93 chILD cases were retrospectively

Table 1: Childhood interstitial lung disease classification.

Specific interstitial lung diseases in children	Non-specific interstitial lung diseases in children
A. Diffuse developmental disorders	**A. Normal host disease**
1. Acinar dyskinesia 2. Congenital alveolar dysplasia 3. Alveolocapillary dysplasia with poor alignment of the pulmonary veins	1. Infectious and post-infectious processes 2. Environmental agent-related disorders: • Hypersensitivity pneumonia • Toxic inhalation 3. Aspiration syndrome 4. Eosinophilic pneumonia
B. Growth abnormalities	**B. Systematic diseases with pulmonary involvement**
1. Pulmonary hypoplasia 2. Chronic neonatal lung disease: • Bronchopulmonary Dysplasia • Acquired chronic lung disease in term newborn 3. Lung structural changes related to chromosomal abnormalities: • Trisomy 2 • Others 4. Associated with congenital heart disease in chromosomally normal children	1. Immune-related diseases 2. Deposit Diseases 3. Sarcoidosis 4. Langerhans cell histiocytosis 5. Neoplastic infiltrates
C. Specific conditions of undefined etiology	**C. Diseases of the immunocompromised host**
1. Pulmonary interstitial glycogenosis 2. Childhood neuroendocrine cell hyperplasia	1. Opportunistic infections 2. Related to therapeutic intervention 3. Related to transplantation and rejection 4. Diffuse alveolar damage of unknown etiology
D. Disease due to defects in surfactant function	**D. Diseases that mimic interstitial diseases**
1. Surfactant Protein B mutations: dominant histological pattern, pulmonary alveolar proteinosis, and variants 2. Surfactant protein C mutations: dominant histological pattern, chronic pneumonitis of childhood; also desquamative and nonspecific interstitial pneumonia 3. ABCA3 mutations: dominant histological pattern, pulmonary alveolar proteinosis and variants. Also chronic pneumonitis of childhood, desquamative interstitial pneumonia, nonspecific interstitial pneumonia 4. Histology compatible with surfactant defects, but without recognized genetic etiology: • Alveolar pulmonary proteinosis • Chronic pneumonitis of childhood • Desquamative interstitial pneumonitis • Nonspecific interstitial pneumonia	1. Arterial hypertensive vascular disease 2. Congestive vascular disease including veno-occlusive disease 3. Congestive changes related to cardiac dysfunction 4. Lymphatic disorders

Adapted from: Kurland G, Deterding RR, *et al.* American Thoracic Society Committee on Childhood Interstitial Lung Disease (chILD) and the chILD Research Network. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy.

reviewed between 1994 and 2011, identifying eight cases of NEHI, including five that had not been previously recognized prior to this review.[6]

Deterding et al., conducted a retrospective review of clinical cases, which included 15 children with signs and symptoms of chILD without an identified etiology. Morphometric analysis suggested that these children could constitute a different group of pediatric patients, characterized by the absence of known lung diseases, along with clinical sings and symptoms of chILD and idiopathic neuroendocrine cells hyperplasia of infancy. Clinically, the mean age of onset of symptoms was 3.8 months (range 0 to 11 months) After an average follow up of five years, no deaths were reported and the patients showed improvement.[2]

NEHI's cause is unknown; however, clinical studies have suggested a possible genetic influence, as familial patterns have been observed in some cases and the presence of a heterozygous mutation in the NKX2-1 gene.[7]

A clinical case of NEHI is described focusing on the clinical presentation, the diagnostic process and the importance of early suspicion for timely diagnosis.

CASE PRESENTATION

This is a year and eight months male breastfeeding patient, born at term with a weight of 3,200 g and height of 51 cm. In his hereditary family history stands out a sister with asthma diagnosis. In his pathological personal history there is an evaluation at three months of age by a pediatrician because of poor weight gain, tachypnoea and wheezing, managed with salbutamol aerosol 100 µg every eight hours, with partial improvement; at four months of age he was again assessed because of a picture characterized by wheezing and absence of weight gain, without a treatment modification or establishment of a definitive diagnosis. Hospitalized at five months of age with bronchiolitis diagnosis without taking a respiratory pathogen panel with a normal chest X-Ray, he received hospital treatment with methylprednisolone 2 mg/kg/day, inhaled salbutamol 0.15 mg/kg/day every eight hours and supplemental oxygen one liter per minute, discharged with treatment based on salbutamol with ipratropium bromide aerosol 200 µg/40 mg every eight hours and fluticasone aerosol 100 µg every 12 hours with the use of aerochamber.

Due to the recurrence of the respiratory events, the patient was assessed by the Pediatric Pneumology area without a definitive diagnosis being concluded, he received treatment with fluticasone 100 µg every 12 hour. Despite this, there was no clinical improvement, persisting with poor height-weight gain, hypoxemia and tachypnoea; he was again assessed by Pediatric Pneumology, suspecting interstitial lung disease of the infant, so a chest tomography was performed that showed ground glass that mainly affects segment 3 of the right lung, as well as the middle lobe and lingular region, associated to air trapping data. The patient was assessed by Pediatric Cardiology, which diagnosed pulmonary hypertension and ruled out structural defects. Based on these findings it was decided to begin management with continuous supplemental oxygen at one liter per minute, budesonide/formoterol aerosol 80 µg/4.5 µg two shots every 12 hours, prednisolone 1 mg/kg/day, salbutamol and ipratropium bromide aerosol 200 µg/40 µg every six hours, sildenafil 1.5 mg/kg/day and azithromycin 8 mg/kg/dosis every other day. However, despite the treatment the patient persisted with tachypnoea, wheezing and hypoxemia, so he was referred to our National Medical Center *20 de Noviembre* for a complementary diagnosis. He was assessed by the Pediatric Pneumology Service at one year and two months of age, it was corroborated the presence of hypoxemia of up to 79%, tachycardia and tachypnoea upon removal of supplementary oxygen, in the physical examination with presence of *pectus excavatum* and generalized velcro rales. The approach began ruling out more frequent pathologies such as cystic fibrosis by determining chlorine in sweat, the results were negative (7 y 0 mmol/L), as well as immunodeficiencies with an immunoglobulin profile within the normal limits. Based on the high suspicion of interstitial lung disease of infancy, a chest tomography was performed *(Figure 1)*, which showed air trapping data and ground glass in the middle lobe and lingular region. The echocardiogram showed mild hypoplasia of the transverse aorta, pulmonary systolic pressure 34 mmHg, mean pulmonary pressure 23 mmHg. Based on the clinical data, fulfilling nine points of the NEHI Clinical Score, 3 tomographic findings of butterfly wings and the poor response to systemic steroid treatment, a diagnosis of neuroendocrine cell hyperplasia is concluded.

Within the management, inhaled steroids were initiated at medium doses and a gradual reduction of systemic steroids until their complete suspension, as well as the continuous use of supplemental oxygen at two liters per minute. In the follow-up consultations, daytime suspension of supplemental oxygen was achieved, maintaining saturations of 94-95%. During sleep, supplemental oxygen use by nasal prongs was maintained at 0.25 liters per minute with pulse oximetries of 94-96%. A decrease in dyspnoea events was observed, and no new episodes of wheezing requiring hospital admission have occurred.

DISCUSSION

ChILD manifests itself with symptoms such as tachypnea, crackling, hypoxemia and/or diffuse infiltrates, which should alert the search for more specific interstitial lung disorders. ChILD is difficult to define due to the diversity of diseases

Neumol Cir Torax. 2024; 83 (2): 166-170

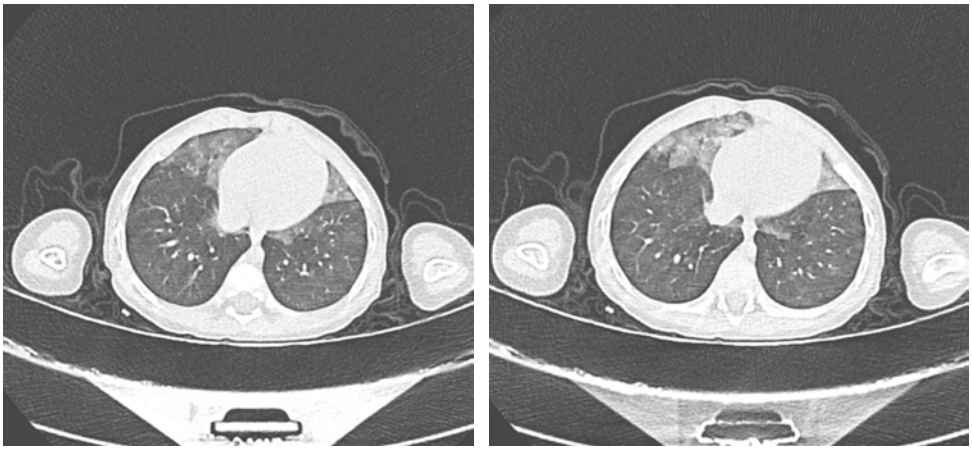

Figure 1:

Simple computed tomography of the chest: ground glass in the middle lobe and lingular region.

it encompasses, forming a large and heterogeneous group, mostly made up of rare disorders. These disorders are associated with considerable morbidity and mortality, presenting significant challenges in both diagnosis and treatment.[8] The American Thoracic Society suggests that, after ruling out common diseases that can cause diffuse lung disease (cysticfibrosis, gastroesophageal reflux and recurrent aspiration, structural airway abnormalities, lung infection, congenital heart disease, congenital or acquired immunodeficiency, primary ciliary dyskinesia), a patient be considered to have «chILD syndrome» if they meet at least three of the following four criteria:[1]

1. Respiratory symptoms (cough, shortness of breath, or exercise intolerance).[1]
2. Respiratory signs (resting tachypnea, auscultation rattles, pulling, acropaquias, growth retardation or respiratory failure).[1]
3. Hypoxemia.[1]
4. Diffuse abnormalities on a chest X-Ray or chest CT scan.[1]

For patients with chILD syndrome it is recommended to perform a series of diagnostic tests to accurately determine the diagnosis of the child. Regarding NEHI, an under-recognized disorder, it is crucial to consider the Clinical Score, which helps identify patients with clinical characteristics compatible with NEHI. This score consists of 10 elements: 1) onset of symptoms before 12 months of age, 2) growth retardation, 3) absence of acropachy, 4) absence of cough in a state of well-being, 5) absence of wheezing in a state of well-being, 6) abnormal chest wall (chest in a barrel or pectus excavatum), 7) crackles, 8) hypoxemia, 9) tachypnoea and 10) retractions. Each element present adds 1 point, and the total score is the sum of these values, with a maximum of 10 points. A score of 7 or higher is considered indicative of NEHI.[3]

Pulmonary function tests in children reveal varying degrees of airflow obstruction. Typical findings on high-resolution computed tomography (HRCT) include ground glass opacities, primarily in the middle lobe, lingula, and/or perihilar regions, along with air trapping showing a mosaic pattern. The diagnosis of INHN can be established clinically by HRCT within an appropriate clinical context. Occasionally a lung biopsy may be necessary, where histopathologic findings of NEHI show an increase in the percentage of neuroendocrine cells in the airways, which can be better identified by bombesin immunostaining.[3,9]

Children with HNHI treated with bronchodilators and glucocorticoids have not experienced improvement in their symptoms, unlike those who might have asthma. Dervaux et al., in a study with a cohort of 54 patients to analyze their long-term evolution, reported that corticosteroids were widely prescribed at the time of diagnosis, but no evident respiratory or nutritional improvement was observed during follow-up. Their results indicate that NEHI shows overall positive, although uneven, improvement over time.[2,10]

In the particular case of our patient, he presented the clinical data to suspect NEHI supported by the main tomographic findings found and no response to systemic steroids, showing clinical improvement over time and only with supportive treatment.

CONCLUSIONS

NEHI is a disease with as yet unknown incidence and prevalence, categorized as a rare disease; however, this could be underestimated due to the low level of recognition of the disease. The diagnosis of NEHI is based on clinical and tomographic findings, highlighting the importance of defining specific clinical characteristics that help physicians in their identification. This would not only facilitate a more accurate diagnosis, but also open new areas for future research, seeking to improve understanding and

management of this under-recognized and potentially under-diagnosed condition.

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

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NCT
Neumología y Cirugía de Tórax
Vol. 83 - No. 2 / April-June 2024

Clinical case
doi: 10.35366/119287

Disseminated coccidioidomycosis with atypical presentation in an immunocompetent patient in Chiapas: clinical case

Coccidioidomicosis diseminada con presentación atípica en paciente inmunocompetente en Chiapas: caso clínico

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ABSTRACT. Coccidioidomycosis is an underdiagnosed infectious disease worldwide, caused by fungi from the *Coccidioides spp*. family. These fungi are typically found in alkaline, sandy soils of warm and arid regions of the western hemisphere, such as northern Mexico. However, due to migratory displacement, cases of coccidioidomycosis have been documented in non-endemic areas. The primary site of involvement is the lungs; pleural effusion is rare. Disseminated coccidioidomycosis affects 1% of infected patients and is associated with more severe outcomes. We present the case of a 28-year-old male from Chiapas, who has a history of residing in Baja California, without immunocompromising conditions, referred to our unit with atypical disseminated coccidioidomycosis characterized by pulmonary consolidations, lymphadenopathy, subcutaneous abscesses, and pleural effusion.

Keywords: disseminated coccidioidomycosis, coccidioidomycosis in immunocompetent, coccidioidomycosis in non-prevalence region.

RESUMEN. La coccidioidomicosis es una enfermedad infecciosa infradiagnosticada a nivel mundial, causada por hongos de la familia *Coccidioides spp*; habitualmente se encuentran en suelos alcalinos y arenosos de regiones cálidas y áridas del hemisferio occidental, como en el norte de México; sin embargo, debido al desplazamiento migratorio se han documentado casos de coccidioidomicosis en regiones no endémicas. El principal sitio de afección son los pulmones; el derrame pleural es poco frecuente. La coccidioidomicosis diseminada afecta al 1% de los pacientes infectados y está asociada con resultados más graves. Se presenta el caso de un masculino de 28 años originario de Chiapas con historia de haber radicado en Baja California, sin inmunocompromiso, referido a nuestra unidad con coccidioidomicosis diseminada de evolución atípica asociada, caracterizada por consolidaciones pulmonares, adenomegalias, abscesos subcutáneos y derrame pleural.

Palabras clave: coccidioidomicosis diseminada, coccidioidomicosis en inmunocompetentes, coccidioidomicosis en regiones no prevalentes.

INTRODUCTION

Coccidioidomycosis (CM) is an infection caused by dimorphic fungi of the family of *Coccidioides spp, first* described by Alejandro Posadas in 1892. They are usually found in alkaline and sandy soils of warm and arid regions of the Western Hemisphere. They thrive in areas with very hot summers and winters without severe temperature drops and, in addition, with low annual rainfall.[1] It is considered a under-diagnosed disease in desert regions of the New World due to its non-specific symptoms, similar clinical findings with other infectious and non infectious diseases, lack of reliable and affordable laboratory tests that allow a timely diagnosis and, in addition, limited existence of updated epidemiological information in Latin America.[2]

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Received: X-10-2024; accepted: XI-06-2024.

How to cite: Jiménez-Villanueva EG, Martínez-Pérez CJ, Santiago-Martínez LA, Escobar-Díaz PS. Disseminated coccidioidomycosis with atypical presentation in an immunocompetent patient in Chiapas: clinical case. Neumol Cir Torax. 2024; 83 (2):171-174. https://dx.doi.org/10.35366/119287

Worldwide endemic areas have been stablished in Mexico, Central America (Guatemala, Honduras) and South America (Argentina, Bolivia, Brazil, Colombia, Paraguay and Venezuela), where genetic studies have shown that the predominant species is *C. posadasii*.[3] In United States, by 2022, according to the Centers for Diseases Control and Prevention (CDC), a total of 17,612 cases were recorded; between 10,000 and 20,000 cases of coccidioidomycosis are reported annually, mainly in Arizona and California, with an annual average of 200 deaths associated with coccidioidomycosis from 1999 to 2021.[4]

Coccidioidomycosis is one of the most prevalente systemic mycoses in Mexico; until 1994, approximately 1,500 cases were reported annually, with the states of Nuevo León, Tamaulipas, Chihuahua, Baja California and Sonora reporting the highest number of cases. As of 1995, coccidioidomycosis was removed from the national epidemiological registry for reportable diseases, therefore the current clinical burden of the disease in Mexico is unknown.[5]

The 60% of infections are asymptomatic, 40% have clinical manifestations similar to the common cold or pneumonia, and, only 1% develop disseminated disease, which can affect any area of the body. Disseminated coccidioidomycosis can be in a single site or in multiple sites, cases of osteomyelitis in pelvic bones, synovitis in knee joint, mediastinal lymphadenopathy, peritonitis and meningitis, infection of soft tissues, intramuscular infection and subcutaneous abscesses have been described.[6] The ethnicity (African, Asian and Hispanic ancestry), immunocompromised states (cancer, organ transplant, corticosteroid therapy, chemotherapy, HIV infection) and some genetic alterations are risk factors for disseminated coccidioidomycosis.[7]

PRESENTATION OF THE CASE

28 year-old male patient, originally from Frontera Comalapa, Chiapas; farmer, without chronic degenerative diseases. History of residence in Tijuana, Baja California, for a year for work reasons, where he worked in an electronics factory.

Current condition started four months prior to hospitalization, with temperature rises, preceded by shivers and followed by diaphoresis, without schedule predominance; occasional dry cough, mMRC 3 dyspnea, nausea and unintentional loss of approximately 15 kg. One month later he reports growth of the left supraclavicular lymph node, in addition, increased volume in the right costal and left dorsal region. External study protocol: chest X-ray with identification of left pleural effusion, left basal consolidation and cavitated node in the same region are identified, so left thoracentesis is performed with the extraction of 1,000 mL liquid and bronchoscopy with bronchial biopsy that reports chronic non-specific inflammation. Diagnostic definition is not achieved so multiple antimicrobial schemes based on clindamycin, cephalosporins and aminopenicillin are initiated, without showing clinical improvement. They decide to start treatment for tuberculosis in intensive phase with four drugs, without favorable clinical evolution, so they make reference to our institution, where we decided to suspend antibiotics and tuberculosis treatment.

External laboratory/imaging studies. Bronchial mucosa biopsy report by fibrobronchoscopy: Bronchial mucosa biopsy report by fibrobronchoscopy: respiratory mucosa with chronic non-specific inflammation; cytopathological broncho alveolar lavage (BAL) with moderate inflammatory reaction, with neutrophilic and lymphocytic characteristics, in addition to reactive mesothelial cells. BAL culture: positive for *Klebsiella spp*, negative for *Mycobacterium tuberculosis*; cytopathological pleural fluid with moderate inflammatory reaction, neutrophilic and lymphocytic, reactive mesothelial cells; pleural fluid cytochemical: glucose 70 mg/dL, lactic dehydrogenase (DHL) 158 U/L, proteins 6.7 g/dL, leukocytes 15-20 cel/mm^3, lymphocytes 95%, Gram staining: negative, adenosine deaminase (ADA) determination 28 U/L. Rapid test for HIV: non-reactive.

Institutional laboratory tests. Hemoglobin 9.9 g/dL, hematocrit 32, mean corpuscular volume (MCV) 80 fL, mean corpuscular hemoglobin (MCH): 31.4 pg, leukocytes 13,190/mm^3, segmented 85%, platelets 1'158,000/mm^3, procalcitonin < 0.5 ng/mL. Expectoration culture: negative. Gram stain and cotton blue stain of left thoracic subcutaneous abscess drainage fluid: identification of macrosiphonated, branched septate hyphae with no apparent forms of reproduction. Direct potassium hydroxide (KOH) examination of left thoracic subcutaneous abscess drainage, double membrane spherules suggestive of *Coccidioides spp*. are identified. Left thoracic subcutaneous abscess drainage culture: development of *Coccidioides spp*; determination of serum IgG and IgM anticoccidioides antibodies: both positive. Portable chest X-Ray: left pleural effusion. Simple computed axial tomography of the chest: left pleural effusion, cervical and mediastinal nodal conglomerates, as well as areas of posterior and left lateral-basal consolidations *(Figure 1)*. Left cervical nodal biopsy for histopathological analysis with identification of giant cells and spherules with endospores inside *(Figure 2)*.

Therefore, it was decided to start treatment with amphotericin B deoxycholate in the intensive phase; with clinical improvement and without eventualities, thus determining hospital discharge. However, two weeks later, the patient presents again with temperature rise, in addition to an increase in volume at the proximal level of the right forearm accompanied by an increase in local temperature and mild erythema. It was decided

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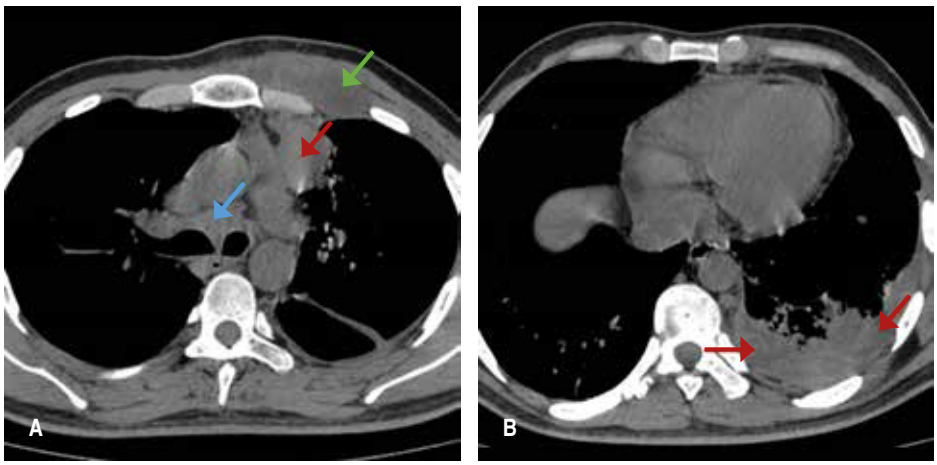

Figure 1:

Simple computed axial tomography of the chest. **A)** Mediastinal window, axial section: left lung consolidation; heterogeneous image suggestive of collection with soft tissue involvement (green arrow) without conditioning erosion of bone structures; mediastinal adenomegalies (blue arrow). **B)** Mediastinal window, axial section: in the left pleural space, pleural effusion is identified (red arrows) that conditions passive atelectasis.

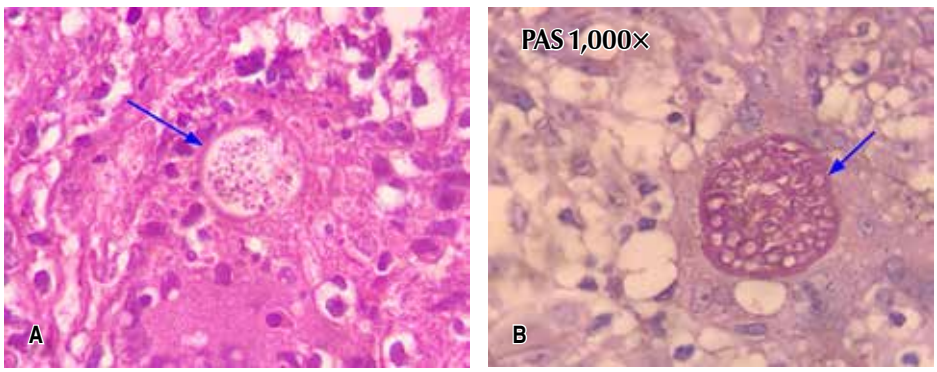

Figure 2:

Histological sections of lung abscess biopsy. Histopathological study of lung abscess: **A)** Hematoxylin and eosin staining: giant cells and spherules with thick walls of 50 µm in diameter are visualized. **B)** Periodic acid Schiff (PAS) staining: endospores are visualized within spherules.

to readmit him and start treatment with liposomal amphotericin B at a dose of 4 mg/kg every 24 hours. Patient with clinical improvement, without temperature increase and with decreased volume in injury, so hospital discharge was decided, with maintenance treatment with itraconazole for follow-up in the Outpatient Clinic area. One year after treatment, the report of IgM anticoccidioides antibodies is negative, so treatment suspension and definitive discharge from the service are decided.

DISCUSSION

Coccidioides spp. are fungi that commonly inhabit arid soils in the border states of the southern United States and northern Mexico, where soil and climate conditions favor the survival of this microorganism. The incidence of coccidioidomycosis has increased significantly in the last two decades in non-endemic regions, most of these cases are imported by patients after traveling or being exposed in endemic areas.[8] Travelers and people on the move who visit or transit to endemic regions determine a high risk of exposure to various microorganisms that are not prevalent in their localities of origin. Our patient had a residence history for one year in Tijuana, Baja California, due to the search for better working conditions, which constitutes his exposure to a region at high risk of infection by *Coccidioides spp*.

Coccidioidomycosis in its disseminated form is uncommon; however, it occurs regularly in subjects in a state of immunocompromise.[7] Pleural effusion in patients with coccidioidomycosis is detected in approximately 5 to 15% of cases; it is a frequent manifestation in pulmonary forms of the infection and it is very rarely observed in patients with disseminated coccidioidomycosis.[9] Immunocompetent patients may be able to «localize» the infection in the lungs by mounting a vigorous inflammatory response, resulting in increased vascular permeability of the pleura due to pro-inflammatory cytokines, resulting in the formation of pleural effusion. Patients with a disseminated form of the disease are less likely to generate an intense inflammatory response in the lungs, which results in less pleural inflammation and formation of pleural effusion.[10] We consider that in the case of our patient -despite not having identified any immunocompromising factor-, since he was not previously exposed to spores of the fungus

Coccidioides spp., he did not have an immunological memory that could have limited the dissemination of the infectious process.

Sample culture continues to be the gold standard for the diagnosis of coccidioidomycosis, followed by histopathological and cytological analysis; however, in addition to being directly dependent on the quality of the sample, this procedure requires a biosecurity level of the laboratory category 3, which conditions a limited availability in public hospitals in Mexico. Our hospital lacks a microbiology laboratory with this requirement, so the culture was performed in a surrogate manner. The identification of macrosiphonated septate hyphae in patients with coccidioidomycosis is a rare microbiological finding; however, there are isolated reports of this finding in disseminated infections associated with spherules with endospores inside.

CONCLUSIONS

The incidence of coccidioidomycosis has increased in recent times in places of low prevalence in relation to a phenomenon of global population mobility. Coccidioidomycosis is a diagnostic challenge in immunocompetent patients due to atypical presentation in its disseminated form.

Acknowledgements: the authors extend their gratitude to Dr. Ana Karen López Villatoro for her collaboration in the description of the radiological images; and also to Dr. Ángel Medardo Molina Cruz for his collaboration in the histopathological description of the nodal biopsy.
Conflict of interests: the authors declare no conflict of interests.

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NCT
Neumología y Cirugía de Tórax
Vol. 83 - Núm. 2 / April-June 2024

Letter to the editor

doi: 10.35366/119288

Endogamy and medicine

Endogamia y medicina

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How to cite: Torre-Bouscoulet L. Endogamy and medicine. Neumol Cir Torax. 2024; 83 (2):175-176. https://dx.doi.org/10.35366/119288

Once upon a time two young fish were swimming together when suddenly they came across an old fish who greeted them and said, «Good morning, boys How's the water?» The two young fish kept swimming for a while, until eventually one of them looked at the other and asked, «What the hell is the water?»
David Foster Wallace (2005)

The word endogamy refers to marriage or reproduction between people with common ancestry; that is, between subjects of the same family, lineage or geographical, religious or ethnic group. From a social point of view, endogamous behavior is the rejection of the incorporation of members from outside a particular group.[1] The objective, explicit or not, of endogamy is to avoid heterogeneity. Homogeneity is always more comfortable, more secure. The tribes, with their endogamous behaviors, intended to guarantee their functioning, to remain unchanged, to remain homogeneous, in peace. Group cohesion was the most important thing. The union of the group was the great strategy for survival.

The apparent advantages of inbreeding are short-lived and are overshadowed by its enormous disadvantages. Human history abounds with examples of inbreeding groups for the purpose of preserving blood purity. The religious/ideological purpose of maintaining «blood purity» is a biologically very costly undertaking because of the negative consequences on adaptive capacity. Inbred biological systems decrease genetic diversity which limits the evolutionary process. Recessive genetic diseases are a good example of the negative consequences of inbreeding.[2] Inbreeding plays in favor of extinction. On the contrary, exogamy - with its biological, social and cultural heterogeneity - favors survival. Diversity is the best tool for adaptation.[3]

In medical groups, as in tribal societies, endogamic behaviors are frequently practiced, promoting unity among members and rejection of outsiders. By refusing the incorporation of new subjects and therefore of new ideas, the development of that group is limited. During specialist training and in professional life, it is advisable to have an exogamic attitude. The experience of exposing ourselves to the scientific community, whether at congresses or during academic stays, even with the publication of scientific articles, helps us to recognize our strengths and weaknesses and thus fosters an atmosphere of humility and aspiration to achieve more far-reaching objectives. If we limit ourselves to thinking that we are intellectually self-sufficient, we not only foster an atmosphere of arrogance but also of inbreeding and stagnation in development. We cannot - nor should we - believe that we are extraordinarily competent or worthy of inordinate recognition just because members of the tribe think so. We must not be tempted to believe our own inventions. We must expose ourselves to the world order so that we can build a better idea of ourselves, our hospitals, our universities, etc., and with that perspective plan and carry out ambitious projects that will lead us down the path of development. If we continue to wallow in our own mythology, we will be in a mediocre, limiting and, naturally, inbred environment. Self-satisfied pats on the back only lead to more inbreeding.

There are many first-hand examples. When a new element is incorporated there is usually an expectant and defensive attitude in the rest of the group members, without recognizing that this new member will generate a different dynamic (perhaps better or worse) to which the group will have to adapt. That is to say, the new element will represent an adaptive challenge for the group and, with it, its members will have to develop, individually, new adaptive skills to continue being useful to the group. Those who fail to develop these skills will be removed from the group. The question would be: How can we as physicians or medical institutions or societies develop these adaptive skills? Medical knowledge and competencies are not enough to adapt; on the contrary, knowledge can be so rigid that it limits adaptation. The best way to promote these skills is to incorporate external elements that give heterogeneity to the group and to the subjects that form the group. Exogamy is a very important ingredient in the development of subjects, institutions and societies.

An example of exogamy has been experienced by those of us dedicated to respiratory physiology. The exogamous atmosphere of acceptance of external elements and heterogeneity allowed respiratory physiology to be nourished by the talent of pediatric pulmonologists, occupational physicians, sports physicians, anesthesiologists, respiratory therapy graduates, allergists, kinesiologists, epidemiologists, cardiologists, biomedical engineers, physicists, etc., which has allowed us to advance with more solid medical education programs, with a broader scope and with a fabulous opportunity for professional interaction. The same has happened with the Mexican Academy of Sleep Medicine,[4] initially we were four members and the annual meetings had a minimal scope; now, more than a decade later and thanks to inclusive and exogamic practices, more than 500 people register each year for the international congress of the specialty. From these scientific meetings with heterogeneous participants, new ideas, projects and strategies emerge;

in a word, development emerges and is reaffirmed. It is in diversity that opportunities for biological, social, academic, etc. development are found.

Specialists in training must develop critical thinking based on the heterogeneity of intellectual discussions, they must question the status quo and expose themselves to scientific dissent based on evidence, they must move away from the comfort of inbreeding where we are all as good as our imagination allows. Mexico is the country of inbreeding; we are the best in the world at everything and, at the same time, we lose at everything. As the *vox populi* says: «we played like never before and lost like always». We believe our stories; we create social and pseudoscientific mythology that is immediately embraced by a large number of people regardless of their level of schooling. We must encourage our residents, especially pulmonology residents, to break the paradigm of inbreeding and venture to expose themselves to other ways of thinking and doing. Rotations abroad and participation in congresses are a good start to accept and adopt the foreign, the heterogeneous. Those who remain in endogamy are well on the way to scientific extinction.

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