

# ALERTA

Scientific Journal of the National Institute of Health

San Salvador, El Salvador, Central America, July-December 2024



OPEN ACCESS

ISSN: 2617-5274

Volume 7, n.º 2

**Carotid-cavernous fistula with  
secondary ocular hypertension: case report**

[www.alerta.salud.gob.sv](http://www.alerta.salud.gob.sv)

## Authorities

### National Institute of Health, El Salvador

Xochitl Sandoval López, MD.  
Director

Carlos Hernández Ávila, MD.  
Chief of Governance and Management Unit

## Editorial Committee

Nadia Patricia Rodríguez Villalta, MD.  
Editor in Chief and Editor, Narrative section  
National Institute of Health, El Salvador  
✉ [nadia.rodriguez@salud.gob.sv](mailto:nadia.rodriguez@salud.gob.sv)

Edgar Quinteros Martínez, MSc.  
Editor, Original Article section  
National Institute of Health, El Salvador  
✉ [edgar.quinteros@salud.gob.sv](mailto:edgar.quinteros@salud.gob.sv)

Fátima Larisa Chavarría Rodríguez, MD.  
Editor, Case Report section  
National Institute of Health, El Salvador  
✉ [flarisa.chavarria@salud.gob.sv](mailto:flarisa.chavarria@salud.gob.sv)

Cristian Balmore Romero Castro, MD.  
Editor, Case Report section  
National Institute of Health, El Salvador  
✉ [cristian.castro@salud.gob.sv](mailto:cristian.castro@salud.gob.sv)

Susana Peña Martínez, MD.  
San Rafael Hospital, El Salvador  
✉ [susana.pena@salud.gob.sv](mailto:susana.pena@salud.gob.sv)

Carlos Hernández Ávila, MD.  
National Institute of Health, El Salvador  
✉ [carlos.havila@salud.gob.sv](mailto:carlos.havila@salud.gob.sv)

Karina Mendoza Reyes, MD.  
Dr. María Isabel Rodríguez National Women's Hospital (HNM), El Salvador  
✉ [karina.mendoza@salud.gob.sv](mailto:karina.mendoza@salud.gob.sv)

Víctor David Franco, MD.  
Salvadoran Social Security Institute  
✉ [victor.franco@iss.gov.sv](mailto:victor.franco@iss.gov.sv)

Ana María Soriano Hatch, MD.  
Don Bosco University, El Salvador  
✉ [asoriano@udb.edu.sv](mailto:asoriano@udb.edu.sv)

Willy Vladimir González, MD.  
University of El Salvador  
✉ [wily.gonzalez@ues.edu.sv](mailto:wily.gonzalez@ues.edu.sv)

Laura Chavarría de Cocar, MSc.  
Gerardo Barrios University, El Salvador  
✉ [lchavarria@ugb.edu.sv](mailto:lchavarria@ugb.edu.sv)

Emiliano Mariscal, MD.  
National University of Mar Del Plata, Argentina  
✉ [manuelemilianomariscal@gmail.com](mailto:manuelemilianomariscal@gmail.com)

Delmy Virginia Granados Castro, MD.  
Dr. José Antonio Saldaña National Neurology and Family Medicine Hospital, El Salvador  
✉ [delmy.granados@salud.gob.sv](mailto:delmy.granados@salud.gob.sv)

Vicente Artola Arita, MD.  
University Medical Center Groningen, Netherlands  
✉ [v.a.artola.arita@umcg.nl](mailto:v.a.artola.arita@umcg.nl)

Montserrat Amorós Gómez, MD.  
International University of La Rioja, Spain  
✉ [montserrat.amoros@unir.net](mailto:montserrat.amoros@unir.net)

Andrea Vallecampo, MD.  
Evangelical University of El Salvador  
✉ [andrea.vallecampo@uees.edu.sv](mailto:andrea.vallecampo@uees.edu.sv)

Veralís Morán, MPH.  
National Institute of Health, El Salvador  
✉ [everalis.moran@salud.gob.sv](mailto:everalis.moran@salud.gob.sv)

## Style correction

Luis Trejo, BA.  
Promotion of Health Department, Minsal  
✉ [luis.trejo@salud.gob.sv](mailto:luis.trejo@salud.gob.sv)

Hazel García, MD.  
Instituto Nacional de Salud, El Salvador  
✉ [hazel.garcia@salud.gob.sv](mailto:hazel.garcia@salud.gob.sv)

Edwin López Morán, BS.  
Editorial Unit, Regulation Directorate, MINSAL  
✉ [edwin.lmoran@salud.gob.sv](mailto:edwin.lmoran@salud.gob.sv)

Fátima Larisa Chavarría Rodríguez, MD.  
National Institute of Health, El Salvador  
✉ [flarisa.chavarria@salud.gob.sv](mailto:flarisa.chavarria@salud.gob.sv)

Cesar Mateo Gavidia, MD.  
National Institute of Health, El Salvador  
✉ [cesar.gavidia@salud.gob.sv](mailto:cesar.gavidia@salud.gob.sv)

Karina Vanessa Alam, MD.  
National Institute of Health, El Salvador  
✉ [karina.alam@salud.gob.sv](mailto:karina.alam@salud.gob.sv)

## Design and layout

Román Cabezas, MDES.  
National Institute of Health, El Salvador  
✉ [roman.cabezas@salud.gob.sv](mailto:roman.cabezas@salud.gob.sv)

## Cover photo

Adolfo Panameño  
Photographer  
✉ [adolfopanameño@gmail.com](mailto:adolfopanameño@gmail.com)

## Editorial contribution and Spanish proofreading

Edwin López Morán, BS.  
Editorial Unit, Regulation Directorate, MINSAL  
✉ [edwin.lmoran@salud.gob.sv](mailto:edwin.lmoran@salud.gob.sv)

## Editorial support

Editorial assistant 1  
National Institute of Health, El Salvador  
✉ [ralertaasistenteed1@gmail.com](mailto:ralertaasistenteed1@gmail.com)

Editorial assistant 2  
National Institute of Health, El Salvador  
✉ [ralertaasistenteed2@gmail.com](mailto:ralertaasistenteed2@gmail.com)

Hazel García, MD.  
National Institute of Health, El Salvador  
✉ [hazel.garcia@salud.gob.sv](mailto:hazel.garcia@salud.gob.sv)

Fátima Larisa Chavarría Rodríguez, MD.  
Medical-Technical correction  
National Institute of Health, El Salvador  
✉ [flarisa.chavarria@salud.gob.sv](mailto:flarisa.chavarria@salud.gob.sv)

Morena Flores  
Librarian  
National Institute of Health, El Salvador  
✉ [morkikafior@yahoo.com](mailto:morkikafior@yahoo.com)

## Translation and proofreading

Jorge Llanes, MEST.  
English translation  
National Institute of Health, El Salvador  
✉ [jorge.llanes@salud.gob.sv](mailto:jorge.llanes@salud.gob.sv)

Fressia Cerna, MCRP/ID.  
English translation, review of Inclusive topics  
National Institute of Health, El Salvador  
✉ [fressia.cerna@salud.gob.sv](mailto:fressia.cerna@salud.gob.sv)

## Scientific Committee

Alberto Baly Gil, PhD.  
Institute of Tropical Medicine Pedro Kourí (IPK Cuba)  
✉ [baly@ipk.sld.cu](mailto:baly@ipk.sld.cu)

Ana Ruth Escoto Castillo, PhD.  
The National Autonomous University of Mexico  
✉ [ana.escoto.1@gmail.com](mailto:ana.escoto.1@gmail.com)

Alexandre Ribó, PhD.  
Independent consultant, Spain  
✉ [alexandre4rt@gmail.com](mailto:alexandre4rt@gmail.com)

Dina Larios López, PhD.  
Ohio University, The U.S.  
✉ [lopezd@ohio.edu](mailto:lopezd@ohio.edu)

Carlos Alexander Ortega, PhD.  
University of El Salvador  
✉ [carlos.ortega@ues.edu.sv](mailto:carlos.ortega@ues.edu.sv)

Lorena Rivas de Mendoza, MD.  
José Simeón Cañas Central American University, El Salvador  
✉ [lirivas@uca.edu.sv](mailto:lirivas@uca.edu.sv)

Carlos Ortez González, MD.  
San Juan de Dios Hospital, Barcelona, Spain  
✉ [ciortez@sjdhospitalbarcelona.org](mailto:ciortez@sjdhospitalbarcelona.org)

Lorena Suárez Idueta, PhD.  
Oxford University, England  
✉ [suareziduet@gmail.com](mailto:suareziduet@gmail.com)

Carlos Vinicio Corea, PhD.  
University of El Salvador  
✉ [vinicio.coreas@gmail.com](mailto:vinicio.coreas@gmail.com)

Marta Castro Peraza, MD., PhD.  
Institute of Tropical Medicine Pedro Kourí (IPK Cuba)  
✉ [martac@ipk.sld.cu](mailto:martac@ipk.sld.cu)

David Saúl Rodríguez, MD.  
The Executive Secretariat of the Council of Ministers of Health of Central America and Dominican Republic  
✉ [drodriguez@sica.int](mailto:drodriguez@sica.int)

Miriam González, MD.  
St. Jude Children's Research Hospital, The U.S.  
✉ [miriam.gonzalez@stjude.org](mailto:miriam.gonzalez@stjude.org)

Douglas Raimundo Velásquez, PhD.  
University of El Salvador  
✉ [velasquezraim@yahoo.es](mailto:velasquezraim@yahoo.es)

Tania Cuadra Zelaya, PhD.  
University of El Salvador  
✉ [ethelcuadra@hotmail.com](mailto:ethelcuadra@hotmail.com)

Héctor Manuel Ramos, MD.  
Epidemiology Directorate, MINSAL  
✉ [hramos@salud.gob.sv](mailto:hramos@salud.gob.sv)

Marvin J. Núñez, PhD.  
University of El Salvador  
✉ [marvinjnunez@gmail.com](mailto:marvinjnunez@gmail.com)

Noé Rigoberto Rivera, PhD.  
University of El Salvador  
✉ [noerigoberto\\_rivera@yahoo.com.ar](mailto:noerigoberto_rivera@yahoo.com.ar)

Yaxsier de Armas Rodríguez, PhD.  
Institute of Tropical Medicine Pedro Kourí (IPK Cuba)  
✉ [yaxsier@ipk.sld.cu](mailto:yaxsier@ipk.sld.cu)

Jorge Pleitez Navarrete, MD.  
National Institute of Health, El Salvador  
✉ [jorge.pleitez@salud.gob.sv](mailto:jorge.pleitez@salud.gob.sv)

Wilfredo Beltetón, MSc.  
National Institute of Health, El Salvador  
✉ [wilfredo.belteton@salud.gob.sv](mailto:wilfredo.belteton@salud.gob.sv)

Jaime Alejandro González Rodas, MD.  
Catholic University of El Salvador  
✉ [jaime.gonzalez@catolica.edu.sv](mailto:jaime.gonzalez@catolica.edu.sv)

Guillermo Edgardo Barahona Escobar, MD.  
Benjamín Bloom Children's Hospital, El Salvador  
✉ [guille\\_barahona@hotmail.com](mailto:guille_barahona@hotmail.com)

## Exchange and subscription

Nadia Patricia Rodríguez Villalta, MD.  
✉ [nadia.rodriguez@salud.gob.sv](mailto:nadia.rodriguez@salud.gob.sv)

Alerta is the property of the National Institute of Health (INS), a unit of the Ministry of Health of El Salvador. The journal meets the requirements of open access. It is biannually published in January and July. Alerta does not charge authors submission and editorial processing fees for published articles. Access to full text articles is free to readers and accepts articles from different health sciences on an ongoing basis. It uses a double-blind peer review system.

Its mission is to be an instrument for dissemination of eminently scientific health information and contribute to evidence-based decision making. Thus, it contributes to the strengthening of health system and of science, technology and innovation in health.

ISSN electronic number: 2617-5274.

Alerta will not publish any kind of commercial advertisement; the mentioned inputs do not imply a recommendation for their use.

The authors are solely responsible for the opinions expressed in their texts, which do not necessarily reflect the opinion or policy of the institution. Mention of specific companies or products of certain manufacturers does not imply their endorsement or recommendation.

## Journal Indexing Services:

Lamjol: <https://www.lamjol.info/index.php/alerta>  
Latindex: <https://www.latindex.org/latindex/ficha/24860>  
LILACS: <http://portal.revistas.bvs.br/index.php?issn=2617-5274&lang=es>

REDIB: [https://redib.org/recursos/Record/oi\\_revista5103-alerta](https://redib.org/recursos/Record/oi_revista5103-alerta)

Amelica: <http://portal.amelica.org/revista/oa?id=419>  
MIAR: <https://miar.ub.edu/issn/2617-5274>  
BIBLAT: <https://biblat.unam.mx/es/revista/alerta-san-salvador>

Periódica: <https://periodica.dgb.unam.mx/>  
Redalyc

## National Institute of Health, El Salvador

Urb. Lomas de Altamira, Bulevar Altamira and Ave. República del Ecuador n.º 33, San Salvador, El Salvador.

URL: <http://alerta.salud.gob.sv/>  
[ralerta@salud.gob.sv](mailto:ralerta@salud.gob.sv)

## License

Alerta is a journal licensed under creative commons 4.0 CC BY: <https://creativecommons.org/licenses/by/4.0/>. The authors agree to allow copying and distribution by any means as long as the author is acknowledged, without additional restrictions.



Attribution 4.0 International (CC BY 4.0)

# Content/Índice

## Editorial

Fostering dialogue and scientific thought

*Fomentando el diálogo y la reflexión científica*

Xochitl Sandoval López ..... 125

## Case report

Acute Vector-transmitted Chagas in Pediatric Age. A Case Report

*Un caso de Chagas agudo en edad pediátrica*

Reina Iris Chávez Fuentes, Maury Reinaldo Silva Granados, Norma Patricia Lemus Pineda ..... 127

Metachronous liver metastasis from a solid pseudopapillary pancreas tumor

*Metástasis hepática metacrónica de un tumor sólido pseudopapilar de páncreas*

Julio Cesar Alfaro Varela, Mario Francisco Interiano Tobar, Glenda Estefanía Álvarez Salazar ..... 133

Successful treatment of a case of carotid-cavernous fistula with secondary ocular hypertension

*Fístula carótido-cavernosa con hipertensión ocular secundaria: reporte de caso*

Daniel Benjamín Mejía Llanes ..... 138

Patient with cutaneous leishmaniasis treated with miltefosine in an endemic area in Brazil

*Paciente con leishmaniasis cutánea tratada con miltefosina en un área endémica de Brasil*

Juan Jorge Milla Espino ..... 146

## Original article

Effects of Trypanosoma cruzi infection in Balb/c and NIH mouse strains

*Efectos de la infección del Trypanosoma cruzi en ratones de las cepas Balb/c y NIH*

Cindy Betsabé Ramírez Merches, Wendy Maribel Campos Portillo, Ana Miriam González Pérez,

José Guillermo Mejía Valencia ..... 152

Diagnostic concordance of thoracic images for Covid-19 disease

*Concordancia diagnóstica de las imágenes torácicas para enfermedad por Covid-19*

Neftalí Alexander Granados Flores, Marlon Alexander Lazo Ferrufino ..... 161

## Narrative review

Use of myo-inositol and other nutritional supplements for the primary prevention of gestational diabetes mellitus

*Uso de mio-inositol y otros suplementos nutricionales para prevención primaria de la diabetes mellitus gestacional*

Lorena Guadalupe Menjivar Ponce, Andrea Sofía Herrera Orantes, César Gerardo Tario Amaya,

Kenny Lissette Abrego de Rodríguez ..... 169

Hyperbaric oxygentherapy as an adjuvant in the treatment of diabetic foot

*Oxigenoterapia hiperbárica como coadyuvante en el tratamiento del pie diabético*

Fabiola Sofía Ventura Cornejo, Finella Nicole Rottmann, Héctor Elías Menjívar Saravia ..... 177

An update on the detection of tuberculosis through molecular testing

*Actualización en la detección de la tuberculosis a través de pruebas moleculares*

Laura Sofía Sánchez Figueroa, Valeria Alexandra Guillén Muñoz, Juan Diego Pérez Pérez, Pablo Alberto Rodríguez Abrego,

Claudia María Caprile Mata, Katherine Lisseth Cartagena López ..... 184

Importance of childhood nutritional status in their cognitive development

*Importancia del estado nutricional de la niñez en su desarrollo cognitivo*

Luz Olivia Bernal Regalado ..... 191

CORB65 scale as an alternative to assess community-acquired pneumonia in primary health care

*Escala CORB65 para valorar Neumonía Adquirida en la comunidad en el primer nivel de atención*

Hugo Daniel Parrales López ..... 198

Effect of chemotherapy on sexual function in patients with non-metastatic breast cancer

*Efecto de quimioterapia en la función sexual de pacientes con cáncer de mama no metastásico*

Daniela Carolina Iraheta Lara, William Alberto Menjivar Palacios, Vilma Elizabeth Vásquez Castillo, Emilio Jacobo Abullarade Navarrete ..... 205

**Letter to editor**

The prelacrimal approach in maxillary sinus pathologies

*Abordaje prelagrimal en las patologías del seno maxilar*

*Javier Isaac Molina Velásquez*.....212

Food and Nutrition Security, a Vital and Imprecise Concept

*La seguridad alimentaria y nutricional, un concepto vital e impreciso*

*Adolfo Martín Hurtado Díaz, Julio Alberto Carpio Cerna, Ingrid Odette Sanabria Solchaga*.....214

Relevance of sanitary law in health legislation

*La importancia del derecho sanitario en la legislación en salud*

*Javier Isaac Molina Velásquez, Susana Patricia Erazo Salas*.....217

# Fostering dialogue and scientific thought

DOI: 10.5377/alerta.v7i2.17860

Xochitl Sandoval López

National Institute of Health (INS), San Salvador, El Salvador.

Correspondence

✉ [dalia.sandoval@salud.gob.sv](mailto:dalia.sandoval@salud.gob.sv)

ORCID: 0000-0002-0988-1313


In this new issue of *Alerta*, we publish four case reports, two original articles, four narrative reviews that address critical issues for the health of the population, such as Chagas disease, cutaneous leishmaniasis, thoracic imaging in COVID-19 disease, an update on the detection of tuberculosis with molecular diagnostic tests, hyperbaric oxygen therapy for the management of diabetic foot and neurocognitive development in childhood in direct relation to nutritional status; there are also three letters to the editor. It is necessary to highlight the relevance of these letters as a vehicle for exchanging ideas and knowledge in the scientific field. Particularly, we position the subject of the prelacriminal approach in maxillary sinus pathologies, highlighting its impact on clinical practice and the need to explore new perspectives to improve therapeutic results.

We also underlined the importance of understanding and applying health law to health legislation. El Salvador has demonstrated its commitment by establishing laws and regulations in the health sector. This legal framework guarantees the protection of patients' rights and establishes clear guidelines for ethical and effective medical treatment.

On the other hand, we enter the complex world of food safety, a vital but unfortunately often imprecise concept. It is essential to reflect on the implications of this term in today's society, where the quality, quantity, and origin of the food we consume have a direct impact on our health and well-being.

At *Alerta*, we encourage open and constructive dialogue on fundamental issues that impact the scientific community and society. Through ideas and experiences, we can move forward to a future with more information and greater safety and health for all.

The importance of original articles in scientific research emphasizes the necessity for an increase in high-quality original articles, which is crucial for the progression of knowledge. The realm open to research, especially in health, should unravel the complexities that distance us from society and reality and produce valuable knowledge to address our most urgent health issues. We want to highlight in this issue both the challenges and the progress made possible by initiatives aimed at fostering dialogue, scientific reflection, and the publication of health research.

 OPEN ACCESS

**Fomentando el diálogo y la reflexión científica**

**Suggested citation:**

Sandoval López X. Fostering dialogue and scientific thought. *Alerta*. 2024;7(2):125-126. DOI: 10.5377/alerta.v7i2.17860

**Received:**

July 9, 2024.

**Accepted:**

July 22, 2024.

**Published:**

July 24, 2024.

**Author contribution:**

XLS: manuscript design writing, revising and editing.

**Conflict of interests:**

The author declared there are not conflicts of interest.



© 2024 by the author. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

The content of the journal presents both the challenges and the progress made possible by initiatives aimed at fostering dialogue, scientific reflection, and the publication of health research. These initiatives are vital for advancing knowledge, improving the practice of medicine and other health disciplines, and developing effective policies to protect and promote the health of populations. Through strengthening these practices, we can ensure that scientific advances translate into tangible benefits for society, making it healthier and more equitable.

To overcome these challenges, it is important to promote open access to scientific publications, encourage continuous training of researchers in communication skills and scientific ethics, and support platforms that facilitate collaboration and knowledge sharing at a global level. Let's keep supporting and promoting scientific excellence!

# Acute Vector-transmitted Chagas in Pediatric Age. A Case Report

DOI: 10.5377/alerta.v7i2.16814

Reina Iris Chávez Fuentes<sup>1\*</sup>, Maury Reinaldo Silva Granados<sup>2</sup>, Norma Patricia Lemus Pineda<sup>3</sup>

1. Ministry of Public Health, National Institute of Health, San Salvador, El Salvador.

2-3. Ministry of Public Health, Health Surveillance Unit, San Miguel, El Salvador.

\*Correspondence

✉ irischavez.r@gmail.com

1.  0009-0001-8461-9948

2.  0009-0006-3058-1776

3.  0009-0007-1972-4374

## Abstract

**Case presentation.** A seven-year-old female patient, with no previous medical history, originally from a rural area of the department of San Miguel, who presented febrile process plus long-term right bpalpebral edema of six weeks of evolution, without accompanying symptoms. Immunoglobulin M for Chagas was positive, direct microscopy by fresh drop and Strout technique was performed with negative results. In community interventions, the presence of the vector and its positivity were identified, as well as the diagnosis of a chronic case in another family member. **Treatment.** The patient was treated with nifurtimox 150 mg every eight hours for 60 days, subsequent controls were performed to investigate side effects of the treatment, and control tests. **Outcome.** With the treatment, the patient evolved with a slight decrease in appetite, and was managed with gastric protectors. Strout's concentrate and fresh gout were negative and the other laboratory tests were within normal ranges.

## Keywords

Chagas Disease, *Trypanosoma cruzi*, Disease Vectors, Neglected Diseases.

## Resumen

**Presentación del caso.** Se trata una niña de siete años de edad, originaria de una zona rural del departamento de San Miguel, quien consultó por presentar fiebre y edema bpalpebral derecho indoloro, de seis semanas de evolución, sin otros síntomas acompañantes. El estudio para el diagnóstico de enfermedad de Chagas fue realizado en una clínica privada; la Inmunoglobulina M para Chagas tuvo un resultado positivo, luego, se realizó la microscopía directa mediante gota al fresco y técnica de Strout con resultado negativo. En las intervenciones comunitarias se identificó la presencia del vector y la positividad del mismo, así como el diagnóstico de un caso crónico en otro miembro de la familia. **Intervención terapéutica.** Se indicó tratamiento con nifurtimox 150 mg cada ocho horas por 60 días y se realizó el seguimiento clínico de la evolución y control de efectos secundarios del tratamiento y exámenes de laboratorio. **Evolución clínica.** Evolucionó con leve disminución del apetito, se manejó con protectores gástricos. El concentrado de Strout y la gota al fresco resultaron negativos y los demás exámenes de laboratorio se mantenían en los rangos normales.

## Palabras clave

Enfermedad de Chagas, *Trypanosoma cruzi*, vectores de enfermedades, enfermedades desatendidas.

## Introduction

Chagas disease is a neglected tropical disease present in the Americas. The protozoan parasite *Trypanosoma cruzi*, the agent of Chagas disease, is a zoonotic pathogen transmitted by triatomine insects.<sup>i</sup>

Transmission can also occur through transfusion of blood components, organ

transplantation, consumption of food or drink contaminated by the vector or its feces, and transmission from mother to fetus during pregnancy.<sup>ii</sup>

It is perceived as a disease linked to poverty because it was once limited to rural areas of Latin America but has spread through migration to non-endemic areas and countries.<sup>iii</sup>

## OPEN ACCESS

### Un caso de Chagas agudo en edad pediátrica

#### Suggested citation:

Chávez Fuentes RI, Silva Granados MR, Lemus Pineda NP. Acute Vector-transmitted Chagas in Pediatric Age. A Case Report. Alerta. 2024;7(2):127-132. DOI: 10.5377/alerta.v7i2.16814

#### Editor:

Larisa Chavarría.

#### Received:

October 3, 2023.

#### Accepted:

May 11, 2024.

#### Published:

July 24, 2024.

#### Author contribution:

RICF<sup>1</sup>, MRSG<sup>2</sup>: study conception, writing, revising, and editing. RICF<sup>1</sup>: manuscript design, literature search, data management or software. RICF<sup>1</sup>, MRSG<sup>2</sup>, NPLP<sup>3</sup>: data collection.

#### Conflict of interests:

The authors declared there was not conflict of interests.



© 2024 by the author. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Chagas disease is endemic in 21 countries in the Americas and affects an estimate of six million people. In the region, there are 30 000 new cases each year, 12 000 deaths on average, and approximately 9000 newborns infected during gestation.<sup>iv</sup> El Salvador has long been endemic for Chagas disease; the first case was identified in 1913.<sup>v</sup>

Prevalence in the country is estimated to be between 1.3 % and 3.7 %. Acute cases are rare because most cases are asymptomatic, and only 1-2 % of infected persons experience symptoms.<sup>vi,vii</sup>

Transmission is no longer limited to the Americas, as cases are reported in multiple regions worldwide.<sup>viii</sup> Triatomine insects act as vectors and acquire the parasite when they feed on the blood of an infected mammal. Infected triatomines transmit the parasite in their feces when they defecate during or immediately after feeding.<sup>ix</sup> Vector-borne transmission was the first mechanism of infection described in the history of Chagas disease.

In a small number of cases, entry signs, such as an indurated skin lesion (chagoma) or unilateral bi-palpebral edema (Romaña's sign), can be detected. Most cases are accompanied by mild symptomatology (95-99 %) and go unnoticed. However, persistent fever, fatigue, lymphadenopathy, hepatomegaly, splenomegaly, rash, and edema may occur.<sup>x</sup>

The treatment of *Trypanosoma cruzi* infection consists of drugs authorized for more than 50 years: nifurtimox (launched by Bayer in 1965) and benznidazole (launched by Roche in 1971); their efficacy is conditioned by the stage of infection and the age of the patients therefore, timely diagnosis and knowledge of the disease become relevant in public health.<sup>xi</sup>

The acute phase may be asymptomatic or present with nonspecific general symptoms or complications such as myocarditis or meningoencephalitis, and the diagnosis in this phase is a challenge for physicians.<sup>xii</sup>

## Case presentation

The patient is a seven-year-old girl with a three-day history of unquantified fever and right bi-palpebral edema, painless, of six weeks of evolution, and no other symptoms (Figure 1), and no history of previous diseases. She was diagnosed with an ocular abscess and treated with doxycycline 50 mg orally every 12 hours and ibuprofen 100 mg orally every 12 hours for 10 days.

The patient did not improve after completing the treatment; she consulted a private clinic, where she was examined by an ophthalmologist who suspected Chagas

disease and immediately ordered the immunoglobulin M (IgM) test for Chagas disease at a private clinical laboratory. The test result was positive. Consequently, she was referred to the nearest first-level healthcare facility and then directed to the second-level hospital.



**Figure 1.** Right bi-palpebral edema, with one month of evolution

The patient attended the hospital after five weeks due to difficulties in the access to public transportation in the area where the home is located to travel to the healthcare facility.

The physical examination described bi-palpebral edema of the right eye, with no other findings, and direct microscopy studies (fresh drop) for *T. cruzi*, which consists of direct microscopic observation in search of mobile trypomastigotes in the drop of blood,<sup>xiii</sup> were negative, as were the Strout concentrate and the other laboratory tests (Table 1).

In addition, in a follow-up after one week, samples were taken for testing the family group (mother, father, paternal grandmother, and two adolescent sisters), which consisted of taking Strout's concentrate, blood count, and general chemistry.

Three weeks later, laboratory tests were completed (Strout's concentrate, complete blood count, general chemistry, and IgM for Chagas disease), of which the IgM for Chagas disease was positive, and the patient was diagnosed as a confirmed case of Chagas disease and classified as a case of Chagas disease that does not affect the heart. Finally, it was registered in the epidemiological surveillance system of El Salvador as a case of Chagas disease in the acute phase.

## Treatment

The second-level vector control team conducted a community visit where they identified the house in a rural area of the department of San Miguel. The house is located in an area of difficult vehicular



access, through a dirt road, in an area that does not have public transportation service (Figure 2). The house is made of clay and wood masonry, with a tin roof, distributed in a single space, divided into sections by plastic and with a dirt floor, on a large plot of land of approximately 7000 m<sup>2</sup> with a lot of vegetation and crops, with multiple piles of firewood stacked in the

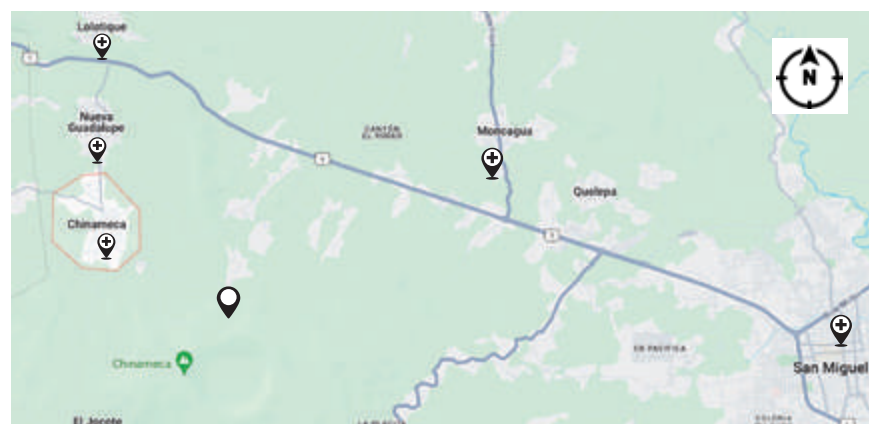
peridomicile and with dogs and chickens as domestic animals (Figure 3).

During entomology control, nine bedbugs were collected with *Triatoma dimidiata* characteristics; three were positive for *Trypanosoma cruzi*. In addition, the test of the paternal grandmother resulted in a case of chronic Chagas disease; she had lived in the place for 20 years.

**Table 1.** Laboratory test results



Test performed	Medical control 1	Medical control 2
Hemoglobin	12.0 g/dL	12.3 g/dL
Hematocrit	34.5 %	36.2 %
Leukocytes	10.0 x10 <sup>3</sup>	8.25 x10 <sup>3</sup>
Neutrophils	51.7 %	53.5 %
Lymphocytes	32.4 %	40.5 %
Platelets	248x10 <sup>3</sup>	370x10 <sup>3</sup>
Protombin time	14.1 sec	-
Thromboplastin time	24.2 sec	-
Blood type	ORh +	-
Direct Bilirubin	0.025 mg/dL	0.04 mg/dL
Indirect Bilirubin	0.17 mg/dL	0.18 mg/dL
Total Bilirubin	0.38 mg/dL	0.42 mg/dL
Creatinine	0.6 mg/dL	0.6 mg/dL
Urea Nitrogen	7.2 mg/dL	7.6 mg/dL
Uric acid	2.3mg/dL	2.4mg/dL
Sodium	142 mmol/L	139.8 mmol/L
Potassium	4.1 mmol/L	4.0 mmol/L
Chlorine	99.7 mmol/L	99.1 mmol/L
Aspartate aminotransferase	32.6 U/L	28.3 U/L
Alanine aminotransferase	17.5 U/L	17.5 U/L
Triglycerides	-	89.8 mg/dL
Fresh drop for <i>T. cruzi</i>	There is no evidence of <i>T. cruzi</i> in the preparation	There is no evidence of <i>T. cruzi</i> in the preparation
Strout concentrate	There is no evidence of <i>T. cruzi</i> in the preparation	There is no evidence of <i>T. cruzi</i> in the preparation
Qualitative IgM Chagas	Positive	2,27 Reactive

Source: clinical record



Source: Google maps.

**Figure 2.** Geographical location of the house

-  Healthcare facility
-  Location of the house

**16,1 km (29 min):** distance from the house to the first level of healthcare service.

The treatment for the patient was nifurtimox, at a dose of 18 mg/kg/dose, 150 mg every eight hours for 60 days, and medical follow-up and laboratory tests every two weeks.

### Outcome

A clinical improvement was evidenced. In the second follow-up, after 27 days of treatment, the patient presented mild hyporexia as a secondary symptom to the drug and was prescribed omeprazole 20 mg daily. In addition, the results of Strout's concentrate and fresh gout were negative and the complementary tests (hemogram, liver, and renal function tests) were within normal ranges (Table 1).

### Clinical diagnostic

The diagnosis of Chagas disease was confirmed by an IgM test, with two positive results through different times of the disease (Figure 4).

### Discussion

The case describes a seven-year old girl with manifestations of the disease in its acute phase. After the study of the clinical, epidemiological, and biological factors, the disease and the presence and positivity of the vector were proven. In the initial clinical picture, she presented Romaña sign and febrile process and had a positive IgM result for Chagas disease.



Figure 3. Photos of the house

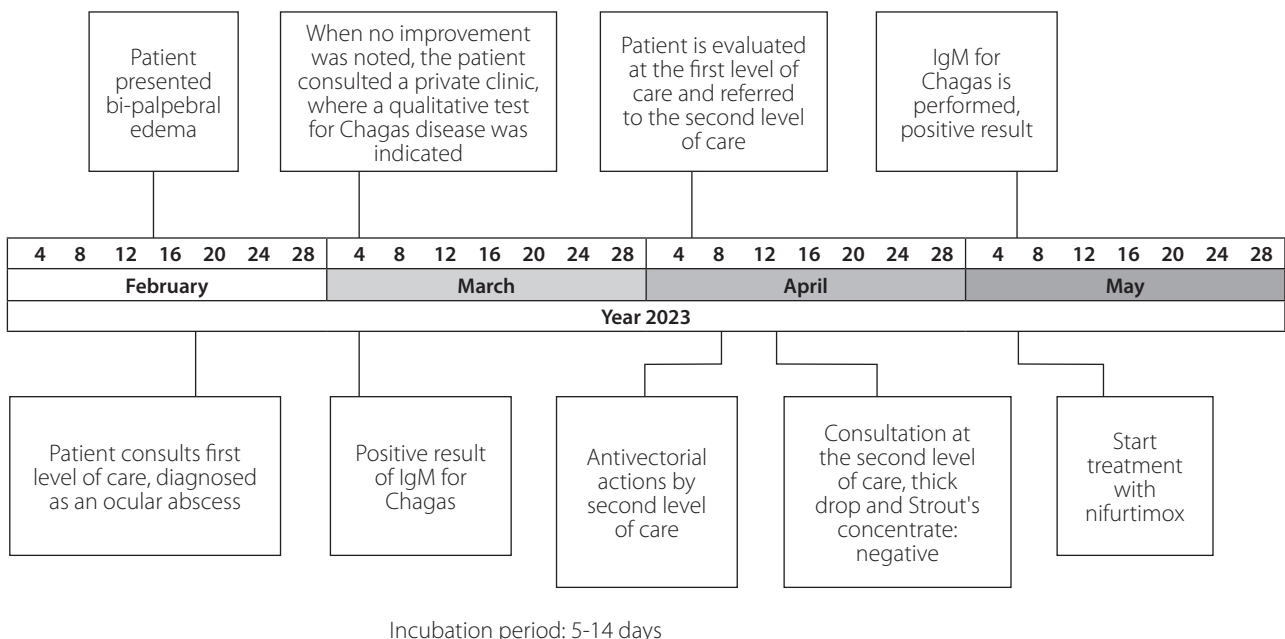


Figure 4. Timeline

Entomological surveillance consisted of analysis of the vectors found in the dwelling with a positivity index of 33.3 %; a high-risk infestation index is considered when it is higher than 5.0 %, according to entomological parameters.<sup>xiii</sup>

The diagnosis of Chagas disease depends on the stage of the disease the patient is found.<sup>xiv</sup> Most patients are asymptomatic during the acute phase; about 30 % progress to detectable organ damage involving mainly the cardiovascular and digestive systems. The acute phase lasts four to eight weeks before it resolves spontaneously, leaving most patients chronically infected if untreated. The parasite in the acute phase can only be detected directly by microscopic observation of a fresh drop, which has motile parasites among red blood cells,<sup>xv</sup> or through Strout's method, which allows the parasites to settle to the bottom of the tube where the sample is processed.<sup>xvi</sup> In El Salvador, according to the guidelines for the prevention, surveillance, and control of vector-borne diseases and zoonoses, "in the acute phase of Chagas disease, the diagnosis must be confirmed using direct methods without prior concentration (fresh drop), or direct concentration methods (microhematocrit and Strout technique)."<sup>xviii</sup>

As for the diagnosis of the case, in the acute phase, there may be a decrease in the parasite load one month after the primary infection. The sensitivity of diagnostic methods is limited in patients with low parasitemia, who present negative successive examinations. If the parasite is difficult to find during the acute phase, it is useful to apply the diagnostic search through specific IgM for *T. cruzi*.<sup>xvii</sup>

The drugs used have some disadvantages, including their efficacy only in the acute or early stages of infection, making early diagnosis of the disease of vital importance.<sup>xviii</sup>

On the other hand, the timeline evaluation shows that there were limitations in the diagnosis due to the lack of inquiry into the epidemiological links of the disease, as a result of the delay in follow-up and treatment due to the difficult access to health-care services by the patient and the family group, which constitutes a geographical and socio-economic barrier in the search for medical care and the initiation of timely medical treatment.<sup>xix</sup>

It is a known fact that the disease is transmitted by the vector residing in the mud walls of rural houses in developing countries; in this sense, the investigation of the epidemiological link is part of the clinical evaluation in those cases that present

symptoms suggestive of the disease for proper diagnosis and treatment. In addition, in this sense, serious health complications are prevented in the future.<sup>xx,xxi</sup>

## Ethical aspects

Assent was obtained from the minor patient and consent from the responsible mother, as her authorization for the publication of the clinical case and images, in accordance to the Helsinki Declaration and international ethical guidelines for health-related research involving human beings.

## Acknowledgments

To Rómulo Vides, medical epidemiologist at Nueva Guadalupe Hospital, San Miguel, and Erick López Echeverría, medical doctor at Healthcare Unit, Chinameca, for their support in the clinical and epidemiological investigation of the patient.

## Funding

There were not external funds for this study.

## References

- i. Busselman RE, Hamer SA. Chagas Disease Ecology in the United States: Recent Advances in Understanding *Trypanosoma cruzi* Transmission Among Triatomines, Wildlife, and Domestic Animals and a Quantitative Synthesis of Vector-Host Interactions. *Annu Rev Anim Biosci*. 2022;10:325-348. DOI: [10.1146/annurev-animal-013120-043949](https://doi.org/10.1146/annurev-animal-013120-043949)
- ii. Bern C, Messenger LA, Whitman JD, Maguire JH. Chagas Disease in the United States: a Public Health Approach. *Clinical Microbiology Reviews*. 2019;33(1):10.1128/cmr.00023-19. DOI: [10.1128/cmr.00023-19](https://doi.org/10.1128/cmr.00023-19)
- iii. Suárez C, Nolder D, García-Mingo A, Moore DA, Chiodini PL. Diagnosis and Clinical Management of Chagas Disease: An Increasing Challenge in Non-Endemic Areas. *RRTM*. 2022;13:25-40. DOI: [10.2147/RRTM.S278135](https://doi.org/10.2147/RRTM.S278135)
- iv. Organización Panamericana de la Salud. Enfermedad de Chagas. OPS-OMS. 2024. Consulted date: 31 de mayo de 2024. Available at: <https://www.paho.org/es/temas/enfermedad-chagas>
- v. Nolan MS, Murray KO, Mejia R, Hotez PJ, Villar Mondragon MJ, Rodriguez S, et al. Elevated Pediatric Chagas Disease Burden Complicated by Concomitant Intestinal Parasites and Malnutrition in El Salvador. *Tropical Medicine and Infectious*

- Disease. 2021;6(2):72. DOI: [10.3390/tropicalmed6020072](https://doi.org/10.3390/tropicalmed6020072)
- vi. Beltrami M, Grande R, Giacomelli A, Sabaini F, Biondo L, Longo M, *et al.* Chagas disease prevalence among migrants from El Salvador in Milan: a cross-sectional study of an often-overlooked population. *Infectious Diseases*. 2023;55(8):559-566. DOI: [10.1080/23744235.2023.2222817](https://doi.org/10.1080/23744235.2023.2222817)
  - vii. Sasagawa E, de Aguilar AVG, de Ramírez MAH, Chévez JER, Nakagawa J, Cedillos RA, *et al.* Acute Chagas disease in El Salvador 2000-2012 - Need for surveillance and control. *Mem Inst Oswaldo Cruz*. 2014;109(2):256-258. DOI: [10.1590/0074-0276140416](https://doi.org/10.1590/0074-0276140416)
  - viii. Peña Callejas G, James González J, Jiménez Cortés G, Fuentes Vicente JA, Salazar Schettino PM, Bucio Torres MI, *et al.* Enfermedad de Chagas: biología y transmisión de *Trypanosoma cruzi*. *TIP Revista Especializada en Ciencias Químico-Biológicas*. 2022;25:1-19. DOI: [10.22201/fesz.23958723e.2022.449](https://doi.org/10.22201/fesz.23958723e.2022.449)
  - ix. Agudelo Higueta NI, Bronze MS, Smith JW, Montgomery SP. Chagas disease in Oklahoma. *Am J Med Sci*. 2022;364(5):521-528. DOI: [10.1016/j.amjms.2022.03.018](https://doi.org/10.1016/j.amjms.2022.03.018)
  - x. Schijman AG, Alonso-Padilla J, Longhi SA, Picado A. Parasitological, serological and molecular diagnosis of acute and chronic Chagas disease: from field to laboratory. *Mem. Inst. Oswaldo Cruz*. 2022;117:e200444. DOI: [10.1590/0074-02760200444](https://doi.org/10.1590/0074-02760200444)
  - xi. Pérez Molina JA, Crespillo Andújar C, Bosch-Nicolau P, Molina I. Trypanocidal treatment of Chagas disease. *Enfermedades infecciosas y microbiología clínica (English ed.)*. 2021;39(9):458-470. DOI: [10.1016/j.eimce.2020.04.012](https://doi.org/10.1016/j.eimce.2020.04.012)
  - xii. Montoya DD, Ríos JPO. Enfermedad de Chagas y sus manifestaciones neurológicas. *Acta Neurológica Colombiana*. 2021;37(1 Supl 1):154-162. DOI: [10.22379/24224022348](https://doi.org/10.22379/24224022348)
  - xiii. Ministerio de Salud. Lineamientos técnicos para la prevención, vigilancia y control de enfermedades transmitidas por vectores y zoonosis. Ministerio de Salud. 2020. 228 p. Available at: <https://asp.salud.gob.sv/regulacion/pdf/lineamientos/lineamientostecnicosparalaprevencionvigilanciaycontroldenfermedadestransmitidasporvectoresyzoonosis-Acuerdo1006.pdf>
  - xiv. Echavarría NG, Echeverría LE, Stewart M, Gallego C, Saldarriaga C. Chagas Disease: Chronic Chagas Cardiomyopathy. *Current Problems in Cardiology*. 2021;46(3):100507. DOI: [10.1016/j.cpcardiol.2019.100507](https://doi.org/10.1016/j.cpcardiol.2019.100507)
  - xv. Teixeira ARL, Nitz N, Guimaro MC, Gomes C. Chagas disease. *Postgrad Med J*. 2006;82(974):788-798. DOI: [10.1136/pgmj.2006.047357](https://doi.org/10.1136/pgmj.2006.047357)
  - xvi. Malik LH, Singh GD, Amsterdam EA. The Epidemiology, Clinical Manifestations, and Management of Chagas Heart Disease. *Clin Cardiol*. 2015;38(9):565-569. DOI: [10.1002/clc.22421](https://doi.org/10.1002/clc.22421)
  - xvii. Castro-Sesquen YE, Tinajeros F, Bern C, Galdos-Cardenas G, Malaga ES, Valencia Ayala E, *et al.* The Immunoglobulin M-Shed Acute Phase Antigen (SAPA)-test for the Early Diagnosis of Congenital Chagas Disease in the Time of the Elimination Goal of Mother-to-Child Transmission. *Clinical Infectious Diseases*. 2021;73(2):e477-e484. DOI: [10.1093/cid/ciaa986](https://doi.org/10.1093/cid/ciaa986)
  - xviii. García Huertas P, Cardona Castro N. Advances in the treatment of Chagas disease: Promising new drugs, plants and targets. *Biomedicine & Pharmacotherapy*. 2021;142:112020. DOI: [10.1016/j.biopha.2021.112020](https://doi.org/10.1016/j.biopha.2021.112020)
  - xix. Jimeno I, Mendoza N, Zapana F, Torre L de la, Torrico F, Lozano D, *et al.* Social determinants in the access to health care for Chagas disease: A qualitative research on family life in the «Valle Alto» of Cochabamba, Bolivia. *PLoS One*. 2021;16(8):e0255226. DOI: [10.1371/journal.pone.0255226](https://doi.org/10.1371/journal.pone.0255226)
  - xx. Santos É, Menezes Falcão L. Chagas cardiomyopathy and heart failure: From epidemiology to treatment. *Rev Port Cardiol (Engl Ed)*. 2020;39(5):279-289. DOI: [10.1016/j.repc.2019.12.006](https://doi.org/10.1016/j.repc.2019.12.006)
  - xxi. Touriz Bonifaz MA, Santos Paladines PR, Falconi San Lucas S., Tobar Moran MR. Caracterización epidemiológica de la enfermedad de Chagas, en la provincia de Guayas del Ecuador. *RECIMUNDO*. 2021;5(3):149-157. DOI: [10.26820/recimundo/5](https://doi.org/10.26820/recimundo/5)

# Metachronous liver metastasis from a solid pseudopapillary pancreas tumor

DOI: 10.5377/alerta.v7i2.17065

Julio Cesar Alfaro Varela<sup>1\*</sup>, Mario Francisco Interiano Tobar<sup>2</sup>, Glenda Estefanía Álvarez Salazar<sup>3</sup>

1-3. Hepato-Pancreato-Biliary Surgery Clinic; Medical, Surgical, and Oncology Hospital of Salvadoran Social Security Institute, San Salvador, El Salvador.

\*Correspondence

✉ drjulioalfaro@hotmail.com

1.  0000-0003-4978-9754

2.  0000-0002-1930-5643

3.  0009-0000-2271-1602

## Abstract

**Case presentation.** A 32-year-old woman consulted for abdominal pain in the epigastrium not associated with meals. She had a history of distal pancreatectomy with spleen preservation due to a tumor in the tail of the pancreas five years earlier. Physical examination showed no abnormalities and imaging studies were performed during his approach. **Treatment.** Computed axial tomography revealed a lesion in the left lateral segment of the liver with characteristics suggestive of metastasis due to his surgical history. Laboratory tests and tumor markers were within normal limits. It was evaluated in a multidisciplinary conference, and a surgical approach was recommended. A left hepatectomy was performed with an uncomplicated postoperative evolution. **Outcome.** Six months postoperatively, there was no evidence of active or residual disease.

## Keywords

Pancreas, Neoplasms, Liver, Metastasis, Metachronous Neoplasm.

## Resumen

**Presentación del caso.** Se trata de una mujer de 32 años quien consultó por dolor abdominal en el epigastrio no asociado a las comidas, tenía el antecedente de una pancreatectomía distal con preservación de bazo debido a un tumor en la cola del páncreas, cinco años previos. En el examen físico no presentó ninguna anormalidad y durante su abordaje se realizaron estudios de imagen. **Intervención terapéutica.** La tomografía axial computarizada evidenció una lesión en el segmento lateral izquierdo del hígado con características sugestivas de metástasis debido a su antecedente quirúrgico. Los exámenes de laboratorio y marcadores tumorales se encontraron dentro de límites normales. Se evaluó en conferencia multidisciplinaria y se recomendó un abordaje quirúrgico. Se realizó una hepatectomía izquierda con una evolución posquirúrgica sin complicaciones. **Evolución clínica.** Luego de seis meses posoperatorios, se encontraba sin evidencia de enfermedad activa o residual.

## Palabras clave

Páncreas, neoplasia, hígado, metástasis, neoplasia metacrónica.

## Introduction

Pseudopapillary solid tumors of the pancreas are considered a rare pathology, representing only 1-2 % of all exocrine tumors of the pancreas.<sup>i</sup> Pseudopapillary solid tumors of the pancreas were first reported by Frantz in 1959; thus, they were known as Frantz's tumors at one time.<sup>ii</sup> Currently, the World Health Organization classifies them as tumors of the digestive

system, of low grade of malignancy, but with the potential to cause metastasis; with a report in the literature of approximately 8334 cases as of 2018.<sup>iii</sup> The cause of these tumors is still unknown.<sup>iv</sup>

About 90 % of the cases occur in young women, with an average age of 23.9 years.<sup>v</sup> Most solid lesions of the pancreas are considered malignant; however, this type of tumor has a less aggressive behavior and rarely metastasizes.<sup>ii</sup>

## OPEN ACCESS

### Metástasis hepática metacrónica de un tumor sólido pseudopapilar de páncreas

#### Suggested citation:

Alfaro Varela JC, Interiano Tobar MF, Álvarez Salazar GE. Metachronous liver metastasis from a solid pseudopapillary pancreas tumor. *Alerta*. 2024;7(2):133-137. DOI: 10.5377/alerta.v7i2.17065

#### Editor:

Larisa Chavarría.

#### Received:

August 30, 2023.

#### Accepted:

May 6, 2024.

#### Published:

July 24, 2024.

#### Author contribution:

JCAV<sup>i</sup>: study conception, manuscript design, literature search, data analysis, writing, revision and edition. MFIT<sup>ii</sup>: manuscript design, data management, data analysis, writing, revision and edition. GEAS<sup>iii</sup>: data collection, data management, data analysis, writing, revision and edition.

#### Conflicts of interest:

The authors declared there was not conflict of interests.



© 2024 by the authors. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Generally, these tumors do not present symptoms and are incidental findings. The presence of metastatic lesions is infrequent, and there is no consensus as to the ideal management in these cases since these solid pseudopapillary tumors of the pancreas do not respond adequately to chemotherapy or radiotherapy, so surgical resection is the ideal curative treatment, even in the presence of metastatic lesions.<sup>vi</sup> Due to the infrequent nature of the pathology, this case is considered to be of interest, as only isolated cases have been reported.

## Case presentation

The patient was a 32-year-old woman who consulted a tertiary-level hospital for abdominal pain located in the epigastrium, not associated with food intake, and did not present jaundice, weight loss, or other symptoms. She had a history of distal pancreatectomy with spleen preservation due to a tumor in the tail of the pancreas five years earlier. The histopathologic biopsy result reported a solid pseudopapillary neoplasm of the pancreas with healthy surgical borders; no nodal status was included. She was referred to a tertiary hospital for evaluation and treatment by oncology. She received chemotherapy and radiotherapy in an unknown amount and three years after discontinuation of follow-up by the specialty.

Vital signs were reported without abnormalities, with a blood pressure of 120/70 mmHg, a heart rate of 72 bpm, and a temperature of 37 °C. A physical examination did not identify masses or signs of peritoneal irritation. Due to the oncologic history, tumor markers (CA19-9 and CEA) were indicated and reported within normal limits, and the rest of the laboratory tests (Table 1).

Abdomino-pelvic tomography described a hypodense lesion in hepatic segment II, with

a well-defined wall and enhancement in the contrasted phase measuring 5.8 × 4.4 × 4.4 cm with a complex cystic component of indeterminate behavior (Figure 1).

A hypodense lesion of 37 Hounsfield Units (HU) in the venous phase and 49 HU in the arterial phase was observed, measuring 5.8 × 4.4 × 4.4 cm with the cystic component.



**Figure 1.** Abdomino-pelvic computed axial tomography

## Treatment

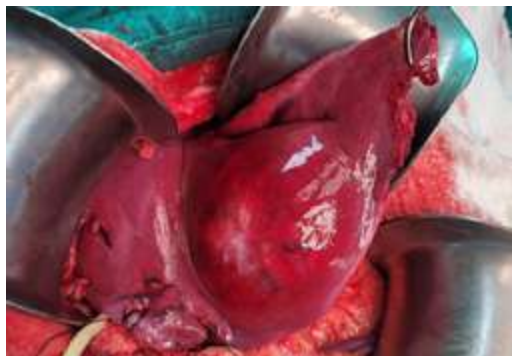
The multidisciplinary hepato-pancreato-biliary committee of the tertiary care hospital evaluated the case, took into account the medical history and the characteristics of the images, and therefore concluded with the presumptive preoperative diagnosis of a hepatic metastasis secondary to the previously removed solid pseudopapillary tumor of the pancreas; consequently, they suggested performing a left lateral hepatectomy (bi-segmentectomy II-III) without the need for preoperative biopsy, and without receiving chemotherapy or radiotherapy preoperatively.

Surgical intervention was performed with a midline approach, in which a mass was evidenced in segments II and III of the liver, measuring 10 × 15 cm in diameter; no other metastatic lesions were found (Figure 2). Vascular control was performed using the Pringle maneuver and continued with the release of the suspensory ligaments of the liver (coronal and triangular). The transection site in the liver was marked, and the hepatectomy was performed with a dissector and ultrasonic aspirator. The estimated blood loss was 200 mL with an operative time of 120 minutes. Hemostasis was verified at the parenchymal transection site, titanium clips were used to occlude the segmental bile duct, and hemostatic material was left in the hepatic remnant (Figure 3).

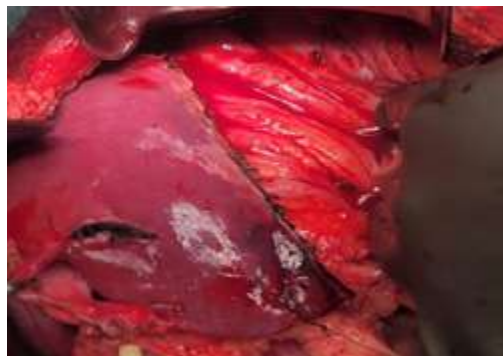
**Table 1.** Laboratory tests

Hemoglobin	14 gr/dL (VN: 12-16)
Plaquettes	255 000 (VN: 150-400 mil)
Aspartate aminotransferase (AST)	25 UI (VN: 0-45 IU)
Alanine aminotransferase (ALT)	20 UI (VN: 0-50 IU)
Total Bilirubin	0,9 mg/dL (VN: < 1,1 mg/dL)
CA 19-9 antigen	0 (VN: 0-35)
Carcinoembryonic antigen (CEA)	0 (VN: 0-5)

\*NV: Normal value.



**Figure 2.** Lesion of the left lateral hepatic lobule, 10 × 15 cm in segments II and III. Release of the triangular and coronary ligaments is observed

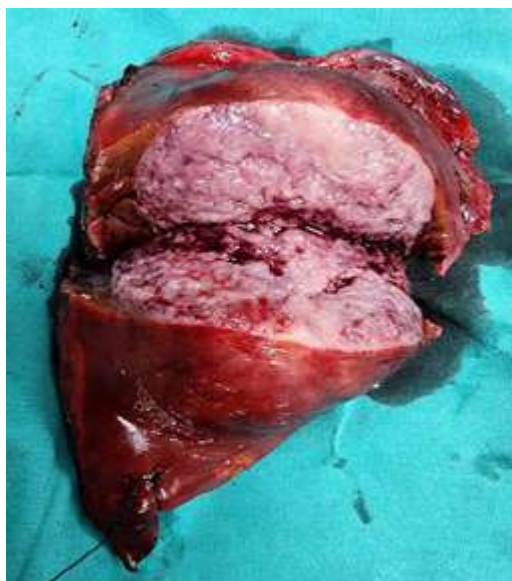


**Figure 3.** Hepatic remnant with the transection zone and macroscopic edges free of tumor

## Outcome

She received analgesia with paracetamol 1 g IV every eight hours in the immediate postoperative period. She also had a satisfactory evolution and was discharged 48 hours after surgery with a follow-up plan in the Oncology Unit. There was no need for transfusion of blood products or special care management.

In the resected specimen, a limited and well-encapsulated large lesion was observed concerning the surface of the liver without involvement of neighboring organs or other metastatic lesions. Examination of the specimen revealed solid tissue with some cystic components of heterogeneous consistency (Figure 4). The pathology report described a metastatic lesion of a pseudopapillary solid tumor of the pancreas, with negative borders and a well-demarcated fibrous capsule. No chemotherapy or radiotherapy was deemed necessary.



**Figure 4.** A solid lesion with well-encapsulated cystic components and macroscopically free surgical margins

## Clinical diagnosis

The definitive diagnosis, based on the anatomopathological study, was a solid pseudopapillary tumor of the pancreas, as a metastatic lesion of the liver, by the history of the tumor in the pancreas.

## Discussion

Pseudopapillary solid tumors of the pancreas are a rare disease that predominates in young women, with a ninefold increase.<sup>v</sup> Although in men it is diagnosed at an advanced age.<sup>vii</sup> Moreover, more aggressive behavior has been reported in men and postmenopausal women, suggesting that the biology of the tumor may be related to estrogen stimulation<sup>!</sup>. The biological behavior is still uncertain.

On the other hand, surgical resection is considered the best therapeutic option in all cases, even in the presence of metastatic lesions or extension to neighboring organs.<sup>viii,ix</sup> The most frequent site of location is the body and tail of the pancreas, followed by the head,<sup>x</sup> and the liver, lymph nodes, omentum, and peritoneum are mentioned as the organs with the highest frequency of metastasis.<sup>xi</sup>

Abdominal pain (51.6 %) and palpation of an abdominal mass (40.2 %) have been described as the main symptoms, although asymptomatic disease occurs in 38.6 % of cases.<sup>x</sup> In approximately 85 % of patients, the disease is limited to the pancreas and metastatic lesions are identified during surgery in only 10 to 15 %.<sup>xii</sup> On the other hand, distant metastases are rare events, occurring in 7.7 % of cases.<sup>xiii</sup> In this case, the site of metastasis was the liver, and was diagnosed six years after the index surgery.

These tumors do not respond to chemotherapy or radiotherapy, which makes surgical treatment their best option.<sup>vi</sup> Because of this, surgery is consid-

ered to be the standard curative procedure with a better survival rate, greater than 97 % at five years, compared to other tumors such as pancreatic adenocarcinomas.<sup>xii</sup> Other treatments, such as radiofrequency ablation or chemoembolization (TACE), are not fully proven as curative.<sup>vi</sup>

Currently, there are no guidelines on the management of these metastatic lesions to the liver.<sup>xiv</sup> Some authors have recommended enucleation of the tumors to preserve the parenchyma in very selected cases, such as peripheral location and a distance greater than 3 mm from the bile duct or the main pancreatic duct; however, they are not accepted.<sup>xv</sup> In cases where metastases are not resectable, liver transplantation has been reported as a therapeutic option with acceptable results.<sup>xvi</sup> Resection of the primary tumor and metastasis is also recommended, providing excellent survival as long as all lesions are removed.<sup>xvii</sup>

Because the present case was solitary and resectable, a surgical procedure was decided upon to offer the best chance of survival, even with the uncertainty of its biological behavior. A meta-analysis demonstrated a mean disease-free time of approximately 150 months in cases with systemic involvement.<sup>xviii</sup> Another study showed that patients with local recurrence or peritoneal implants have a long survival, an average time to report metastases of 8.5 years, and generally in patients older than 36 years.<sup>xix</sup>

The presence of metastases to the liver at the time of diagnosis is common; however, a more aggressive biological behavior compared to metastases in other sites has not been evidenced.<sup>xi</sup> Some authors have described cases that have been successfully treated by multistage surgery for multiple liver lesions.<sup>xiv,xx</sup> Five and ten-year disease-free survival is approximately 70 % and 65 % respectively in cases with aggressive behavior.<sup>xviii</sup> At the molecular level, it has been shown that genetic alterations in BAP1 and KDM6A may be related to the metastatic potential of this type of tumor.<sup>xxi</sup> Because these lesions have an uncertain behavior, it is suggested that follow-up should be longer than five years.<sup>xxii</sup>

## Ethical aspects

This work complies with the standards established in the Declaration of Helsinki and Belmont, respecting the patient's identity and all ethical aspects. The information is confidential, with the patient's informed consent for the disclosure of the information for scientific purposes.

## Funding

No external funds were received for this work.

## References

- i. Antoniou EA, Damaskos C, Garmpis N, Salakos C, Margonis G-A, Kontzoglou K, *et al*. Solid Pseudopapillary Tumor of the Pancreas: A Single-center Experience and Review of the Literature. In Vivo. 2017;31(4):501-510. Available at: <http://iv.iiarjournals.org/content/31/4/501.abstract>
- ii. Huang H-L, Shih S-C, Chang W-H, Wang T-E, Chen M-J, Chan Y-J. Solid-pseudopapillary tumor of the pancreas: Clinical experience and literature review. World Journal of Gastroenterology. 2005;11(9):1403-1409. DOI: [10.3748/wjg.v11.i9.1403](https://doi.org/10.3748/wjg.v11.i9.1403)
- iii. Jena SS, Ray S, Das SAP, Mehta NN, Yadav A, Nundy S. Rare Pseudopapillary Neoplasm of the Pancreas: A 10-Year Experience. Surgery Research and Practice. 2021;2021:e7377991. DOI: [10.1155/2021/7377991](https://doi.org/10.1155/2021/7377991)
- iv. La Rosa S, Bongiovanni M. Pancreatic Solid Pseudopapillary Neoplasm: Key Pathologic and Genetic Features. Archives of Pathology & Laboratory Medicine. 2020;144(7):829-837. DOI: [10.5858/arpa.2019-0473-RA](https://doi.org/10.5858/arpa.2019-0473-RA)
- v. Mao C, Guvendi M, Domenico DR, Kim K, Thomford NR, Howard JM. Papillary cystic and solid tumors of the pancreas: A pancreatic embryonic tumor? Studies of three cases and cumulative review of the world's literature. Surgery. 1995;118(5):821-828. DOI: [10.1016/S0039-6060\(05\)80271-5](https://doi.org/10.1016/S0039-6060(05)80271-5)
- vi. Tanoue K, Mataka Y, Kurahara H, Idichi T, Kawasaki Y, Yamasaki Y, *et al*. Multidisciplinary treatment of advanced or recurrent solid pseudopapillary neoplasm of the pancreas: three case reports. Surgical Case Reports. 2022;8(1):7. DOI: [10.1186/s40792-022-01358-0](https://doi.org/10.1186/s40792-022-01358-0)
- vii. Kotecha K, Pandya A, Gill AJ, Mittal A, Samra J. Pancreatic solid pseudopapillary neoplasm: a single-institution study. ANZ J Surg. 2021;91(11):2453-2458. DOI: [10.1111/ans.17142](https://doi.org/10.1111/ans.17142)
- viii. Cruz MAA, Moutinho-Ribeiro P, Costa-Moreira P, Macedo G. Solid Pseudopapillary Neoplasm of the Pancreas: Unfolding an Intriguing Condition. GE - Portuguese Journal of Gastroenterology. 2021;29(3):151-162. DOI: [10.1159/000519933](https://doi.org/10.1159/000519933)
- ix. Sibio S, Carlo SD. Current highlights on solid pseudopapillary neoplasm of the pancreas. World Journal of Hepatology. 2022;14(1):300-303. DOI: [10.4254/wjh.v14.i1.300](https://doi.org/10.4254/wjh.v14.i1.300)



- x. Yao J, Song H. A Review of Clinicopathological Characteristics and Treatment of Solid Pseudopapillary Tumor of the Pancreas with 2450 Cases in Chinese Population. *BioMed Research International*. 2020; e2829647. DOI: [10.1155/2020/2829647](https://doi.org/10.1155/2020/2829647)
- xi. Law JK, Ahmed A, Singh VK, Akshintala VS, Olson MT, Raman SP, *et al*. A Systematic Review of Solid-Pseudopapillary Neoplasms: Are These Rare Lesions? *Pancreas*. 2014;43(3):331. DOI: [10.1097/MPA.0000000000000061](https://doi.org/10.1097/MPA.0000000000000061)
- xii. Tang LH, Aydin H, Brennan MF, Klimstra DS. Clinically Aggressive Solid Pseudopapillary Tumors of the Pancreas: A Report of Two Cases With Components of Undifferentiated Carcinoma and a Comparative Clinicopathologic Analysis of 34 Conventional Cases. *The American Journal of Surgical Pathology*. 2005;29(4):512. DOI: [10.1097/01.pas.0000155159.28530.88](https://doi.org/10.1097/01.pas.0000155159.28530.88)
- xiii. Wang X, Chen Y-H, Tan C, Zhang H, Xiong J, Chen H, *et al*. Enucleation of pancreatic solid pseudopapillary neoplasm: Short-term and long-term outcomes from a 7-year large single-center experience. *European Journal of Surgical Oncology*. 2018;44(5):644-650. DOI: [10.1016/j.ejso.2018.01.085](https://doi.org/10.1016/j.ejso.2018.01.085)
- xiv. Wójciak M, Gozdowska J, Pacholczyk M, Lisik W, Kosieradzki M, Cichocki A, *et al*. Liver Transplantation for a Metastatic Pancreatic Solid-Pseudopapillary Tumor (Frantz Tumor): A Case Report. *Ann Transplant*. 2018;23:520-523. DOI: [10.12659/AOT.908764](https://doi.org/10.12659/AOT.908764)
- xv. Hu S, Zhang H, Wang X, Sun Z, Ge Y, Yan G, *et al*. Asymptomatic versus symptomatic solid pseudopapillary tumors of the pancreas: clinical and MDCT manifestations. *Cancer Imaging*. 2019;19(1):13. DOI: [10.1186/s40644-019-0198-4](https://doi.org/10.1186/s40644-019-0198-4)
- xvi. Omiyale AO. Solid pseudopapillary neoplasm of the pancreas. *World Journal of Hepatology*. 2021;13(8):896-903. DOI: [10.4254/wjh.v13.i8.896](https://doi.org/10.4254/wjh.v13.i8.896)
- xvii. Ranaweera K, Nandasena M, de Silva U, Jayarajah U, Delwatta S, de Silva C, *et al*. Solid pseudopapillary neoplasm of the pancreas with multiple liver metastases successfully managed with staged resection. *SAGE Open Medical Case Reports*. 2022;10:2050313X221101995. DOI: [10.1177/2050313X221101995](https://doi.org/10.1177/2050313X221101995)
- xviii. Hao EU, Hwang HK, Yoon D-S, Lee WJ, Kang CM. Aggressiveness of solid pseudopapillary neoplasm of the pancreas: A literature review and meta-analysis. *Medicine*. 2018;97(49):e13147. DOI: [10.1097/MD.00000000000013147](https://doi.org/10.1097/MD.00000000000013147)
- xix. González Cámpora R, Rios Martin JJ, Villar Rodriguez JL, Ota Salaverri C, Hevia Vazquez A, Valladolid JM, *et al*. Papillary cystic neoplasm of the pancreas with liver metastasis coexisting with thyroid papillary carcinoma. *Arch Pathol Lab Med*. 1995;119(3):268-273. Available at: <https://pubmed.ncbi.nlm.nih.gov/7887782/>
- xx. Morito A, Eto K, Matsuishi K, Hamasaki H, Morita K, Ikeshima S, *et al*. A case of repeat hepatectomy for liver metastasis from solid pseudopapillary neoplasm of the pancreas: a case report. *Surg Case Rep*. 2021;7(1):60. DOI: [10.1186/s40792-021-01134-6](https://doi.org/10.1186/s40792-021-01134-6)
- xxi. Amato E, Mafficini A, Hirabayashi K, Lawlor RT, Fassan M, Vicentini C, *et al*. Molecular alterations associated with metastases of solid pseudopapillary neoplasms of the pancreas. *J Pathol*. 2019;247(1):123-134. DOI: [10.1002/path.5180](https://doi.org/10.1002/path.5180)
- xxii. Lee G, Sung Y-N, Kim SJ, Lee JH, Song K-B, Hwang DW, *et al*. Large tumor size, lymphovascular invasion, and synchronous metastasis are associated with the recurrence of solid pseudopapillary neoplasms of the pancreas. *HPB*. 2021;23(2):220-230. DOI: [10.1016/j.hpb.2020.05.015](https://doi.org/10.1016/j.hpb.2020.05.015)

## Case report

# Carotid-cavernous fistula with secondary ocular hypertension. A case report

DOI: 10.5377/alerta.v7i2.17067

Daniel Benjamín Mejía Llanes

Ophthalmological Service, Medical Specialties Clinic, Salvadoran Social Security Institute (ISSS). San Salvador, El Salvador.

Correspondence

✉ db.mejia@outlook.com

ORCID 0009-0006-7458-6149

## OPEN ACCESS

### Fístula carótido-cavernosa con hipertensión ocular secundaria: reporte de caso

#### Suggested citation:

Mejía Llanes DB. Carotid-cavernous fistula with secondary ocular hypertension. A case report. *Alerta*. 2024;7(2):138-145. DOI: 10.5377/alerta.v7i2.17067

#### Editor:

Larisa Chavarría.

#### Received:

October 2, 2023.

#### Accepted:

May 6, 2024.

#### Published:

July 24, 2024.

#### Author contribution:

DBML: study conception, manuscript design, data collection and management or software, writing, revising, and editing.

#### Conflicts of interest:

The author declared there are not conflicts of interest.



© 2024 by the author. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

#### Abstract

**Case presentation.** 62 years old female with ten months history of ocular pain, proptosis, and conjunctival hyperemia in left eye, developing swollen upper eyelid. Best corrected visual acuity was 20/30 in her left eye, with and intraocular pressure of 30 mmHg. **Treatment.** Nuclear magnetic resonance of the orbits showed proptosis and dilated superior ophthalmic vein. Initial diagnosis. Abnormal venous drainage and ocular hypertension in the left eye. Topical hypotensive treatment of the left eye was initiated with ocular hypotensive eyedrops. Angiotomography of the orbit and left eye Doppler ultrasound, with upper eyelid emphasis, gave visualization of high flow carotid-cavernous fistula. Cerebral diagnostic and therapeutic angiography with embolization of the fistula in middle meningeal and ascending pharyngeal arteries showed no vascular flow after the procedure. **Outcome.** Positive clinical outcome, with corrected visual acuity conserved and normal eye pressure. Notable relief of ocular congestion and swollen upper eyelid with no proptosis in the left eye. Doppler ultrasound in the upper eyelid showed normal flow rate measurement.

#### Keywords

Carotid-Cavernous Fistula, Ocular Hypertension, Antiglaucoma Agents.

#### Resumen

**Presentación del caso.** Paciente femenina de 62 años con una historia de diez meses de dolor ocular pulsátil, proptosis e inyección conjuntival en el ojo izquierdo; posteriormente presentó un edema palpebral superior izquierdo. Se evaluó con mejor agudeza visual corregida de 20/30 en dicho ojo y presión intraocular de 30 mmHg. **Intervención terapéutica.** Resonancia magnética nuclear de órbitas evidencia proptosis y dilatación de vena oftálmica superior izquierda, por lo que se diagnosticó como defecto del drenaje venoso e hipertensión ocular del ojo izquierdo. Inició tratamiento hipotensor tópico de ojo izquierdo; estudios de imagen angiotomografía de órbitas y ultrasonido doppler de ojo izquierdo, con énfasis en párpado superior, evidencian fístula carótido-cavernosa izquierda de alto gasto. Se realizó angiografía cerebral diagnóstica y terapéutica con embolización de fístula en arterias meníngea media y faríngea ascendente con ausencia de flujo por dichas ramas después de la intervención. **Evolución clínica.** Presentó una evaluación clínica favorable, conservando agudeza visual y presión intraocular dentro de valores normales en ojo izquierdo, con evidente disminución de congestión venosa episcleral, edema de párpado superior y ausencia de proptosis izquierda. Ultrasonido doppler control de párpado superior izquierdo con disminución de flujo venoso a valores normales.

#### Palabras clave

Fístula carótido-cavernosa, hipertensión ocular, agentes antiglaucoma.

## Introduction

An arteriovenous fistula is a lesion resulting from an abnormal communication between arterial and venous flow through a capillary

bed.<sup>i</sup> It has many causes, including trauma or degeneration. Arteriovenous fistulas are classified as direct and indirect.<sup>ii</sup> An incidence of 0.2 % has been reported in patients with brain trauma and up to 4 % in cases with skull base fracture.<sup>iii</sup>

Direct carotid-cavernous fistulas are defined by high vascular flow, with direct communication between the internal carotid artery and the cavernous sinus; trauma is the most frequent cause.<sup>iv</sup> They may also be caused by rupture of aneurysms in the internal carotid artery in the cavernous sinus, Ehlers-Danlos syndrome type IV, or as a result of iatrogenic factors during neuroradiological or surgical interventions.

Indirect low-output carotid-cavernous fistulas are the consequence of communication between the meningeal branches of the internal or external carotid artery and the cavernous sinus; they are associated with degenerative processes in older patients with arterial hypertension, vascular pathologies, or atherosclerosis. Other causes may be fibromuscular dysplasia, Ehlers-Danlos syndrome type IV,<sup>v</sup> and internal carotid artery dissection.

There is also the Barrow classification based on angiographic criteria related to direct carotid-cavernous fistula. Barrow A, when there is a direct connection between the internal common carotid artery and the cavernous sinus; Barrow B when there is indirect communication between the meningeal branches of the internal carotid artery and the cavernous sinus; Barrow C, if the communication is indirect between the branches of the external carotid artery and the cavernous sinus; and Barrow D, if the communication is indirect between the meningeal branches of the internal and external carotid artery.<sup>vi</sup>

Direct fistulas manifest with episcleral vascular tortuosity, pulsatile proptosis, and audible ocular murmur.<sup>vii</sup> Because of the associated anomalous vascular flow, it can result in ocular ischemic damage by shunting arterial blood into the venous system, resulting in venous drainage obstruction due to increased vascular resistance.<sup>viii</sup> The resulting increase in intraocular pressure may cause glaucomatous optic neuropathy,<sup>ix,x</sup> choroidal effusion, non-granulomatous anterior uveitis, or damage to cranial nerves II, IV, or VI, by congestion in the orbit, or increased pressure in the cavernous sinus.<sup>xi</sup> On the contrary, indirect fistulas present less vascular flow than direct fistulas; their clinical presentation may be insidious, with less orbital congestion and chronic red eye due to arterialization of conjunctival vessels. Increased episcleral venous pressure may result in elevated intraocular pressure,<sup>iii</sup> with a similar risk of glaucomatous damage to the optic nerve.

Among the complementary studies, angio-resonance can be of diagnostic help; however, digital cerebral angiography is the

most sensitive procedure for diagnosis, since it allows the definition of the anatomy of the fistula, type of blood flow, collateral circulation, and therapeutic surgical strategy.<sup>vii</sup>

The treatment of carotid-cavernous fistula is interdisciplinary and individualized.<sup>ix,xiii</sup> Indirect fistulas may resolve spontaneously; therefore, conservative management, applying direct pressure on the eyeball or internal carotid compression with the contralateral hand, is recommended. A more aggressive approach is made based on the patient's clinical evolution. Endovascular intervention in direct fistulas is performed with detachable balloons and stents for larger fistulas, liquid embolic agents, and coil wires for smaller ones through transarterial access.<sup>xiii-xv</sup> En algunas ocasiones, puede valorarse el abordaje venoso central o periférico. For some cases, a central or peripheral venous approach must be considered. Additionally, venous access through orbitotomy has been reported.<sup>xvi</sup>

Additionally, to each case accordingly, it is important to control intraocular pressure with antiglaucomatous medications<sup>vi</sup> to prevent secondary glaucomatous neuropathy.

The differential diagnosis is varied. The following are considered among them: cavernous sinus thrombosis, retrobulbar hemorrhage secondary to traumatism, thyroid orbitopathy, orbital vasculitis, sarcoidosis, infections, benign or malignant tumors, and metastasis in the orbit.<sup>i</sup>

## Case presentation

This is a 62-year-old woman who consulted with a ten-month history of mild to moderate pulsatile left eye pain, with foreign body sensation, conjunctival injection, and sporadic epiphora, accompanied by four months of noticing a progressive, pulsatile, slightly mobile, and non-painful tumor in the inner third of the left upper eyelid. The patient reported a medical history of arterial hypertension and denied trauma or other medical or surgical history.

Physical examination identified best corrected visual acuity of 20/30 in the right eye and 20/25 in the left eye. Exophthalmometry at an interorbital distance of 106 mm, degree of ocular prominence of 18 mm in the right eye, and 22 mm in the left eye with evident left proptosis. Extraocular movements were preserved.

In addition, pulsation of the eyeball was palpated, and the ocular murmur was auscultated (Dandy's triad). Mild ptosis edema, pulsatile and non-painful in the left upper eyelid, was evaluated. In the slit lamp, the measure of the intraocular pressure was 20 mmHg in the right eye and 30 mmHg in the left eye. Similarly,

superior episcleral and nasal vascular congestion (Figure 1) and inferior chemosis were identified. Fundoscopy of the left eye showed mild dilatation and tortuosity of the superior and inferior temporal venous vessels (Figure 2).

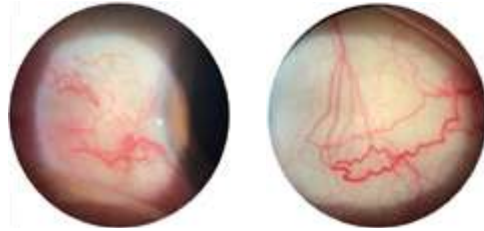


Figure 1. Slit lamp evaluation left eye

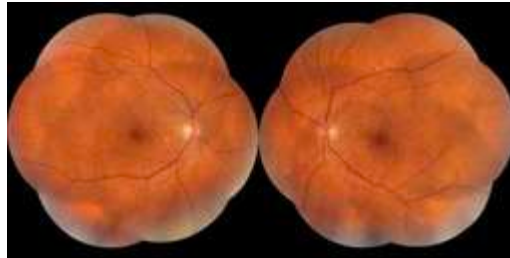


Figure 2. Fundoscopy of both eyes

## Therapeutic intervention

Treatment was initiated with a topical hypotensive with timolol 0.5 %, dorzolamide 2 %, and brimonidine 0.2 % every 12 hours in the left eye. In addition, ophthalmologic studies

of optic nerve and ganglion cell optical coherence tomography, 24:2 campimetry in both eyes and magnetic resonance imaging of orbits and brain were indicated.

The MRI of orbits performed on the same consultation day reported proptosis and dilatation of the left superior ophthalmic vein (Figure 3).

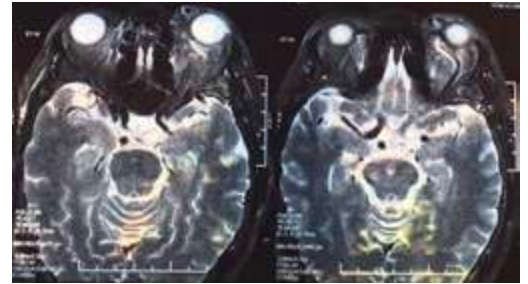


Figure 3. Magnetic resonance of orbits and brain

Optical coherence tomography of the optic nerve showed that the thickness and number of nerve fibers in both eyes were within the normal range, with 80 % symmetry. The cup/disc ratio was symmetrical, within normal mean in both eyes; a decrease in neuroretinal rim thickness was not reported. The thickness of ganglion cells in the macula was within normal values (Figure 4).

The result of the 24:2 campimetry of both eyes showed a nasal and temporal step in the

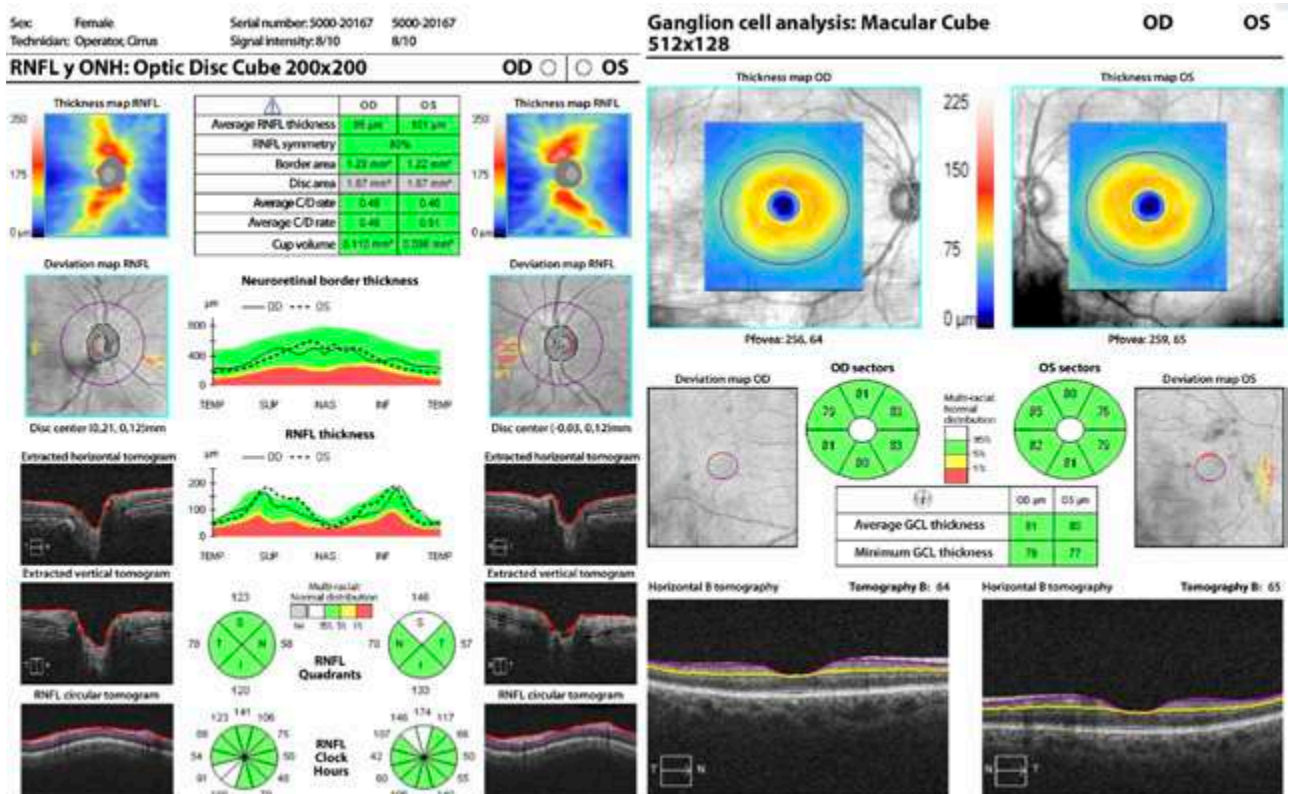
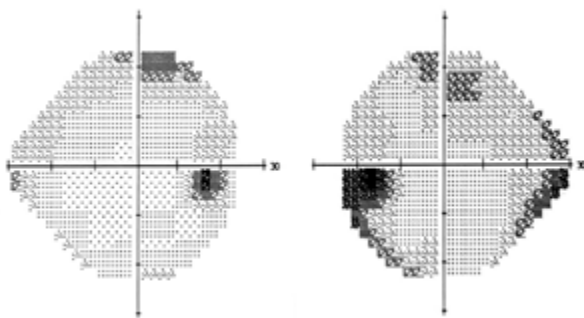


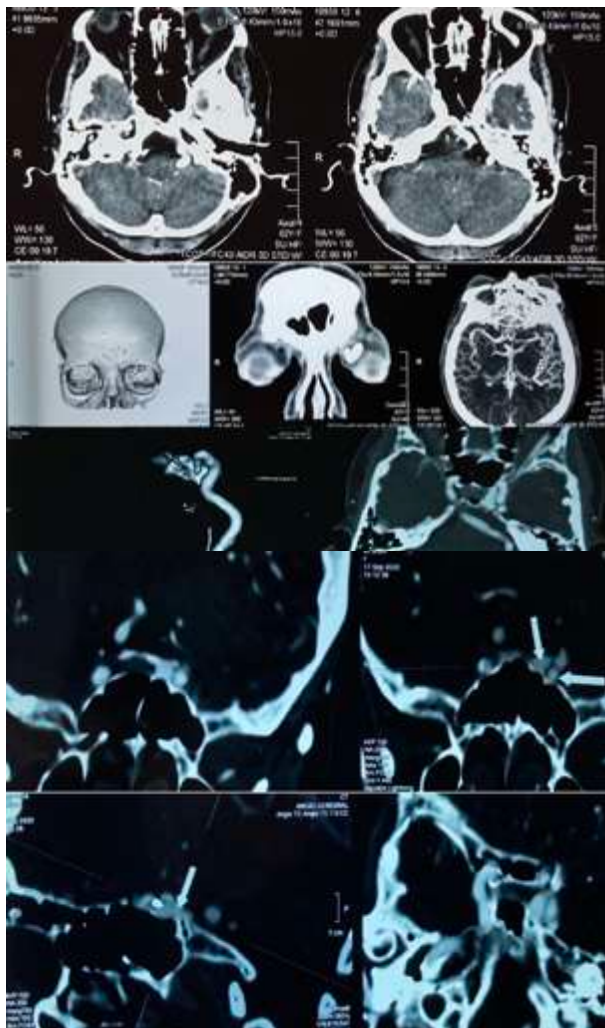
Figure 4. Optical coherence tomography of optic nerve and ganglion cells both eyes

left visual field (Figure 5); however, it presented 11 % of false negative errors and 1 % of false positive errors with a time duration of six minutes for SITA-Standard strategy; therefore, the interpretation was as inconclusive.

On the other hand, a venous drainage defect was identified in the left eye, consequently, an angio-tomography of orbits and brain was performed after 15 days, which showed a left carotid-cavernous fistula with the presence of arterial blood in the venous phase at the level of the cavernous sinus and vascular congestion in the superior ophthalmic vein (Figure 6).



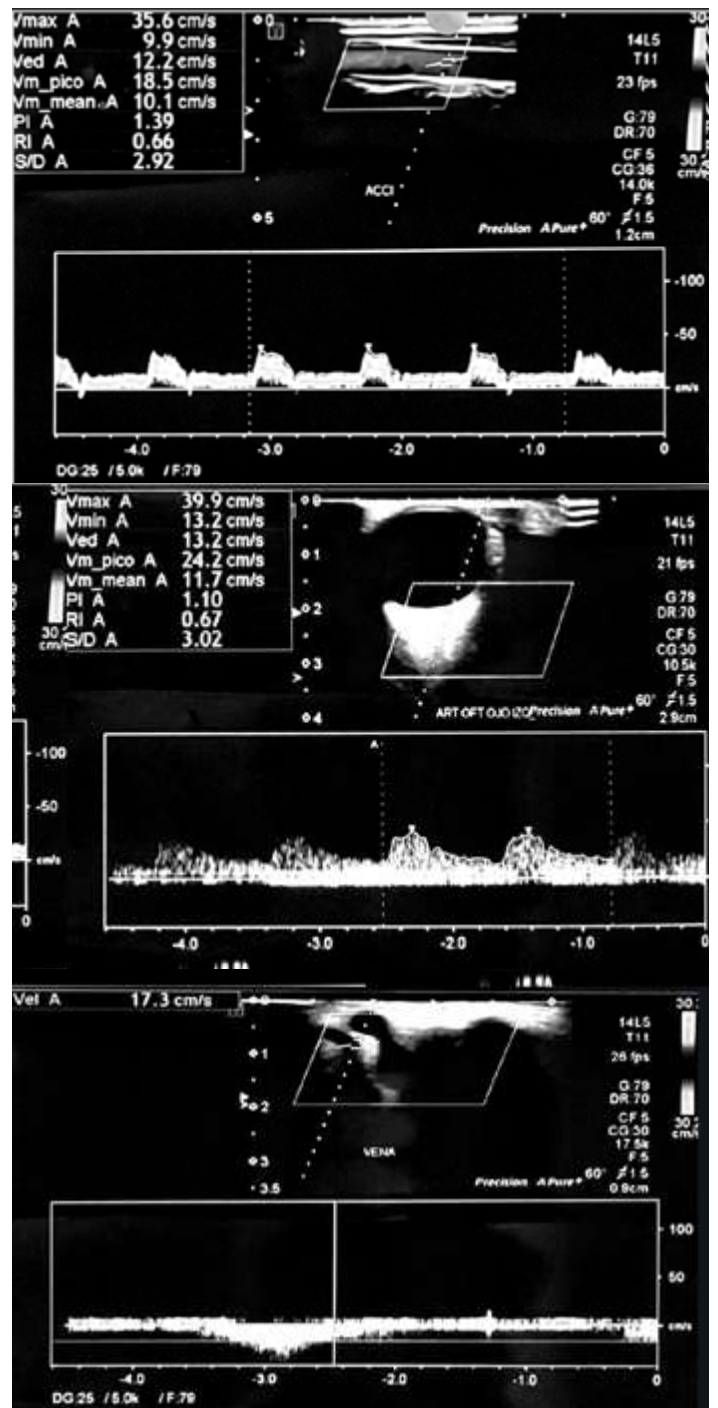
**Figure 5.** Campimetry 24:2 both eyes



**Figure 6.** Cerebral angio-tomography of orbits and brain

After a month, a venous Doppler ultrasound of the upper eyelid was performed, which showed a venous vascular dilatation in the left upper eyelid. The ophthalmic veins presented a high vascular flow of 27 and 18 cm/s (Figure 7), which indicated a high-expenditure carotid-cavernous fistula. Moreover, cerebral magnetic angio-resonance imaging showed greater detail on the collateral circulation of the cavernous fistula (Figure 8).

After six months, diagnostic and therapeutic cerebral angiography was conducted through the right femoral artery approach using the Seldinger technique. During this procedure,



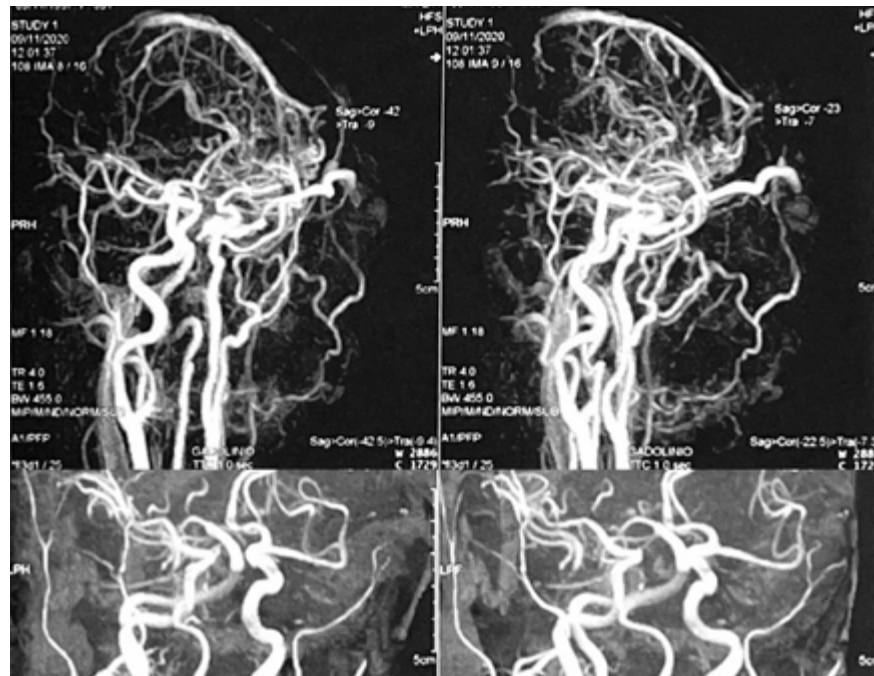
**Figure 7.** Venous doppler ultrasound of left upper eyelid

an anatomical defect of the "bovine" aortic arch was identified (Figure 9A), and a fistula with afferents to the middle meningeal artery (internal maxillary artery branch) and ascending pharyngeal artery with drainage to the left cavernous sinus (Figure 9B). An embolization with Coils and Onyx® was performed in the internal maxillary artery, and the Cosmos 10 3D 0.5 x 22 cm, the Hidrosoft Helical 10 0.5 x 15 cm,

and then 1 mL of Onyx® were placed; finally, the absence of flow in the branches (middle meningeal and superior pharyngeal) was assessed (Figure 9C and D).

## Outcome

The clinical evolution was satisfactory, with a best corrected visual acuity of 20/25 in



**Figure 8.** Cerebral magnetic resonance angiography



**Figure 9.** Diagnostic and therapeutic cerebral angiography. A. Bovine" aortic arch defect. B. Diagnostic cerebral angiography. C. and D. Therapeutic cerebral angiography (post-procedure)

the left eye; in addition, intraocular pressure was 17 mmHg, within normal values, and with an evident decrease in episcleral venous congestion (Figure 10) and edema of the left upper eyelid. Exophthalmometry performed at an interorbital distance of 106 mm with a prominence measurement of 18 mm for both eyes indicated an improvement in the initial proptosis of the left eye. Venous Doppler ultrasonography of the control left upper eyelid reported a flow of 2.6 to 3.1 cm/s, in the expected values of palpebral venous flow.

On the other hand, in the optical coherence tomography analysis study of the optic nerve and ganglion cells after treatment,

there was no evidence of progression in the damage of the optic disc or ganglion cells (Figure 11), preventing damage secondary to the initial ocular hypertension.

## Clinical diagnosis

Left carotid-cavernous fistula with high output and secondary ocular hypertension in the left eye.

## Discussion

Timely clinical diagnosis, through complementary imaging studies, is essential to reduce the complications associated

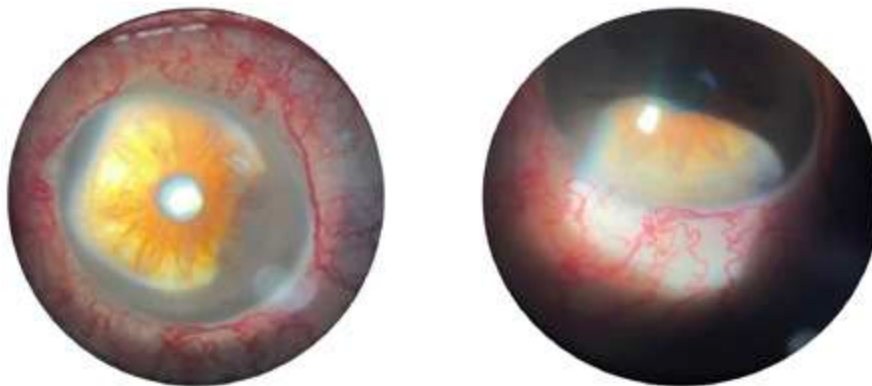


Figure 10. Slit-lamp evaluation of the left eye, post-treatment

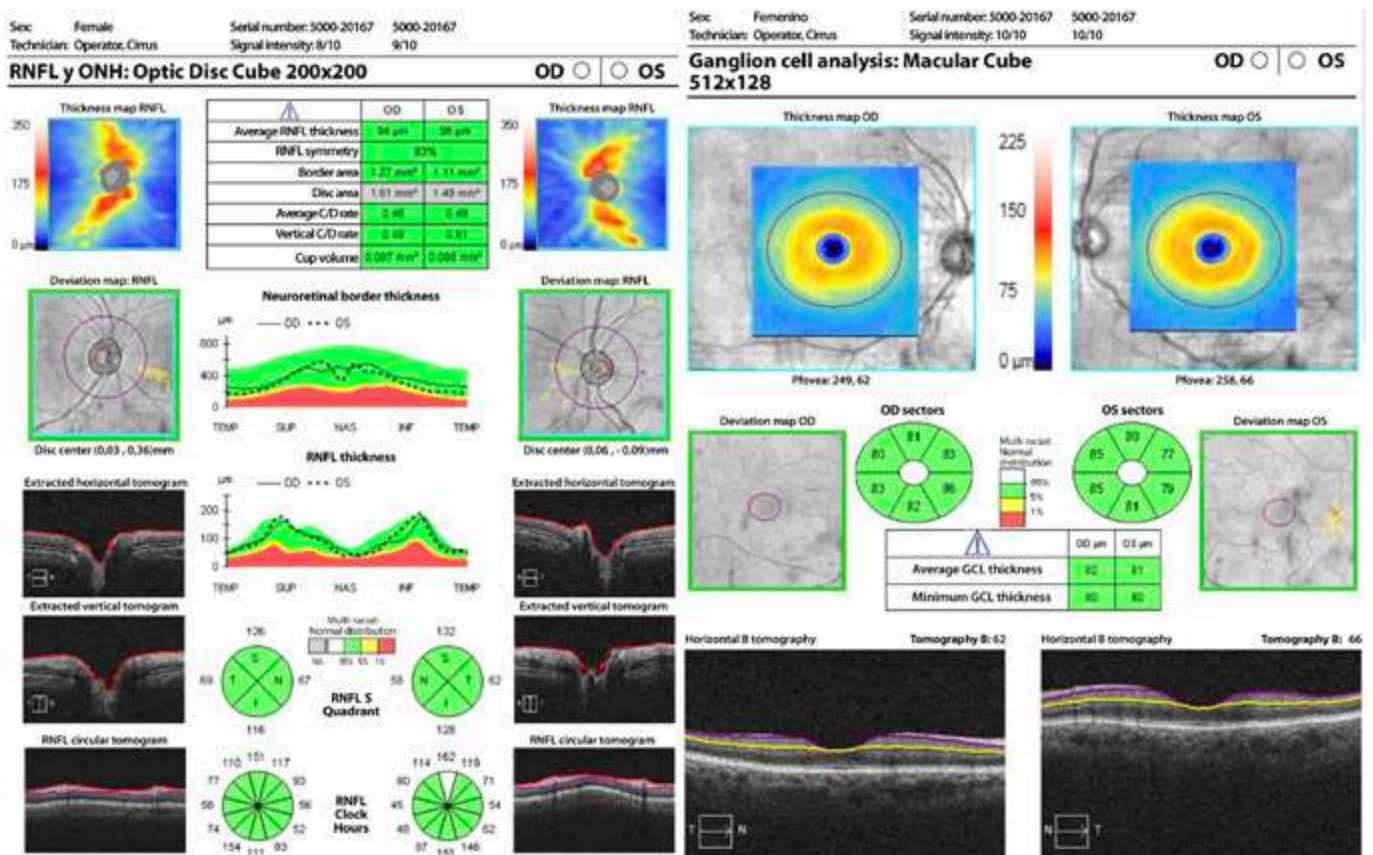


Figure 11. Optical coherence tomography of optic nerve and ganglion cells in both eyes, post left treatment

with ocular hypertension secondary to increased episcleral venous flow resistance in the carotid-cavernous fistula, with greater emphasis on the associated visual sequelae. The clinical features manifested as a high-output fistula, evidenced in imaging studies and the vascular flow velocity of the left upper eyelid; however, the vascular defect shown in the diagnostic cerebral angiography corresponds to that of an indirect Barrow C fistula, as it is associated with communication of branches of the external carotid artery and the cavernous sinus. However, some communication by meningeal branches of the internal carotid artery, associated with an indirect fistula type D, can be evidenced.<sup>vi</sup>

On the other hand, it is recommended to consider the venous approach for the left internal carotid artery afferents, thus avoiding late recanalization. Likewise, diagnostic imaging and treatment through cerebral angiographic embolization is the mainstay of treatment of this pathology,<sup>ii</sup> which allows preservation of visual acuity and avoids neurological sequelae in other pairs of cranial nerves.<sup>iv</sup> Similarly, topical hypotensive treatment provides a protective approach to the optic nerve, reducing ocular hypertension secondary to arteriovenous fistula.<sup>ix</sup>

In this case, best corrected visual acuity was preserved, with intraocular pressure within normal values; after treatment, there was no evidence of secondary glaucomatous optic neuropathy. A multidisciplinary approach is necessary for the management and follow up of the clinical evolution to achieve favorable treatment results and resolve the clinical condition.<sup>xiii-xv</sup>

## Ethical aspects

The Declaration of Helsinki 2013 was complied with, keeping the patient's data confidential as the affiliation number. The clinical case is governed by the ethical principles of non-maleficence, justice, beneficence, and autonomy. The patient is aware of the public presentation of her clinical case through informed consent.

## Acknowledgements

To Luis Edgardo Piche Lozano, Ophthalmology Specialty Coordinator and Alexis Castro Pérez, Chief of the Ophthalmology Service for their support in the analysis of this case. To José Roberto Corvera Urquilla, neuro-radiologist, chief of the Radiology Service of the Medical Specialty Clinic of the Salvadorean Social Security Institute for the interpretation of the imaging studies, and

to Cándido Omar Ortiz Vásquez and Dania Elizabeth Trinidad Arévalo, neurosurgeons and neuro-interventionists. All from the Salvadorean Social Security Institute.

## Funding

Institutional support from the Salvadorean Social Security Institute for complementary imaging studies, as well as pharmacological treatment and endovascular intervention procedures.

## References

- i. Bobby S. Korn. 2022-2023 Basic and Clinical Science Course, Section 07: Oculofacial Plastic and Orbital Surgery print 7°. San Francisco: American Academy of Ophthalmology; 2022. 377p.
- ii. Stacey AW, Gemmete JJ, Kahana A. Management of Orbital and Periocular Vascular Anomalies. *Ophthalm. Plast. Reconstr. Surg.* 2015;31(6):427-436. DOI: [10.1097/IOP.0000000000000504](https://doi.org/10.1097/IOP.0000000000000504)
- iii. Liang W, Xiaofeng Y, Weiguo L, Wusi Q, Gang S, Xuesheng Z. Traumatic Carotid Cavernous Fistula Accompanying Basilar Skull Fracture: a Study on the Incidence of Traumatic Carotid Cavernous Fistula in the Patients With Basilar Skull Fracture and the Prognostic Analysis About Traumatic Carotid Cavernous Fistula. *J. Trauma Inj. Infect. Crit. Care.* 2007;63(5):1014-1020. DOI: [10.1097/TA.0b013e318154c9fb](https://doi.org/10.1097/TA.0b013e318154c9fb)
- iv. Hamedani H, Hellmann D, Boyce W, Alesio ND. Traumatic carotid-cavernous fistula: A case report. *Radiol. Case Rep.* 2022;17(6):1955-1958. DOI: [10.1016/j.radcr.2022.02.065](https://doi.org/10.1016/j.radcr.2022.02.065)
- v. Henrard C, Belge H, Fastré S, Di Monaco S, Revencu N, Hammer F, *et al.* Cervical artery dissection: fibromuscular dysplasia versus vascular Ehlers-Danlos syndrome. *Blood Press.* 2019;28(2):139-143. DOI: [10.1080/08037051.2018.1557507](https://doi.org/10.1080/08037051.2018.1557507)
- vi. Barrow DL, Spector RH, Braun IF, Landman JA, Tindall SC, Tindall GT. Classification and treatment of spontaneous carotid-cavernous sinus fistulas. *J. Neurosurg.* 1985;62(2):248-256. DOI: [10.3171/jns.1985.62.2.0248](https://doi.org/10.3171/jns.1985.62.2.0248)
- vii. Sarkis Y, Worden A, Schreiber T, Lapitz A. High index of suspicion: diagnosing a carotid-cavernous fistula. *BMJ Case Rep.* 2023;16(3):e253473. DOI: [10.1136/bcr-2022-253473](https://doi.org/10.1136/bcr-2022-253473)
- viii. Chiu Y-J, Shih Y-J, Lee W-J, Liu Y-C. A man with proptosis of the left eye. *Ann. Emerg. Med.* 2022;80(5):420-455. DOI: [10.1016/j.annemergmed.2022.04.013](https://doi.org/10.1016/j.annemergmed.2022.04.013)



- ix. Kang JM, Tanna AP. Glaucoma. *Med. Clin. North Am.* 2021;105(3):493-510. DOI: [10.1016/j.mcna.2021.01.004](https://doi.org/10.1016/j.mcna.2021.01.004)
- x. Xia Y. A red eye induced by a spontaneous carotid cavernous fistula. *Am. J. Emerg. Med.* 2018;36(12):2336.e1-2336.e2. DOI: [10.1016/j.ajem.2018.08.055](https://doi.org/10.1016/j.ajem.2018.08.055)
- xi. Li S, Feng B, Feng Y, Pang Z, Lin Y. Carotid-cavernous fistula(CCF) presenting as paroxysmal painful ophthalmoplegia. *BMC Ophthalmol.* 2019;19(1):48. DOI: [10.1186/s12886-019-1039-8](https://doi.org/10.1186/s12886-019-1039-8)
- xii. Adam CR, Shields CL, Gutman J, Kim HJ, Hayek B, Shore JW, *et al.* Dilated Superior Ophthalmic Vein: Clinical and Radiographic Features of 113 Cases. *Ophthal. Plast. Reconstr. Surg.* 2018;34(1):68-73. DOI: [10.1097/IOP.0000000000000872](https://doi.org/10.1097/IOP.0000000000000872)
- xiii. Xinxing L, Jihui Z. Clinical Research of Combined Arteriovenous Approach Embolization on Complex Carotid-Cavernous Fistulas Liu J, editor. *BioMed Res. Int.* 2021;2021:1-5. DOI: [10.1155/2021/5580957](https://doi.org/10.1155/2021/5580957)
- xiv. Holland LJ, Mitchell Ranzcr K, Harrison JD, Brauchli D, Wong Y, Sullivan TJ. Endovascular treatment of carotid-cavernous sinus fistulas: ophthalmic and visual outcomes. *Orbit.* 2019;38(4):290-299. DOI: [10.1080/01676830.2018.1544261](https://doi.org/10.1080/01676830.2018.1544261)
- xv. Alexander MD, Halbach VV, Hallam DK, Cooke DL, Ghodke BV, Dowd CF, *et al.* Long-Term Outcomes of Endovascular Treatment of Indirect Carotid Cavernous Fistulae: Superior Efficacy, Safety, and Durability of Transvenous Coiling Over Other Techniques. *Neurosurgery.* 2019;85(1):E94-E100. DOI: [10.1093/neuros/nyy486](https://doi.org/10.1093/neuros/nyy486)
- xvi. Heran MKS, Volders D, Haw C, Shewchuk JR. Imaging-Guided Superior Ophthalmic Vein Access for Embolization of Dural Carotid Cavernous Fistulas: Report of 20 Cases and Review of the Literature. *Am. J. Neuroradiol.* 2019 40(4):699-702. DOI: [10.3174/ajnr.A5994](https://doi.org/10.3174/ajnr.A5994)

## Case report

# Patient with cutaneous leishmaniasis treated with miltefosine in an endemic area in Brazil

DOI: 10.5377/alerta.v7i2.17752

Juan Jorge Milla Espino

University of Brasilia, Brazil.

Correspondence

✉ [jmilla360@gmail.com](mailto:jmilla360@gmail.com)

ORCID: 0000-0001-8241-7042

## OPEN ACCESS

### Paciente con leishmaniasis cutánea tratada con miltefosina en un área endémica de Brasil

#### Suggested citation:

Milla Espino JJ. Patient with cutaneous leishmaniasis treated with miltefosine in an endemic area in Brazil. *Alerta*. 2024;7(2):146-151. DOI: 10.5377/alerta.v7i2.17752

#### Editor:

Larisa Chavarría.

#### Received:

November 23, 2023.

#### Accepted:

April 26, 2024.

#### Published:

July 24, 2024.

#### Author contribution:

JJME: study conception, writing, revising, and editing.

#### Conflicts of interest:

The author declared there are not conflicts of interest.



© 2024 by the author. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

#### Abstract

**Case presentation.** The patient is a 45-year-old woman with an oval-shaped ulcer on the left thigh, with well-defined and raised borders, no discharge, no crust, and painless; she presented a lesion of 60 days of evolution, which started as a punctate papule of progressive increase in size and depth until it became an ulcer, four weeks after a three-day trip to a rural area endemic for American tegumentary leishmaniasis. **Treatment.** The diagnosis of localized cutaneous leishmaniasis was confirmed; consequently, the patient received outpatient treatment with miltefosine 50 mg orally every eight hours for 28 days, accompanied by clinical and laboratory follow-up. **Outcome.** There were mild side effects, including nausea that subsided with treatment with ondansetron and omeprazole, and later hyporexia, which persisted until the end of treatment. There were no significant laboratory alterations. The patient was periodically evaluated according to the recommendations of the Brazilian Ministry of Health, and the lesion improved gradually, reaching a clinical cure on the 90th day.

#### Keywords

Cutaneous Leishmaniasis, Drug Therapy, Neglected Diseases.

#### Resumen

**Presentación del caso.** Se trata de una mujer de 45 años con úlcera en el muslo izquierdo, con forma ovalada, bordes bien definidos y elevados, sin secreción, sin costra, e indolora, que presentó una lesión de 60 días de evolución, que inició como una pápula puntiforme de aumento progresivo en tamaño y profundidad hasta generar una úlcera, después de cuatro semanas de haber realizado un viaje de tres días a un área rural endémica para leishmaniasis tegumentaria americana. **Intervención terapéutica.** Se confirmó el diagnóstico de leishmaniasis cutánea localizada, en consecuencia, recibió tratamiento ambulatorio con miltefosina de 50 mg por vía oral cada ocho horas por un total de 28 días, acompañado de seguimiento clínico y de laboratorio. **Evolución clínica.** Se presentaron efectos secundarios leves, entre ellos, las náuseas que cedieron con el tratamiento con ondansetrón y omeprazol, luego presentó hiporexia, que persistió hasta el final del tratamiento. No hubo alteraciones laboratoriales significativas. La paciente fue evaluada periódicamente según las recomendaciones del Ministerio de Salud de Brasil y se observó una mejoría clínica gradual de la lesión, hasta que en la evaluación del día noventa fue determinada la cura clínica.

#### Palabras clave

Leishmaniasis cutánea, quimioterapia, enfermedades desatendidas.

## Introduction

Leishmaniasis is a neglected tropical disease caused by the intracellular protozoa of Leishmania. The transmission cycle is complex and involves hematophagous vectors *Phlebotomus* or *Lutzomyia spp.* and vertebrate hosts that function as reservoirs. Worldwide,

between 1.5 and 2 million new cases are reported, and 70 000 deaths occur each year.<sup>i</sup> It is endemic in 88 countries, 72 considered developing countries. According to the World Health Organization, in 2018, 94 % of all new cases of leishmaniasis were reported in seven countries: Brazil, India, Kenya, Somalia, South Sudan, Ethiopia and Sudan.<sup>ii</sup>

In the Americas, the most common clinical form is known as American tegumentary leishmaniasis (ATL),<sup>iii</sup> which is also subdivided into localized cutaneous leishmaniasis, diffuse cutaneous leishmaniasis, and mucosal leishmaniasis.<sup>iv</sup> Clinical manifestations are varied and depend on the species of *Leishmania* involved and the type and magnitude of the host immune response. In broad terms, it is described as a lymphocyte-mediated immune response. On the one hand, a Th2-type response characterized by antibody production is ineffective in controlling infection and is associated with disseminated forms with high parasitemia. On the other hand, an overly robust Th1-type response with highly elevated levels of interferon- $\gamma$  and TNF is characterized by low parasitemia, and abundant tissue damage evidenced in the mucosal type.<sup>v</sup> The best response is a moderate Th1-type response, which effectively controls the infection and allows evolution to cure possible.<sup>vi</sup>

There are few therapeutic options available and those present complications such as high toxicity, high production costs, limited effectiveness, problems in administration, and the development of resistance.<sup>ii</sup> The first-line treatment in Brazil is meglumine antimoniate; it has been in use since 1940.<sup>vii, viii</sup> The administration is for 20 days, intravenously or intramuscularly, with the possibility for an extension based on clinical evolution. The medication should not be indicated for pregnant women due to teratogenicity; in addition, it is also not recommended as the first option for individuals over 50 years-old, with known hypersensitivity to the drug, and with certain chronic conditions such as cardiopathy, renal and hepatic disease. Furthermore, some adverse effects have been described, including pancreatitis, pancytopenia, peripheral neuropathy, joint stiffness, gastrointestinal symptoms, nephrotoxicity,<sup>ii</sup> and the most serious of them, the alteration of cardiac repolarization, which manifests itself as an extension of the QT segment, inversion and flattening of the T wave.<sup>iv</sup> Also, There are reports of as much as 40 % of therapeutic failure.<sup>ix</sup>

Alternative treatments for leishmaniasis include amphotericin B, pentamidine isethionate, and miltefosine.<sup>x</sup> These medications were originally developed for other diseases and repurposed for leishmaniasis treatment, a widespread practice for neglected diseases.<sup>vii</sup>

Miltefosine was initially developed for the treatment of metastatic breast cancer<sup>ii</sup>, approved by the Food and Drug Administration in 2014,<sup>xi</sup> and incorporated into the Brazilian Health System in 2018.<sup>xii</sup> Although

it is a teratogenic drug, it has some advantages compared to the others, such as its oral administration route with efficacy equivalent to that of pentavalent antimonial but with a lower incidence of adverse effects.<sup>ix</sup> However, it may cause gastrointestinal symptoms, hepatotoxicity, and nephrotoxicity.<sup>ii</sup>

## Case presentation

The patient, a 45-year-old female school-teacher, and resident in the city of Cuiabá, the capital of the state of Mato Grosso in the central-western region of Brazil, with a history of hysterectomy two years earlier due to uterine myomatosis; she was receiving daily treatment for arterial hypertension, with hydrochlorothiazide 12.5 mg and olmesartan 20 mg. The patient denied other chronic diseases.

The patient consulted for an ulcer on the left thigh after 60 days of evolution. It started as a papule with a progressive increase in size and depth, four weeks after a three-day trip to the municipality of Chapada dos Guimarães, a rural area in the State of Mato Grosso. Two individuals who accompanied her on this trip developed similar lesions.

When the condition started, the patient attended a primary care clinic and was treated with amoxicillin and clavulanic acid for five days without improvement, which caused her to consult again; on this occasion, she received treatment with cephalexin and acyclovir for seven days; she did not remember the doses of the drugs, and did not notice any improvement either. During the third consultation, the suspected diagnosis was ATL. As a result, the patient was referred to the state center for leishmaniasis cases in the city of Cuiabá, where she was received after six weeks.

Physical examination revealed an oval, painless ulcer with raised, well-defined, and hyperchromic borders. Fibrin presented at the base of the lesion without purulent secretion, crust, or any other alteration (Figure 1A).

A scraping, aspirate, and tissue sample for biopsy of the edge of the lesion and sent for anatomopathological study, direct parasitological study, culture, and polymerase chain reaction molecular study; the culture report and PCR study were positive; in the direct parasitological study there was no evidence of amastigotes, and it was considered negative. Finally, there was no report of the anatomopathological study.

## Treatment

The patient was prescribed outpatient treatment with miltefosine, 50 mg every eight

hours for 28 days. She received counseling regarding the potential adverse effects of the drug and a clinical and laboratory follow-up plan. Contraceptive methods were not offered due to the history of hysterectomy.

## Outcome

In the first control, the patient reported moderate-intensity nausea; she received daily treatment with ondansetron 4 mg and omeprazole 20 mg. Also, since the second week, she presented hyporexia until the end of the treatment. In the third and fourth control, a gradual improvement of the ulcer was evidenced by the growth of granulation tissue in the wound bed (Figure 1B). During this period, the nutritional status evaluation registered a loss of 2.5 kg of weight, and weekly laboratory tests did not present ranges out of the normal ones (Table 1).

After 63 days of treatment, there was evidence of re-epithelialization of the ulcer (Figure 1C). Finally, on day 90, the patient had a complete re-epithelialized lesion, without crusting, desquamation, or infiltration, and smooth to palpation; therefore, the clinical cure was concluded (Figure 1D).

## Clinical diagnostic

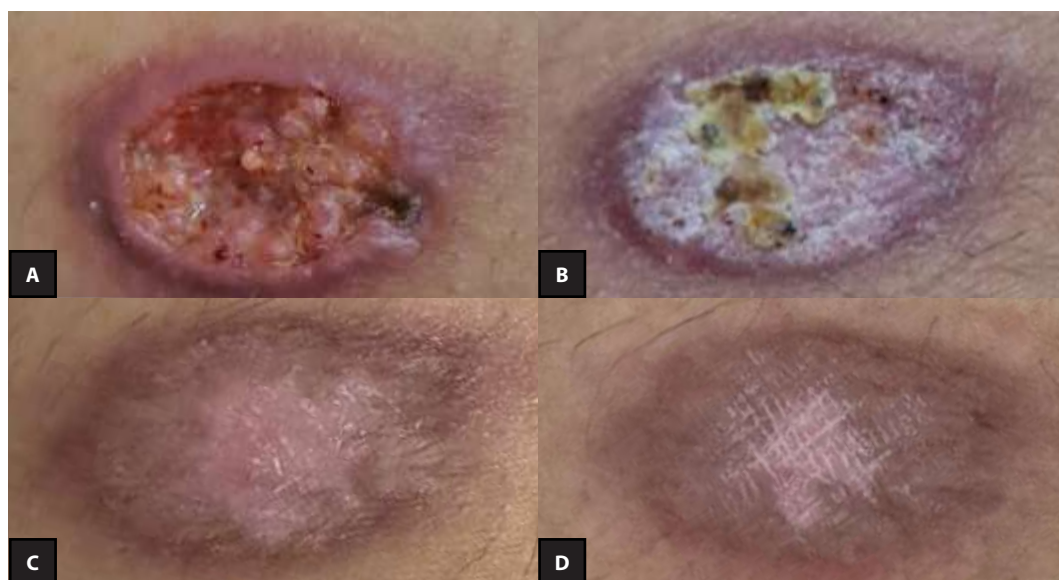
Localized cutaneous leishmaniasis was diagnosed based on clinical history, physical examination findings, and laboratory test results.

## Discussion

Brazil reported a total of 13 044 new cases of ATL in 2022. The State of Mato Grosso was the third state with the highest number of cases, with 9.58 % of cases. At the national level, 73.85 % of the cases were male and the most affected age group was between 20-39 years old.<sup>xiii</sup> Rural workers have been among particularly vulnerable groups for developing leishmaniasis since agriculture, forestry, and other extractive activities increase exposure to the vector.<sup>xiv</sup>

Three epidemiological patterns have been identified: wild, which occurs in areas of dense vegetation; occupational or leisure, associated with tourism and extractive industries; and rural or peri-urban, related to migration to rural areas in the countryside.<sup>iv</sup> This case falls under the occupational or leisure epidemiological pattern. However, the patient's characteristics differ from the typical epidemiological profile of the disease, since it is about a female who belongs to the least affected age group and her occupation and place of residence and work is in the urban area. It is worth considering that the disease can affect anyone.

The *Leishmania* species responsible for the infection in this case, was not identified since this procedure is not part of the protocol for the diagnostic routine of the Julio Müller University Hospital. However, the main species in the central-western region of the country is *Leishmania (Viannia)*



**Figure 1.** Clinical evolution of the lesion during the follow-up period. A. [Day 1] Ulcer with an area of 2.86 cm<sup>2</sup>, raised, well-defined and hyperchromic borders, base of the lesion with fibrin, but with a clean appearance, without purulent discharge or crust. B. [Day 28] Ulcer of 3.06 cm<sup>2</sup>, in the process of re-epithelialization, but with abundant crusting and desquamation, slightly elevated hyperchromic edges. C. [Day 63] Re-epithelialized lesion, slight desquamation persists, slightly elevated hyperchromic borders. D. [Day 90] Re-epithelialized lesion, hypochromic center, hyperchromic and smooth borders on palpation, no crusting or desquamation. Clinical cure.

*braziliensis*, which is widely distributed in Brazil and Latin America in general.<sup>iv</sup>

The clinical manifestations of the case were typical; the first sign is usually the formation of a papule at the site of the bite, followed by the formation of a nodule, and finally, an ulcer within two to eight weeks.<sup>xv</sup> The ulcers are generally round or oval, with well-marked and raised borders, have an erythematous base, and are painless.<sup>iv</sup>

The patient's treatment was successful, as it met the clinical criteria for cure established by the Brazilian Ministry of Health. These criteria include complete re-epithelialization of all skin lesions within 90 days and the disappearance of crusting, desquamation, infiltration, and erythema within 180 days of follow-up.<sup>iv</sup> In this case, all criteria were met within 90 days. The patient underwent periodic evaluations with laboratory tests, which did not show significant

alterations during the treatment. Nausea presented at the beginning of treatment, as well as hyporexia, are known and frequent adverse effects of the miltefosine drug<sup>xvi</sup> consequently, weight loss may occur.

Other drugs commonly used for treating cutaneous leishmaniasis include meglumine antimoniate, amphotericin B, and pentamidine isethionate.<sup>x</sup> Meglumine antimoniate has been the first-line treatment for several decades but has significant disadvantages. Treatment is usually administered intravenously at a dose between 10 and 20 mg/kg/day for 20 days, which can make adherence to treatment difficult.<sup>vii</sup> Systemic treatment instead of the use of intralesional administered treatment is favored.<sup>xvii</sup> The drug is linked to numerous adverse effects such as pancreatitis, pancytopenia, peripheral neuropathy, joint stiffness, gastrointestinal symptoms, nephrotoxicity,<sup>ii</sup> and also more

**Table 1.** Weekly nutritional evaluation and laboratory tests during the treatment period

	Day 1	Day 7	Day 14	Day 21	Day 28
Weight (Kg)	96.5	96.1	96.8	95.3	94
Body mass index	36.7	36.6	36.9	36.3	35,8
Alanine aminotransferase (U/L)	16	25	29	35	30
Aspartate aminotransferase (U/L)	14	19	18	20	20
Alkaline phosphatase (U/L)	65	71	71	69	-
Gamma-glutamyl transpeptidase (U/L)	55	49	53	64	-
Creatinine (mg/dL)	0.8	0.8	0.9	0.7	0,8
Urea (mg/dL)	33	31	38	42	-
Glucose (mg/dL)	118	116	116	112	-
Amylase (U/L)	52	49	56	61	51
Lipase (U/L)	41	43	34	36	35
Total Bilirubin (mg/dL)	0.2	0.3	0.3	0.2	-
Direct Bilirubin (mg/dL)	0.1	0.2	0.2	0.1	-
Indirect Bilirubin (mg/dL)	0.1	0.1	0.1	0.1	-
Hemoglobin (g/dL)	13.5	13.9	13.8	14.5	-
Hematocrit (%)	41.9	41.9	40	41.1	-
Leukocytes (cells/mm <sup>3</sup> )	7080	7240	7620	6770	-
Platelets (cells/mm <sup>3</sup> )	311 000	301 000	281 000	325 000	-
Serologic test for syphilis	Non-reactive	-	-	-	-
Hepatitis B virus surface antigen	Non-reactive	-	-	-	-
Antibody to hepatitis B virus surface antigen	Non-reactive	-	-	-	-
Human immunodeficiency virus	Non-reactive	-	-	-	-
Antibodies to hepatitis C virus	Non-reactive	-	-	-	-
Electrocardiogram	No anomalies	-	-	-	-

Source: clinical record.

severe manifestations such as QT segment extension, T-wave inversion, and flattening.<sup>iv</sup>

Amphotericin B is administered intravenously on daily bases. A total dose of 25-40 mg/kg; the total duration of treatment is variable and depends on the case and the patient's tolerance to the drug. Some adverse effects include fever, chills, tremors, dyspnea, flushing, tachycardia, hypotension, arthralgia, myalgia, and risk of nephrotoxicity.<sup>iv</sup>

Pentamidine isethionate is administered intravenously every other day, with three to ten total doses depending on the clinical course. Treatment is associated with hypoglycemia, hyperglycemia, hypotension, arrhythmias, QT interval prolongation, nephrotoxicity, leukopenia, hepatotoxicity, pancreatitis, and neuropathies.<sup>xviii</sup>

In the case described, treated with miltefosine, there was a complete cure; the advantages of this drug contributed to its adherence, such as the oral route of administration, its ambulatory use, and its higher safety profile, compared to other available drugs.

## Ethical aspects

This case report complies with the Helsinki declaration and international ethical guidelines. The confidentiality of the patient's data was respected.

## Acknowledgements

To the staff of the Julius Müller University Hospital and the Nucleus of Tropical Medicine of the University of Brasilia.

## Funding

There was not external funding for this work.

## References

- i. Saini I, Joshi J, Kaur S. Unwelcome prevalence of leishmaniasis with several other infectious diseases. *Int. Immunopharmacol.* 2022;110:109059. DOI: [10.1016/j.intimp.2022.109059](https://doi.org/10.1016/j.intimp.2022.109059)
- ii. Sasidharan S, Saudagar P. Leishmaniasis: where are we and where are we heading? *Parasitol. Res.* 2021;120(5):1541-1554. DOI: [10.1007/s00436-021-07139-2](https://doi.org/10.1007/s00436-021-07139-2)
- iii. Coutinho De Oliveira B, Duthie MS, Alves Pereira VR. Vaccines for leishmaniasis and the implications of their development for American tegumentary leishmaniasis. *Hum. Vaccines Immunother.* 2020;16(4):919-930. DOI: [10.1080/21645515.2019.1678998](https://doi.org/10.1080/21645515.2019.1678998)
- iv. Saúde M da. Manual de vigilância da Leishmaniose tegumentar. 1°. Brasília: Ms; 2016. Available at: [https://bvsm.s.saude.gov.br/bvs/publicacoes/manual\\_vigilancia\\_leishmaniose\\_tegumentar.pdf](https://bvsm.s.saude.gov.br/bvs/publicacoes/manual_vigilancia_leishmaniose_tegumentar.pdf)
- v. Scott P, Novais FO. Cutaneous leishmaniasis: immune responses in protection and pathogenesis. *Nat. Rev. Immunol.* 2016;16(9):581-592. DOI: [10.1038/nri.2016.72](https://doi.org/10.1038/nri.2016.72)
- vi. Kaye P, Scott P. Leishmaniasis: complexity at the host-pathogen interface. *Nat. Rev. Microbiol.* 2011;9(8):604-615. DOI: [10.1038/nrmicro2608](https://doi.org/10.1038/nrmicro2608)
- vii. Carvalho SH, Frézard F, Pereira NP, Moura AS, Ramos LMQC, Carvalho GB, *et al.* American tegumentary leishmaniasis in Brazil: a critical review of the current therapeutic approach with systemic meglumine antimoniate and short-term possibilities for an alternative treatment. *Trop. Med. Int. Health.* 2019;24(4):380-391. DOI: [10.1111/tmi.13210](https://doi.org/10.1111/tmi.13210)
- viii. Valencia C, Arévalo J, Dujardin JC, Llanos-Cuentas A, Chappuis F, Zimic M. Prediction Score for Antimony Treatment Failure in Patients with Ulcerative Leishmaniasis Lesions Carvalho EM, editor. *PLoS Negl. Trop. Dis.* 2012;6(6):e1656. DOI: [10.1371/journal.pntd.0001656](https://doi.org/10.1371/journal.pntd.0001656)
- ix. Martins SS, Barroso DH, Rodrigues BC, Da Motta JDOC, Freire GSM, Pereira LIDA, *et al.* A Pilot Randomized Clinical Trial: Oral Miltefosine and Pentavalent Antimonials Associated With Pentoxifylline for the Treatment of American Tegumentary Leishmaniasis. *Front. Cell. Infect. Microbiol.* 2021;11:9. DOI: [10.3389/fcimb.2021.700323](https://doi.org/10.3389/fcimb.2021.700323)
- x. Pradhan S, Schwartz RA, Patil A, Grabbe S, Goldust M. Treatment options for leishmaniasis. *Clin. Exp. Dermatol.* 2022;47(3):516-521. DOI: [10.1111/ced.14919](https://doi.org/10.1111/ced.14919)
- xi. Soto JA, Berman JD. Miltefosine Treatment of Cutaneous Leishmaniasis. *Clin. Infect. Dis.* 2021;73(7):e2463-e2464. DOI: [10.1093/cid/ciaa1461](https://doi.org/10.1093/cid/ciaa1461)
- xii. Ministério da Saúde. Orientações sobre o uso da miltefosina para o tratamento da Leishmaniose Tegumentar no âmbito do Sistema Único de Saúde. Brasil: Ministério da Saúde; 2020. p. 16. Report No.: 13. Available at: [https://www.gov.br/conitec/ptbr/midias/relatorios/2018/relatorio\\_miltefosina\\_leishmaniosetegumentar.pdf](https://www.gov.br/conitec/ptbr/midias/relatorios/2018/relatorio_miltefosina_leishmaniosetegumentar.pdf)
- xiii. Ministério da Saúde. Sistema de Informação de Agravos de Notificação. Brasil - Sinan Net. 2023. Available at: <https://portalsinan.saude.gov.br/>
- xiv. Augusto De Oliveira Guerra J, Vale Barbosa Guerra MDG, Vasconcelos ZS, Da Silva Freitas N, Rodrigues Fonseca F, Celso Andrade Da Silva Júnior R, *et al.* Socioenvironmental aspects of the Purus Region - Brazilian Amazon: Why relate them

- to the occurrence of American Tegumentary Leishmaniasis? Munderloh UG, editor. PLOS ONE. 2019;14(2):e0211785. DOI: [10.1371/journal.pone.0211785](https://doi.org/10.1371/journal.pone.0211785)
- xv. Volpedo G, Pacheco-Fernandez T, Holcomb EA, Cipriano N, Cox B, Satoskar AR. Mechanisms of Immunopathogenesis in Cutaneous Leishmaniasis And Post Kala-azar Dermal Leishmaniasis (PKDL). Front. Cell. Infect. Microbiol. 2021;11:1-16. DOI: [10.3389/fcimb.2021.685296](https://doi.org/10.3389/fcimb.2021.685296)
- xvi. Pijpers J, Den Boer ML, Essink DR, Ritmeijer K. The safety and efficacy of miltefosine in the long-term treatment of post-kala-azar dermal leishmaniasis in South Asia - A review and meta-analysis Sundar S, editor. PLoS Negl. Trop. Dis. 2019;13(2):e0007173. DOI: [10.1371/journal.pntd.0007173](https://doi.org/10.1371/journal.pntd.0007173)
- xvii. De Vries HJC, Schallig HD. Cutaneous Leishmaniasis: A 2022 Updated Narrative Review into Diagnosis and Management Developments. Am. J. Clin. Dermatol. 2022;23(6):823-840. DOI: [10.1007/s40257-022-00726-8](https://doi.org/10.1007/s40257-022-00726-8)
- xviii. Hafiz S, Kyriakopoulos C. Pentamidine StatPearls. 2023. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK557586/>

# Effects of *Trypanosoma cruzi* infection in Balb/c and NIH mouse strains

DOI: 10.5377/alerta.v7i2.16425

Cindy Betsabé Ramírez Merches<sup>1</sup>, Wendy Maribel Campos Portillo<sup>2</sup>, Ana Miriam González Pérez<sup>3</sup>, José Guillermo Mejía Valencia<sup>4</sup>

1-2. School of Biology, School of Natural Sciences and Mathematics, University of El Salvador, San Salvador, El Salvador.

3. Laboratory in Vector Entomology, Health Research and Development Center, University of El Salvador, San Salvador, El Salvador.

4. Animal laboratory, Health Research and Development Center. University of El Salvador, San Salvador, El Salvador.

\*Correspondence

✉ neftaligranados.dr@gmail.com

1.  0009-0003-9820-36302.  0000-0002-3278-83283.  0000-0002-7891-297X4.  0000-0003-4527-9175
 OPEN ACCESS

## Efectos de la infección del *Trypanosoma cruzi* en ratones de las cepas Balb/c y NIH

### Suggested citation:

Ramírez Merches CB, Campos Portillo WM, González Pérez AM, Mejía Valencia JG. Effects of *Trypanosoma cruzi* infection in Balb/c and NIH mouse strains. Alerta. 2024;7(2):152-160. DOI: 10.5377/alerta.v7i2.16425

### Editor:

Edgar Quinteros.

### Received:

July 18, 2023.

### Accepted:

June 27, 2024.

### Published:

July 24, 2024.

### Author contribution:

CBRM<sup>1</sup>, WMCP<sup>2</sup>, AMGP<sup>3</sup>, JGMV<sup>4</sup>: literature search, data analysis, writing, revising and editing. CBRM<sup>1</sup>, WMCP<sup>2</sup>: data collection. AMGP<sup>3</sup>, JGMV<sup>4</sup>: manuscript design. WMCP<sup>2</sup>: study design and data or software management.

### Conflicts of interest:

The authors declared there are not conflicts of interest.



© 2024 by the authors. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

### Abstract

**Introduction.** Chagas disease is an infection caused by the parasite *Trypanosoma cruzi* and transmitted by the vector *Triatoma dimidiata*, known in El Salvador as “chinche picuda”. This disease has always been of scientific interest in animal models. **Objective.** Identify the effect of *Trypanosoma cruzi* infection in mice of different strains (BALB/c and NIH) and sex. **Methodology.** Eight groups were established: four infected with *Trypanosoma cruzi* and four uninfected groups, distributed by strain and sex, with five mice per group. The body weight of the mice was recorded for six weeks. In addition, blood samples from the infected groups were prepared on slides for parasitemia counts. At the end of the study, the spleen and heart were extracted from both groups for statistical analyses. **Results.** The infected groups showed an increase in weight compared to their control groups. In the NIH strain, females had higher parasitemia, whereas in the BALB/c strain, males had higher parasitemia. The organs of the infected groups were significantly larger compared to those of the control groups, except in the heart of the BALB/c strain. Regarding organ weight, significant differences were observed only in the heart of the male BALB/c strain, while the opposite was true for the spleen. **Conclusion.** Males of the BALB/c strain are more susceptible to *Trypanosoma cruzi*, presenting higher levels of parasitemia among the groups studied.

### Keywords

*Trypanosoma cruzi*, Parasitaemia, Blood, Animal Experimentation, Chagas Disease.

### Resumen

**Introducción.** La enfermedad de Chagas es una infección causada por el parásito *Trypanosoma cruzi* y transmitida por el vector *Triatoma dimidiata*, conocido en El Salvador como «chinche picuda». Esta enfermedad siempre ha sido de interés científico en modelos animales. **Objetivo.** Identificar el efecto de la infección por *Trypanosoma cruzi* en ratones de diferentes cepas (BALB/c y NIH) y sexo. **Metodología.** Se establecieron ocho grupos: cuatro infectados con *Trypanosoma cruzi* y cuatro grupos no infectados, distribuidos por cepa y sexo, con cinco ratones por grupo. Durante seis semanas se registró el peso corporal de los ratones. Además, se prepararon muestras de sangre de los grupos infectados en láminas para realizar los conteos de parasitemia. Al final del estudio, se extrajeron el bazo y el corazón de ambos grupos para los análisis estadísticos. **Resultados.** Los grupos infectados mostraron un incremento de peso en comparación a sus grupos controles. En la cepa NIH, las hembras presentaron una mayor parasitemia, mientras que en la cepa BALB/c fueron los machos los de mayor parasitemia. Los órganos de los grupos infectados fueron significativamente más grandes comparados a los de los grupos de control, excepto en el corazón de la cepa BALB/c. Respecto al peso de los órganos, se observaron diferencias significativas únicamente en el corazón de los machos de la cepa BALB/c, mientras que en el bazo ocurrió lo contrario. **Conclusión.** Los machos de la cepa BALB/c son más susceptibles al *Trypanosoma cruzi*, presentando niveles de parasitemia más altos entre los grupos estudiados.

### Palabras clave

*Trypanosoma cruzi*, parasitemia, sangre, experimentación animal, enfermedad de Chagas.

## Introduction

The flagellate protozoan *Trypanosoma cruzi* (*T. cruzi*) is the causative agent of American trypanosomiasis or Chagas disease, a disease of public health importance that

persists as endemic in large areas of Latin America. Transmission occurs mainly using triatomine vectors, nocturnal hematophagous insects belonging to the subfamily Triatominae of the order Hemiptera, family Reduviidae, which feed on mammal blood.<sup>1</sup>



The natural reservoirs are armadillos, marsupials, rodents, bats, wild primates, and domestic animals such as dogs and cats. The parasite has been isolated in more than 150 species of domestic and wild mammals.<sup>ii</sup>

The life cycle of *T. cruzi* is complex, involving transmission by insect vectors and infection of vertebrate hosts, most of which are mammals, including humans, which are susceptible hosts.<sup>iii</sup>

Understanding the pathophysiology of *T. cruzi* infection in laboratory animals is a significant achievement in studying Chagas disease. Controlled experimental models allow the analysis of different parameters related to the host and the parasite, which cannot be addressed in humans for practical and ethical reasons.<sup>iv,v</sup>

Most of the studies of the acute phase of the disease are performed in animal models since this phase of the disease, generally in humans, goes unnoticed because it is self-limited and has non-specific clinical manifestations, which leads to most cases going undiagnosed. The most widely used model to study this disease is the laboratory mouse since it is one of the best-studied species from the immunological point of view. The experimental acute infection progresses differently depending on the parasite strain, mouse strain, virulence, inoculation dose, number of parasites, age, sex, and genetic profile, among other factors.<sup>v,vi,vii</sup> Pathogenic strains of *Trypanosoma cruzi* generally cause acute disease and high mortality in susceptible strains of mice, although these models are considered accurate representations of the infection process in humans. However, they are crucial for investigating immune responses, endocrine and metabolic states, and their interactions since this acute stage goes unnoticed in humans, except in cases of oral infection.<sup>vii</sup>

Different strains of mice differ in susceptibility or resistance to infection, evidencing

a complex genetic control of parasitemia levels and survival of infected animals.<sup>viii,ix,x</sup> Therefore, in this study we evaluated the effect of *Trypanozoma cruzi* infection in mice of different strains (BALB/c and NIH) and sex.

## Methodology

### Experimental design

A total of 40 healthy mice were used. They underwent clinical checks to evaluate their fur, eyes, skin, and mucous membranes. The mice were divided into eight groups, each consisting of five mice. Four groups were infected with parasites (cases), and four remained healthy (controls). The groups were categorized based on strain (NIH and BALB/c) and sex (refer to Table 1).

The control group was assessed for body weight, heart and spleen size, and weight. All mice were randomly chosen and were around five to six weeks old. The study lasted six weeks, with the first week dedicated to parasite inoculation and the following five weeks for counting parasite levels twice a week. Each infected mouse was evaluated ten times using a Leica microscope.

Currently, there is no ethics committee for laboratory animals in El Salvador. However, the study was conducted by international ARRIVE standards.<sup>xi</sup>

### Parasite collection

*Trypanosoma cruzi* parasites in their metacyclic trypomastigote stage were obtained from a sample of feces of the vector *Triatoma dimidiata* collected in the Huisiltepeque canton, city of Tenancingo, department of Cuscatlán, El Salvador. Vector feces were diluted in 0.5 mL of 0.9 % normal saline, and the presence of *Trypanosoma cruzi* was verified by direct observation using a bright-field microscope. This preparation was provided

**Table 1.** Initial body weight, final body weight and percentage increase in grams of the experimental groups

Group	Initial weight	Final weight	Increase %	p-value
NIH (females) Control	24.63 ± 2.62	26.93 ± 2.50	9.56 ± 5.06	-
NIH (females) Infected	22.94 ± 2.21	28.44 ± 2.29	24.22 ± 5.70	0.005*
NIH (males) Control	26.60 ± 5.23	31.08 ± 5.63	17.17 ± 4.53	-
NIH (males) Infected	22.15 ± 7.64	33.43 ± 4.16	60.49 ± 18.64	0.102
BALB/c (females) Control	24.40 ± 0.87	27.63 ± 0.85	13.33 ± 5.65	-
BALB/c (females) Infected	27.08 ± 0.93	33.24 ± 1.37	22.80 ± 4.84	0.030*
BALB/c (males) Control	21.78 ± 0.77	28.98 ± 0.81	33.20 ± 6.04	-
BALB/c (males) Infected	17.32 ± 0.83	30.10 ± 2.96	73.69 ± 13.08	0.001*

Values are expressed as the mean ± standard deviation. Significant differences between groups are expressed when \*p-value < 0.05.

Weight expressed in grams.

by the Laboratory in Vector Entomology of the Health Research and Development Center of the University of El Salvador.

## Experimental animals

Mice of the NIH and BALB/c strains from the Animal Laboratory of the Center for Health Research and Development of the University of El Salvador were used. The mice were fed a diet of Tecnutral pelleted concentrate for rodents and free access to water. All animals were kept at a temperature of  $22 \pm 2$  °C and a controlled relative humidity between 50-60 %, with a light-dark cycle of 12/12 hours. For individual identification, they were individually marked with picric acid.

## Parasite inoculation

The mouse with the highest parasitemia (blood trypomastigotes) was identified and blood was drawn from the submandibular vein to obtain  $1 \times 10^5$  parasites/mL in saline. This amount was necessary to reach to infect the mice. Subsequently, mice were restrained and immobilized and each mouse was inoculated intraperitoneally with  $1 \times 10^4$  parasites/0.1 mL of the previously prepared solution using a 1 mL tuberculin syringe. The following formula was used to calculate the number of parasites required to achieve infection,<sup>xii</sup> where:

$C_1$ :  $1 \times 10^5$  parasites

$V_1$ : 1 mL of 0,9 % normal saline

$$V_2 = \frac{C_1 V_1}{C_2}$$

$C_2$ : Amount of parasites in the infected mouse

$V_2$ : Amount of blood needed

## Body weight

The initial body weight in grams of all groups was recorded using a COBOS scale before parasite inoculation. Subsequently, weighing was performed once a week until the end of the experiment.

## Parasite count

Perform the count, a blood sample of approximately 10  $\mu$ L was drawn from the tail of each infected mouse. Then, 5  $\mu$ L of blood were taken with an Accumax<sup>®</sup> micropipette, which were deposited on a slide and immediately covered with a coverslip to obtain a thin and homogeneous layer. Subsequently,

it was taken to the microscope for observation at 40x and a parasite count was performed in 50 fields, counting from left to right and vice versa.

## Organ size and weight

Once the parasitemia counts were completed, all animal groups underwent cervical dislocation for euthanasia. The organs (heart and spleen) were then removed to evaluate their appearance, size (measured in centimeters), and weight (measured in grams).

## Statistical analysis

The data was analyzed using IBM<sup>®</sup> SPSS 21 and Microsoft Excel 365 for statistical analysis. The Student's T-test was used to compare body and organ weights, while a one-way analysis of variance (ANOVA) was used for parasite counts. A difference between experimental groups was considered significant when  $p < 0.05$ . The results are mostly expressed as Mean  $\pm$  Standard Deviation.

## Results

### Body weight

Table 1 indicates that the *Trypanosoma cruzi* groups obtained a greater percentage increase in body weight compared to their control groups (uninfected mice), with most having a p-value  $< 0.05$  except for the male NIH strain group, which obtained a p-value = 0.102.

### Parasite counts

Mice infected with *T. cruzi* of NIH and BALB/c strains presented different results in terms of sex, reflected in Table 2 and Figure 1. All groups of mice evaluated survived until the end of the study. The peak of parasitemia occurred at counts seven and eight.

Figure 1-A graphically compares the number of parasites observed during the investigation. In the NIH strain, it can be seen that the group of females presented a higher parasitemia through time, having its maximum point at parasite count seven. Figure 1-B shows the BALB/c strain, where the males presented the highest parasitemia, reaching its maximum at the seventh parasite count.

### Organ size and weight

Once the parasite count was completed, the heart and spleen were extracted from the

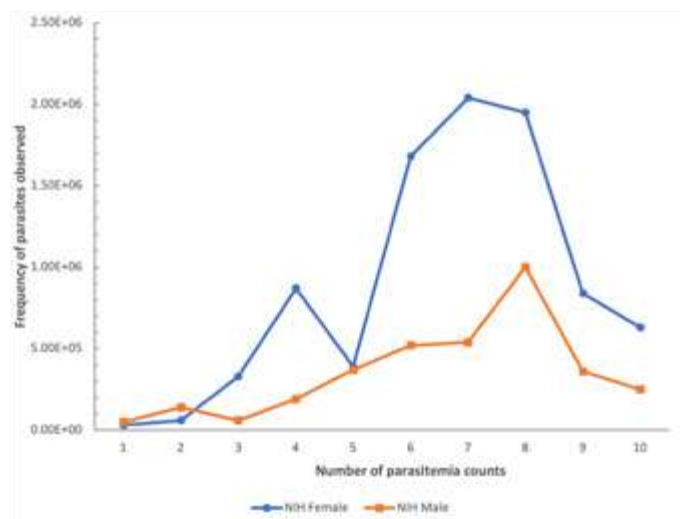
eight groups of mice. Table 3 shows that the size of both organs in the groups infected with *T. cruzi* showed an increase when compared with their control groups, except in the heart of the BALB/c strain where no significant differences in size were obtained, while in the spleen almost all showed significant differences, with the exception of the male group of the BALB/c strain that obtained a p value = 0.053 with respect to its control group.

The weight of the organs analyzed between the control and infected groups can be seen in Table 4. They showed significant differences for the heart only in the group of the BALB/c strain males with a p-value = 0.008. On the other hand, in the spleen, the only group that did not show differences compared to their control was the BALB/c strain males with a p-value = 0.061, despite having a very high mean.

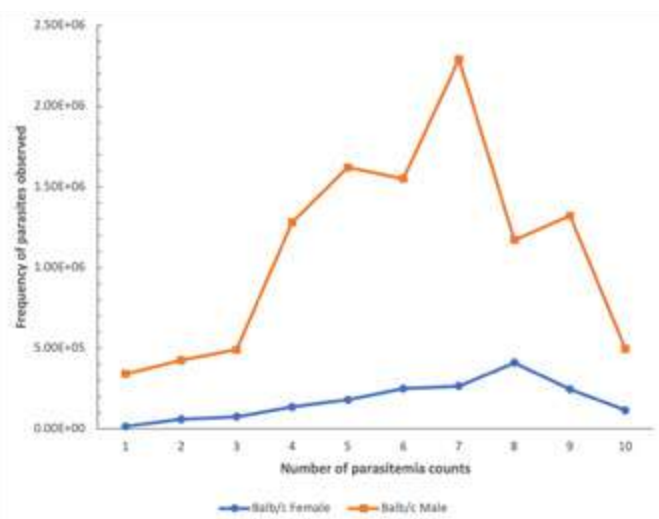
## Discussion

The fundamental interest in this study was to demonstrate the acute phase of *Trypanosoma cruzi* infection in an animal model using BALB/c and NIH strain mice after a six-week observation period.

However, the results obtained in this study contradict the findings of other authors<sup>xiii,xiv,xv,xvi,xvii</sup> who have shown that infection with this parasite causes a statistically significant decrease in body weight in BALB/c and Cba/j mice approximately thirty days after infection.<sup>xiii,xiv,xv</sup> This weight loss is attributed to a marked depletion of body fat and an increase in water retention, suggesting that the disease induces true cachexia, which is considered one of the manifestations of the inflammatory reaction to this infection.<sup>xvi,xvii</sup>



**Figure 1.** (A) Behavior of parasite counts (*T. cruzi*) of the NIH strain for both sexes over time (six weeks)



**Figure 1.** (B) Graphical behavior of parasite counts (*T. cruzi*) of the BALB/c strain for both sexes over time (six weeks)

**Table 2.** Median values of the number of parasites (*T. cruzi*) per milliliter (mL) in the experimental groups

Groups/Count	NIH (females)	NIH (males)	BALB/c (females)	BALB/c (males)
1	0	5.00E+04	0	3.00E+05
2	0	5.00E+04	7.50E+04	4.00E+05
3	1.50E+05	5.00E+04	5.00E+04	3.00E+05
4	7.50E+05	1.00E+05	1.25E+05	8.75E+05
5	7.50E+05	3.00E+05	1.00E+05	1.60E+06
6	7.50E+05	3.50E+05	2.00E+05	1.10E+06
7	7.50E+05	5.00E+05	1.50E+05	2.20E+06
8	7.50E+05	8.00E+05	4.75E+05	1.10E+06
9	7.50E+05	3.50E+05	2.50E+05	1.60E+06
10	7.50E+05	1.00E+05	1.50E+05	6.00E+05

Values expressed as median, significant differences (\*) between groups are expressed when p-value < 0.05.

Besides, these studies show weight loss is associated with pronounced hypoglycemia and is a consequence of a multifactorial process that includes the increase in proinflammatory cytokines, the reduction in food intake at the end of the infection, the hepatic involvement caused by the parasite, leading to deficiencies in the gluconeogenic pathway, and the high energy demand caused by the activation of the immune system.<sup>xv</sup>

Variations in body weight can be inversely influenced by metabolic disorders and hormonal imbalances. Major hormones influencing body weight include glucocorticoids, prolactin, dehydroepiandrosterone, growth hormone, testosterone, and leptin. Alteration in the structure or resistance to the hormone leptin can inhibit satiety and lead to energy imbalance, resulting in obesity and increasing susceptibility to infections and

**Table 3.** Size of organs (heart and spleen) in centimeters mainly affected in experimental mice

Organ	Group	Mean ± S.D.	p-value
Heart	NIH (females) Control	0.68 ± 0.17	0.073
	NIH (females) Infected	0.86 ± 0.09	
	NIH (males) Control	0.87 ± 0.24	0.966
	NIH (males) Infected	0.88 ± 0.08	
	BALB/c (females) Control	0.95 ± 0.10	0.071
	BALB/c (females) Infected	0.82 ± 0.08	
	BALB/c (males) Control	1.00 ± 0.08	
	BALB/c (males) Infected	0.94 ± 0.09	
Spleen	NIH (females) Control	1.88 ± 0.15	0.000*
	NIH (females) Infected	2.66 ± 0.15	
	NIH (males) Control	1.75 ± 0.33	0.002*
	NIH (males) Infected	2.48 ± 0.11	
	BALB/c (females) Control	2.00 ± 0.08	0.000*
	BALB/c (females) Infected	2.52 ± 0.13	
	BALB/c (males) Control	1.73 ± 0.38	
	BALB/c (males) Infected	2.56 ± 0.63	

Values are expressed as the mean ± standard deviation (S.D.). Significant differences between groups are expressed when \*p < 0.05.

**Table 4.** Weight in grams of affected organs (heart and spleen) in experimental mice

Organ	Group	Mean ± S.D.	p-value
Heart	NIH (females) Control	0.17 ± 0.01	0.060
	NIH (females) Infected	0.14 ± 0.03	
	NIH (males) Control	0.16 ± 0.03	0.685
	NIH (males) Infected	0.14 ± 0.06	
	BALB/c (females) Control	0.16 ± 0.04	0.076
	BALB/c (females) Infected	0.21 ± 0.03	
	BALB/c (males) Control	0.20 ± 0.04	
	BALB/c (males) Infected	0.13 ± 0.02	
Spleen	NIH (females) Control	0.13 ± 0.03	0.020*
	NIH (females) Infected	0.37 ± 0.15	
	NIH (males) Control	0.14 ± 0.02	0.007*
	NIH (males) Infected	0.32 ± 0.08	
	BALB/c (females) Control	0.13 ± 0.01	0.001*
	BALB/c (females) Infected	0.38 ± 0.07	
	BALB/c (males) Control	0.16 ± 0.09	
	BALB/c (males) Infected	0.35 ± 0.16	

Values are expressed as mean ± standard deviation (SD). Significant differences between groups are expressed when \*p-value < 0.05.

inflammation,<sup>xviii,xix</sup> which could explain the findings observed in this study.

Concerning parasitemia, the results show that in the BALB/c strain, the females showed greater resistance than the males, presenting a lower number of parasites in the blood during the acute phase of Chagas disease, as previously reported.<sup>xx</sup> In contrast, male mice of the NIH strain were the most resistant to parasitemia.

It is important to note that the blood trypomastigotes of *T. cruzi*, as in this research, are visualized more rapidly compared to when they are inoculated in their metacyclic form, obtained directly from the insect or from transformations carried out *in vitro*, as has been documented in different studies with other strains of mice.<sup>xxi,xxii</sup> Some similar investigations mention a variety of patterns in the relationship between the parasite and the host. In this case, experimental mice acquire the disease using an established or predetermined inoculation that can be modulated by multiple variables that depend on the host, among which we have sex and genetic composition.<sup>xx</sup> Furthermore, infection in laboratory strains of mice can vary from highly resistant to highly susceptible strains, suggesting a genetically established basis.<sup>vii,xxiii,xxiv</sup>

Despite the different strains of mice and parasites, it is clear that multiple factors can influence infection, such as inoculum size (amount of parasites administered) and host age, although experimentally, young adults are used for this kind of *in vivo* models.<sup>vii,xxi</sup>

It has also been demonstrated that there are genes involved in resistance or susceptibility to the disease, and among these, the most important in determining the number of parasites are those related to the response of the immune system.<sup>xxv</sup> It has been documented that the virulence capacity of *T. cruzi* to establish the infection of a host is associated with the state-specific expression of genes and their polypeptide products; many of these molecules are regulated during the differentiation and development of the different stages of the parasite that are related to the evasion of the host's defenses.<sup>xxvi,xxvii,xxviii</sup> Among the genetic factors associated with resistance or susceptibility to a variety of infectious agents are those usually linked to the Major Histocompatibility Complex (MHC), whose genes code for proteins responsible for the induction of the immune response against a variety of antigens.<sup>xxix</sup>

Infection by protozoa such as *T. cruzi* is also usually influenced by the control that sex hormones can exert.<sup>xxx,xxxi</sup> In the case of females, this may be due to the effect produced by estrogens that stimulate the phagocytic activity of the macro-

phage and increase the local inflammatory response.<sup>xxxii,xxxiii,xxxiv</sup> The development of infection with this parasite seems to have different responses between males and females in murine models; in some cases, sex does not seem to be a determinant in the number of parasites in infected animals.<sup>vii</sup> On the other hand, host defense against aggression seems to depend on the state of development of the immune system for both sexes and on the stimulation of the response of this system, possibly acting in association with some hormonal and genetic factors but independently.<sup>xviii,xx</sup>

In Chagas disease, some of the main organs affected by the parasite in mammals are the heart and spleen, and sometimes the intestine.<sup>xxxv</sup> It is reported in this research that the group of infected BALB/c females showed an increase in heart weight, which is plausible since the parasite may be lodged in the tissue, causing the organ to increase in size. There was only a significant change in the decrease in heart weight for the male BALB/c strain group, contrary to what happened with the spleen. As for organ size, the infected groups showed an increase, except for the heart of the BALB/c strain.

No studies have been found that compare the size and weight of affected organs at the macroscopic level. Instead, they are directly evaluated at the microscopic level using histological sections. One study mentions that an increase in heart size may be caused by the ablation of fats, leading to endoplasmic reticulum stress and mitochondrial oxidative stress, causing biventricular dilatation and increased parasite load in infected mice during the early chronic stages of infection.<sup>xxxvi</sup> The increase in spleen size may be related to an important parasite antigen called cruzipain, which increases the number of cells of this organ, granularity, and size.<sup>xxxvii</sup> On the other hand, the parasite uses the antigen to propagate within the host.<sup>xxxviii</sup> Furthermore, evidence shows that adipose tissue is the major reservoir for *T. cruzi*, which can be reactivated during periods of immunosuppression and create a state of inflammation that affects a variety of metabolic pathways.<sup>xxxix</sup>

One of the limitations of this research was not knowing to which type of strain or discrete taxonomic units (DTU) the parasite belonged; these are methods for genetic classification that have been developed previously to determine the different ways of interacting with its host and its geographic distribution; some studies reveal that in El Salvador the so-called *Trypanosoma cruzi* I (TcI) prevails according to this classification, but it must be taken into account that it

can vary from TcI to TcVI in Latin America.<sup>xl,xii</sup> Another important limitation was not having histological sections of the possible infected organs, mainly the spleen, which would have allowed us to observe the absence or presence of amastigote nests in the tissues and to confirm which of the strains and sexes in this study were more resistant or vulnerable to the parasite according to the damage caused.<sup>xii</sup>

Some of the most outstanding recommendations are to perform molecular biology studies such as gene expression analysis through the quantitative polymerase chain reaction (qPCR) technique and immunohistochemistry techniques, which allow measuring protein expression and thus obtaining more detailed information for the interpretation of the results based on the genes involved to combat this disease on the part of the host.<sup>xxviii,xliii</sup> It is important to consider that other tests, such as *in vitro* tests, can provide more reliable and conclusive results.

## Conclusion

The group of male mice of the BALB/c strain was the most susceptible, presenting the greatest increase of parasites in the blood compared to the other infected groups. On the other hand, The female group of this strain showed the highest observed resistance to parasite load. However, contrary patterns were observed in the NIH strain, so it is difficult to affirm that sex is a determining factor in the behavior of this disease. Regarding body weight, the size, and weight of the organs, mainly in the heart, did not show significant differences, which could be because some of them were probably not so infected at that time, as was the case with the spleen.

Regarding body weight, the size and weight of the organs (heart and spleen) show results that are difficult to explain.

## Acknowledgements

To the students of the School of Biology who participated in this research to obtain the results.

## Funding

No external funds were received for this work.

## References

- i. Duschak V. G. Sulfatación y sulfotopos en *Trypanosoma cruzi*, agente causal de la Enfermedad de Chagas. Ciencia e investigación. 2022;72(3):59-78. Available at: <http://hdl.handle.net/11336/230541>
- ii. Murillo-Godínez. Enfermedad de Chagas (trypanosomiasis americana). Med. interna Méx. 2018;34(6):959-970. DOI: [10.24245/mim.v34i6.2217](https://doi.org/10.24245/mim.v34i6.2217)
- iii. Álvarez-Hernández DA, Franyuti-Kelly GA, Díaz-López-Silva R, González-Chávez AM, González-Hermosillo-Cornejo D, Vázquez-López R. Chagas disease: Current perspectives on a forgotten disease. Revista Médica del Hospital General de México. 2018;81(3):154-164. DOI: [10.1016/j.hgmx.2016.09.010](https://doi.org/10.1016/j.hgmx.2016.09.010)
- iv. Avalos-Borges EE, Rios LE, Jiménez-Coello M, Ortega-Pacheco A, Garg NJ. Animal Models of *Trypanosoma cruzi* Congenital Transmission. Pathogens. 2022;11(10):1172. DOI: [10.3390/pathogens11101172](https://doi.org/10.3390/pathogens11101172)
- v. Peña-Callejas G, González J, Jiménez-Cortés JG, Fuentes-Vicente JA, Salazar-Schettino PM, Bucio-Torres MI. *et al.* Enfermedad de Chagas: biología y transmisión de *Trypanosoma cruzi*. TIP Revista Especializada en Ciencias Químico-Biológicas. 2022;25:e449. DOI: [10.22201/fesz.23958723e.2022.449](https://doi.org/10.22201/fesz.23958723e.2022.449)
- vi. Kaufman CD, Farré C, Biscari L, Pérez AR, Alloati A. *Trypanosoma cruzi*, Chagas disease and cancer: putting together the pieces of a complex puzzle. Front Cell Dev Biol. 2023;11:1260423. DOI: [10.3389/fcell.2023.1260423](https://doi.org/10.3389/fcell.2023.1260423)
- vii. González FB. Modulación inmuno-endócrina y metabólica en la infección por *Trypanosoma cruzi*. rehip.unr.edu.ar. 2017. Consulted date: Mach 22, 2023. Available at: <http://hdl.handle.net/2133/7327>
- viii. Arias-Del-Angel JA, Santana-Solano J, Santillán M, Manning-Cela RG. Motility patterns of *Trypanosoma cruzi* trypomastigotes correlate with the efficiency of parasite invasion in vitro. Sci Rep. 2020;10(1):15894. DOI: [10.1038/s41598-020-72604-4](https://doi.org/10.1038/s41598-020-72604-4)
- ix. Macaluso G, Grippi F, Di Bella S, Blanda V, Gucciardi F, Torina A, *et al.* A Review on the Immunological Response against *Trypanosoma cruzi*. Pathogens. 2023;12(2):282. DOI: [10.3390/pathogens12020282](https://doi.org/10.3390/pathogens12020282)
- x. Queiroga TBD, Pereira NS, da Silva DD, Andrade CM, de Araújo Júnior RF, Brito CRDN, *et al.* Virulence of *Trypanosoma cruzi* Strains Is Related to the Differential Expression of Innate Immune Receptors in the Heart. Front Cell Infect Microbiol. 2021;11:696719. DOI: [10.3389/fcimb.2021.696719](https://doi.org/10.3389/fcimb.2021.696719)
- xi. The ARRIVE Guidelines: Animal Research: Reporting of In Vivo. Experiments. Originally published in PLOS Biology, 2010. Available at: <https://journals.plos.org/>

[plosbiology/article?id=10.1371/journal.pbio.1000412#:~:text=The%20ARRIVE%20guidelines%20consist%20of,%3B%20details%20of%20housing%20and](https://doi.org/10.1371/journal.pbio.1000412#:~:text=The%20ARRIVE%20guidelines%20consist%20of,%3B%20details%20of%20housing%20and)

- xii. Muradás RMG, Bosque PM, Del Carmen Sansón Ortega M, Pintos RRS. Química. Primera edición. Mexico. Grupo Editorial Patria. 2014. 225 p.
- xiii. Figueiredo VP, Silva MC, Souza DMS, Coelho Junior D, Lopes LR, Azevedo MA, *et al.* *Trypanosoma cruzi* infection increases atherosclerotic lesion in ApoE-deficient mice. *Microb Pathog.* 2022;171:105730. DOI: [10.1016/j.micpath.2022.105730](https://doi.org/10.1016/j.micpath.2022.105730)
- xiv. González Florencia. Modulación inmunoendocrina y metabólica en la infección por *Trypanosoma cruzi*. Argentina. Instituto de Inmunología Clínica y Experimental de Rosario, Universidad Nacional de Rosario. 2017. Consulted date: March 22, 2023. Available at: <http://hdl.handle.net/2133/7327>
- xv. Sousa Oliveira CV, Moreno-Loaiza O, Figueiredo-Vanzan D, Peroba Ramos I, Mata-Santos H, Torres Bozza M, *et al.* IL-1 $\beta$  is not critical to chronic heart dysfunction in mice with Chagas disease. *Front Immunol.* 2022;13:1010257. DOI: [10.3389/fimmu.2022.1010257](https://doi.org/10.3389/fimmu.2022.1010257)
- xvi. Flores-Villegas AL, Jiménez-Cortés JG, González J, Moreno-Rodríguez A, Pérez-Cabeza de Vaca R, Segal-Kischinevsky C, *et al.* Parasitemia and Differential Tissue Tropism in Mice Infected with *Trypanosoma cruzi* Isolates Obtained from Meccus phyllosoma in the State of Oaxaca, Mexico. *Pathogens.* 2022;11(10):1141. DOI: [10.3390/pathogens11101141](https://doi.org/10.3390/pathogens11101141)
- xvii. do Carmo Neto JR, da Costa AWF, Braga YLL, Lucio FH, Dos Santos Martins ALM, Dos Reis MA, *et al.* The Colombian Strain of *Trypanosoma cruzi* Induces a Proinflammatory Profile, Neuronal Death, and Collagen Deposition in the Intestine of C57BL/6 Mice Both during the Acute and Early Chronic Phase. *Mediators Inflamm.* 2022;1:7641357. DOI: [10.1155/2022/7641357](https://doi.org/10.1155/2022/7641357)
- xviii. Pérez AR, Morrot A, Carvalho VF, de Meis J, Savino W. Role of Hormonal Circuitry Upon T Cell Development in Chagas Disease: Possible Implications on T Cell Dysfunctions. *Front Endocrinol.* 2018;9:334. DOI: [10.3389/fendo.2018.00334](https://doi.org/10.3389/fendo.2018.00334)
- xix. Quintanar JL, Salinas E. Papel dual de la leptina en la obesidad. *Lux Médica.* 2022;17(50). DOI: [10.33064/50lm20223664](https://doi.org/10.33064/50lm20223664)
- xx. de Oliveira Cardoso F, Salles Domingues C, Zaverucha do Valle T, da Silva Calabrese K. How Do Mouse Strains and Inoculation Routes Influence the Course of Experimental *Trypanosoma cruzi* Infection? Chagas Disease - From Cellular and Molecular Aspects of *Trypanosoma cruzi*-Host Interactions to the Clinical Intervention. 2022. DOI: [10.5772/intechopen.104461](https://doi.org/10.5772/intechopen.104461)
- xxi. Reboreda-Hernandez Oscar A, Gonzalez-Rodriguez Nayeli, Cruz-Gonzalez Andrea Rebeca, Roman-Cedillo Alan, Ortiz-Butron Rocío. Influencia de la inoculación oral en la enfermedad de Chagas en modelo murino. *Horiz. sanitario.* Consulted date: January 3, 2023. 2021;20(2):198-206. Available at: [http://www.scielo.org.mx/scielo.php?script=sci\\_arttext&id=S2007-74592021000200198](http://www.scielo.org.mx/scielo.php?script=sci_arttext&id=S2007-74592021000200198)
- xxii. Jansen AM, Xavier SC, Roque ALR. *Trypanosoma cruzi* transmission in the wild and its most important reservoir hosts in Brazil. *Parasites Vectors.* 2018;11(1):502. DOI: [10.1186/s13071-018-3067-2](https://doi.org/10.1186/s13071-018-3067-2)
- xxiii. Ramírez-Tolosa G, Sosoniuk-Roche E, Valck C, Aguilar-Guzmán L, Ferreira VP, Ferreira A. *Trypanosoma cruzi* Calreticulin: Immune Evasion, Infectivity, and Tumorigenesis. *Trends Parasitol.* 2020;36(4):368-381. DOI: [10.1016/j.pt.2020.01.007](https://doi.org/10.1016/j.pt.2020.01.007)
- xxiv. León CM, Montilla M, Vanegas R, Castillo M, Parra E, Ramírez JD. Murine models susceptibility to distinct *Trypanosoma cruzi* I genotypes infection. *Parasitology.* 2017;144(4):512-519. DOI: [10.1017/S0031182016001980](https://doi.org/10.1017/S0031182016001980)
- xxv. De Castro TBR, Canesso MCC, Boroni M, Chame DF, Souza DL, de Toledo NE, *et al.* Differential Modulation of Mouse Heart Gene Expression by Infection With Two *Trypanosoma cruzi* Strains: A Transcriptome Analysis. *Front Genet.* 2020;11:1031. DOI: [10.3389/fgene.2020.01031](https://doi.org/10.3389/fgene.2020.01031)
- xxvi. Ramírez-Tolosa G, Ferreira A. *Trypanosoma cruzi* Evades the Complement System as an Efficient Strategy to Survive in the Mammalian Host: The Specific Roles of Host/Parasite Molecules and *Trypanosoma cruzi* Calreticulin. *Front Microbiol.* 2017;8:1667. DOI: [10.3389/fmicb.2017.01667](https://doi.org/10.3389/fmicb.2017.01667)
- xxvii. Mateus J, Guerrero P, Lasso P, Cuervo C, González JM, Puerta CJ, Cuéllar A. An Animal Model of Acute and Chronic Chagas Disease with the Reticulotropic Y Strain of *Trypanosoma cruzi* That Depicts the Multifunctionality and Dysfunctionality of T Cells. *Front Immunol.* 2019;10:918. DOI: [10.3389/fimmu.2019.00918](https://doi.org/10.3389/fimmu.2019.00918)
- xxviii. San Francisco J, Astudillo C, Vega JL, Catalán A, Gutiérrez B, Araya JE, *et al.* *Trypanosoma cruzi* pathogenicity involves virulence factor expression and upregulation of bioenergetic and biosynthetic pathways. *Virulence.* 2022;13(1):1827-1848. DOI: [10.1080/21505594.2022.2132776](https://doi.org/10.1080/21505594.2022.2132776)
- xxix. Holguín-Barrera ML, García-Agudelo L, Vargas-Rodríguez LJ, Vacca Bryan F. Chagas

- agudo por transmisión oral: serie de casos Orally transmitted acute Chagas: a case series. *Rev. Colomb. Cardiol.* 2023;30(4):203-206. DOI: [10.24875/rccar.22000045](https://doi.org/10.24875/rccar.22000045)
- xxx. Moulton VR. Sex Hormones in Acquired Immunity and Autoimmune Disease. *Front Immunol.* 2018;9:2279. DOI: [10.3389/fimmu.2018.02279](https://doi.org/10.3389/fimmu.2018.02279)
- xxxii. Lasrado N, Jia T, Massilamany C, *et al.* Mechanisms of sex hormones in autoimmunity: focus on EAE. *Biol Sex Differ* 2020;11(1):50. DOI: [10.1186/s13293-020-00325-4](https://doi.org/10.1186/s13293-020-00325-4)
- xxxiii. Lugo-Villarino G, Cougoule C, Meunier E, Rombouts Y, Vérollet C, Balboa L. Editorial: The Mononuclear Phagocyte System in Infectious Disease. *Front Immunol.* 2019;10:1443. DOI: [10.3389/fimmu.2019.01443](https://doi.org/10.3389/fimmu.2019.01443)
- xxxiiii. Reyes AC, Encina JLR. *Trypanosoma cruzi* Infection: Mechanisms of Evasion of Immune Response. In: De Souza, W., editor. *Biology of Trypanosoma cruzi*. London: IntechOpen. 2019. DOI: [10.5772/intechopen.84359](https://doi.org/10.5772/intechopen.84359)
- xxxv. Scott NA, Mann ER. Regulation of mononuclear phagocyte function by the microbiota at mucosal sites. *Immunology.* 2020;159(1):26-38. DOI: [10.1111/imm.13155](https://doi.org/10.1111/imm.13155)
- xxxvi. Hines Chaves KD, Zumbado Vásquez R, Castro Corrales V. Enfermedad de Chagas: afección cardiaca. *Rev Medica Sinerg.* 2019;4(5):101-10. DOI: [10.31434/rms.v4i5.212](https://doi.org/10.31434/rms.v4i5.212)
- xxxvii. Lizardo K, Ayyappan JP, Oswal N, Weiss LM, Scherer PE, Nagajyothi JF. Fat tissue regulates the pathogenesis and severity of cardiomyopathy in murine chagas disease. *PLoS Negl Trop Dis.* 2021;15(4):e0008964. DOI: [10.1371/journal.pntd.0008964](https://doi.org/10.1371/journal.pntd.0008964)
- xxxviii. Gutierrez BC, Lammel E, González-Cappa SM, Poncini CV. Early Immune Response Elicited by Different *Trypanosoma cruzi* Infective Stages. *Front Cell Infect Microbiol.* 2021;11:768566. DOI: [10.3389/fcimb.2021.768566](https://doi.org/10.3389/fcimb.2021.768566)
- xxxviii. Soprano LL, Ferrero MR, Landoni M, García GA, Esteva MI, Couto AS, Duschak VG. Cruzipain Sulfotopes-Specific Antibodies Generate Cardiac Tissue Abnormalities and Favor *Trypanosoma cruzi* Infection in the BALB/c Mice Model of Experimental Chagas Disease. *Front Cell Infect Microbiol.* 2022;11:814276. DOI: [10.3389/fcimb.2021.814276](https://doi.org/10.3389/fcimb.2021.814276)
- xxxix. Vega-Robledo Gloria Bertha, Rico-Rosillo María Guadalupe. Tejido adiposo: función inmune y alteraciones inducidas por obesidad. *Rev. alerg. Méx.* 2019;66(3):340-353. DOI: [10.29262/ram.v66i3.589](https://doi.org/10.29262/ram.v66i3.589)
- xl. Padilla CP, Alvarado U, Ventura G, Luna Caipo D, Suárez M, Tuñoque JR, *et al.* Detección de unidades discretas de tipificación de *Trypanosoma cruzi* en triatomíneos recolectados en diferentes regiones naturales de Perú. *biomedica.* 2017; 37(2):167-79. Available at: <https://revistabiomedica.org/index.php/biomedica/article/view/3559>
- xli. Villagran-Herrera ME, Martínez-Ibarra JA, Sánchez-Moreno M, Hernández-Montiel HL, Mercado-Curiel RF, Camacho-Calderón N, *et al.* The Mouse Model as a Tool for Histological, Immunological and Parasitological Studies of *Trypanosoma cruzi* Infection. *Chagas Disease - Basic Investigations and Challenges.* InTech; 2018. DOI: [10.5772/intechopen.77168](https://doi.org/10.5772/intechopen.77168)
- xlii. Chatelain E, Scandale I. Animal models of Chagas disease and their translational value to drug development. *Expert Opin Drug Discov.* 2020;15(12):1381-1402. DOI: [10.1080/17460441.2020.1806233](https://doi.org/10.1080/17460441.2020.1806233)



# Diagnostic concordance of thoracic images for Covid-19 disease

DOI: 10.5377/alerta.v7i2.18157

Neftalí Alexander Granados Flores<sup>1\*</sup>, Marlon Alexander Lazo Ferrufino<sup>2</sup>

1-2. Salvadoran Social Security Institute; San Salvador, El Salvador.

\*Correspondence

✉ neftaligranados.dr@gmail.com

1. ☎ 0000-0002-6346-1977

2. ☎ 0000-0002-3693-5188

## Abstract

**Introduction.** Reverse transcription polymerase chain reaction (RT-PCR) is the gold standard method for diagnosing SARS-CoV-2 disease. However, due to limited accessibility to this test during the pandemic, diagnostic imaging was used to support diagnostic suspicion and avoid delays in medical care. **Objective.** Determine the accuracy of diagnostic imaging (chest X-ray and computed tomography) in diagnosing SARS-CoV-2 infection, compared to RT-PCR result. **Methodology.** An analytical cross-sectional study was conducted. The imaging reports of 138 patients were compared with their RT-PCR results to calculate sensitivity, specificity, positive predictive value, and negative predictive value for both chest X-ray and computed tomography. Concordance between the imaging results and RT-PCR was measured using Cohen's Kappa index and Bayes factor. **Results.** Computed tomography showed a sensitivity of 92.9 %, a specificity of 64 %, a positive predictive value of 92.1 %, and a negative predictive value of 66.7 %. On the other hand, X-rays showed a sensitivity of 86 %, a specificity of 52.9 %, a positive predictive value of 92.9 %, and a negative predictive value of 34.6 %. **Conclusion.** Computed tomography showed moderate diagnostic concordance and is particularly useful in cases of moderate to high clinical suspicion, diagnostic discrepancy, or the need to confirm complications. On the other hand, X-rays showed low diagnostic concordance and should be used in combination with RT-PCR for a definitive diagnosis, especially in cases of high clinical suspicion.

## Keywords

SARS-CoV-2, Sensitivity and Specificity, Tomography, X-rays, Predictive Value of Tests.

## Resumen

**Introducción.** La reacción en cadena de la polimerasa de transcripción inversa (RT-PCR) es el estándar de oro para el diagnóstico de enfermedad por SARS-CoV-2. En el contexto de la pandemia con accesibilidad limitada a esta prueba, las imágenes diagnósticas aportaron hallazgos que sustentan la sospecha diagnóstica, evitando retrasos en atención médica. **Objetivo.** Determinar la sensibilidad, especificidad, valor predictivo positivo y negativo de las imágenes diagnósticas y su concordancia respecto al resultado de RT-PCR. **Metodología.** Estudio transversal analítico. Se comparó el resultado del reporte por imágenes con los resultados de RT-PCR en 138 pacientes. Se calculó la sensibilidad, especificidad, valor predictivo positivo y valor predictivo negativo para los rayos X de tórax y tomografía computarizada para el diagnóstico de infección por SARS-CoV-2. Se utilizó el índice Kappa de Cohen y el factor de Bayes para medir la concordancia y fuerza de asociación entre las variables. **Resultados.** La tomografía computarizada presentó una sensibilidad de 92,9 %, una especificidad del 64 %, un valor predictivo positivo de 92,1 % y un valor predictivo negativo de 66,7 %; mientras que, los rayos X presentaron una sensibilidad del 86 %, una especificidad del 52,9 %, un valor predictivo positivo de 92,9 % y un valor predictivo negativo del 34,6 %. **Conclusión.** La tomografía mostró concordancia diagnóstica moderada; su utilidad es mayor en casos de sospecha clínica moderada-alta, discrepancia diagnóstica o confirmación de complicaciones. Los rayos X mostraron concordancia diagnóstica baja; este método es de utilidad en casos de alta sospecha clínica, pero necesita comprobación con RT-PCR para un diagnóstico definitivo.

## Palabras clave

SARS-CoV-2, Sensibilidad y Especificidad, Tomografía, Rayos X, Valor Predictivo de las Pruebas.

## Introduction

COVID-19, a disease caused by SARS-CoV-2, a virus belonging to the *Coronaviridae* family, is characterized by its high contagiousness morbidity and mortality. This disease trig-

gered the most important health emergency of the modern era, causing the collapse of health systems in many countries due to the consumption of human and financial resources, claiming the direct or indirect lives of 14.9 million people in its first two years.<sup>1</sup>

 OPEN ACCESS

**Concordancia diagnóstica de las imágenes torácicas para enfermedad por Covid-19**

### Suggested citation:

Granados Flores NA, Lazo Ferrufino MA. Diagnostic concordance of thoracic images for Covid-19 disease. *Alerta*. 2024;7(2):161-168. DOI: 10.5377/alerta.v7i2.18157

### Editor:

Edgar Quinteros.

### Received:

July 21, 2023.

### Accepted:

June 27, 2024.

### Published:

July 24, 2024.

### Author contribution:

NAGF1: study conception, manuscript design, literature search, data collection, data management or software, writing, revising and editing. NAGF1, MALF2: data analysis.

### Conflicts of interest:

The author declared there are no conflicts of interest.



© 2024 by the authors. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

In El Salvador, the first reported case of SARS-CoV-2 was on March 18, 2020. Since then, the incidence spread exponentially throughout the national territory, reaching 555 confirmed cases, with 12 deaths and 26 accumulated recovered cases up to May of the same year.<sup>ii</sup> This generated the need for accurate and timely diagnoses, so the Ministry of Health indicated the performance of 29 931 RT-PCR tests until May 2020, i.e., an average of 599 tests per day nationwide.<sup>ii</sup>

RT-PCR is known to be highly specific but has the disadvantage of variable sensitivity (60-70 % to 95-97 %), depending on the stage of the disease at which the test is performed. False negatives are more likely in the early stages, with a 100 % probability if performed on the first day of exposure to the virus, 38 % on the day of symptom onset, and 20 % on the third day of symptoms.<sup>iii</sup> This fact, together with the need for structured equipment for its handling, interpretation time, and transmission of results to local operational levels, complicated its systematic application in the face of overcrowded emergency units and the need to provide rapid patient care.

Therefore, they began to rely on available imaging tests to confirm the diagnosis, classify the severity of the disease, evaluate complications and rule out other simulating entities, avoiding delays in the initiation of treatment.

Although definitive diagnosis of SARS-CoV-2 infection is based on any of the three types of laboratory tests (polymerase chain reaction, antigen detection tests, or antibody detection tests),<sup>iv</sup> the World Health Organization (WHO) recommended performing thoracic imaging studies in the following scenarios: symptomatic patients when RT-PCR is not available, results are delayed or there is high clinical suspicion with negative laboratory test.<sup>iii</sup>

In addition, it suggests performing imaging studies complementary to the clinical and laboratory approach in suspected patients, confirmed non-hospitalized or with mild symptoms to decide on hospital admission, or with moderate or severe symptoms to help determine the type of care and therapeutic management.<sup>iii</sup>

Several imaging techniques are available for the management of patients with clinical suspicion of SARS-CoV-2 infection, such as radiography, computed tomography (CT), and lung ultrasound. These methods are complementary to each other and offer options for the evaluation of the different organs and systems according to the evolutionary stage of the disease; imaging tests are also important for the

timely identification of acute complications of the disease and chronic sequelae in the pulmonary parenchyma.<sup>iii</sup>

The objective of the research was to determine the sensitivity, specificity, positive and negative predictive value of diagnostic images and their concordance concerning the RT-PCR result in patients who consulted with suspected SARS-CoV-2 infection at the General Hospital of the Salvadoran Social Security Institute (HG-ISSS) from March to September 2020.

## Methodology

An observational study was conducted at the General Hospital of the Salvadoran Social Security Institute (HG-ISSS) from March to September 2020. The study evaluated clinical records, diagnostic imaging studies (X-rays and CT scans), and RT-PCR results for SARS-CoV-2 in patients with suspected SARS-CoV-2.

The study universe included patients who consulted from March to September 2020 at the HG-ISSS with respiratory symptoms suspicious of SARS-CoV-2 disease, regardless of the time of evolution and severity, totaling 1309 patients identified.

This study included 214 patients with suspected SARS-CoV-2 who underwent X-rays, CT scans, and RT-PCR tests during the research period.

The sample size of 214 patients was calculated using the finite population equation, with a sampling error of 0.05 and a 95 % confidence interval. The calculated prevalence of SARS-CoV-2 disease is 1.14 %, based on data from the Salvadoran population and the report of the Office of the Resident Coordinator and the Office for the Coordination of Humanitarian Affairs (OCHA) of May 11, 2020. The theoretical sensitivity and specificity of RT-PCR were used to obtain a sample size of 138 patients.

The sample was selected by simple random sampling, including patients who met the inclusion criteria: clinical suspicion of SARS-CoV-2 disease, imaging studies, and RT-PCR test, and excluding those with incomplete clinical record data.

A data collection instrument was used, which consisted of a self-completion sheet divided into three sections. The first section included patient demographic variables such as sex, age, medical history, and symptoms described in the clinical history of the emergency unit. The second part focused on the radiological and tomographic reports in 64 slices, in high-resolution single phase with reconstruction in pulmonary and soft tissue window. These reports were classified according to the Coronavirus Classification

System (CO-RADS), which classifies the findings as typical, atypical, indeterminate, or negative. They were interpreted by institutional radiologists with an average experience in diagnostic imaging of five years.

In the case of Chest X-rays, these were performed on stationary digital equipment and interpreted by ten radiology and imaging resident physicians in their third (five residents) and fourth (five residents) year of training, who have at least two years of previous medical specialty (surgery, internal medicine or gynecology). The same CO-RADS classification categories adapted to chest radiography were applied. The segmentation of the interpreters according to the imaging study modality into radiologist and radiology resident physicians is stipulated by the administrative organization of the Radiology and Imaging Department HG-ISSS, so it was adopted in the methodological design of this research.

The third section addressed the results of RT-PCR tests obtained from the internal databases of the HG-ISSS epidemiology department, considering only those reported with positive or negative results.

Double-entry tables were constructed with the data collected to determine sensitivity, specificity, and positive and negative predictive values, using Microsoft Excel 365® and the Epi Info™ automatic calculators for analysis. Statistical analysis was performed with the STATA 14 program, calculating Cohen's Kappa index ( $k$ ) to evaluate the concordance of the instruments of the categorical measures, considering the value of one as perfect concordance, 0 to 0.99 as weak concordance, 0 to -0.99 as weak discordance, -1 as total discordance and  $> 0.75$  as acceptable concordance. Confidence intervals (CI) were taken into consideration. In addition, the Bayes factor (BF) was calculated to measure the strength of association based on Jeffrey's value classification scheme: weak (1.1-3), moderate (3.1-10), strong (10-30), very strong (30-100) and extreme ( $>100$ ).

The study was conducted by the principles of the Declaration of Helsinki, with prior authorization from the ethics committee of the Salvadoran Social Security Institute for the review of clinical records and the generation of a protected database, guaranteeing the confidentiality and exclusive scientific use of the participants' information.

## Results

A total of 138 patients with suspected SARS-CoV-2 disease were studied. Of the total, 58 % were men, with a mean age of

58  $\pm$  ten years. Most of them were economically active (contributors), resided in urban areas, having completed basic education (9th grade). The most affected age group was 61-65, with 26 patients representing 19 % of the total cases (Figure 1).

Comorbidity was present in 73.9 % of the patients. Arterial hypertension was the most frequent, with 61.6 %, followed by diabetes *mellitus* with 39.1 % and obesity with 28.3 %. These categories were not mutually exclusive; therefore, a patient could present more than one comorbidity. There was no comorbidity in 26.1 % of the patients. In 93.5 % of the cases, symptoms were reported as the reason for consultation (Table 1), the most common being fever (77.5 %), cough (68.8 %), general malaise (56.5 %), and dyspnea (45.6 %). Only 6.5 % of patients were asymptomatic.

When evaluating diagnostic imaging, 62 % and 63 % of patients were categorized with typical findings on radiographs and CT, respectively (Table 2).

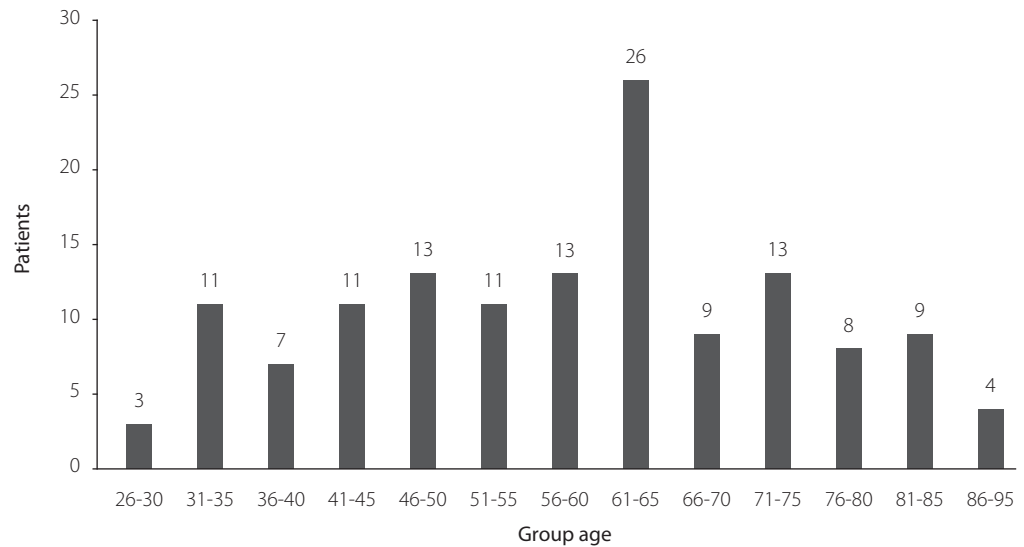
The main radiographic findings were "patchy opacities" (43 %) and alveolar-interstitial infiltrates (22 %), predominantly bilateral (40 %) and peripheral (38 %), mainly affecting the lower third in almost half of the cases. On CT, the findings included "ground-glass opacity" (43 %) and alveolar-interstitial infiltrates (22 %), identical to those reported by X-ray (Table 3). Furthermore, CT lesions were predominantly peripherally distributed (59 %), predominantly affecting the lower lobes (69.6 %) with no predilection for laterality, followed by the middle lobe (58.7 %) and left upper lobe (35.5 %).

Specific signs were identified in the air bronchogram in some cases, including fibrous bands and perivascular thickening; septal thickening (interlobular) and "crazy paving" pattern (ground glass associated with septal thickening) were reported less frequently. 33.3 % of the cases did not report specific signs in the tomographic report.

Extrapulmonary manifestations included pleural effusion in 10 % and enlarged lymph nodes in 1 % of cases (Table 3).

Of the total number of patients evaluated, 82 % had a positive RT-PCR test result for SARS-CoV-2, used as the gold standard for evaluating imaging methods.

Cohen's Kappa index was calculated to evaluate the diagnostic agreement between the imaging methods: 0.32 (95 % CI 0.17-0.47) for X-rays, indicating a low diagnostic agreement (0.2-0.4), and 0.58 (95 % CI 0.42-0.73) for CT, representing a moderate diagnostic agreement (0.4-0.6). In addition, values were obtained to specify the degree of probative strength, obtaining



**Figure 1.** Age distribution of patients with suspected SARS-CoV-2

**Table 1.** Characterization of patients with suspected SARS-CoV-2

Variables	Values
<b>Number of patients</b>	138
<b>Average age in years</b>	58 ± 10
<b>Sex</b>	
Male	58%
Female	42%
<b>Initial evaluation</b>	
Symptomatic	93.5%
Asymptomatic	6.5%
<b>Clinical history</b>	
Comorbidities	73.9 %
No comorbidities	26.1 %

**Table 2.** Diagnostic classification of thoracic imaging for SARS-CoV-2

Classification (Interpretation)	X-ray (Resident physician)	CT (Radiologist)
Typical findings	62 %	63 %
Atypical findings	12 %	15 %
Indeterminate findings	7 %	5 %
Negative findings	19 %	17 %

for X-rays the BF of 1.8 corresponding to a weak probative strength (1.1 - 3) and CT the BF of 3.6 concerning a moderate probative strength (3.1 - 10) (Table 4).

## Discussion

The sensitivity and specificity of different imaging methods for detecting SARS-CoV-2 infection show mixed evidence. For X-rays,

reports indicate relatively lower sensitivity (15.5 - 69 %) but higher specificity (89 - 97 %). The positive predictive value (PPV) is 83.8 %, and the negative predictive value (NPV) is 50.1 %.<sup>v-viii</sup>

These data appear to conflict with those reported in the study. However, it is important to note that the international data were obtained from studies conducted at the outset of the pandemic, when the clinical

and imaging behavior of SARS-CoV-2 infection was not yet fully understood. This could explain the high sensitivity and positive predictive value currently observed. The low specificity observed in the study, in comparison to international studies (89-97 %),<sup>v-viii</sup> may be attributed to technical factors that influence the image, as well as the level of experience of the medical personnel who corroborated the interpretation. In particular, the interpretations were mainly performed by personnel in their last year of training in diagnostic imaging.

Based on this, X-rays, being cheaper and more accessible, could be most useful in cases of high clinical suspicion to confirm positivity. Some studies suggest its usefulness as a diagnostic alternative in emergency departments, especially when access to RT-PCR tests is limited or in situations where false negatives are suspected.<sup>ix</sup>

It is important to note that the absence of X-ray findings does not rule out the presence of the disease, especially in the early stages. Some studies report that up to 38.8 % of symptomatic patients with SARS-CoV-2 have a normal chest X-ray at the time of diagnosis, which suggests a low diagnostic sensitivity in the early stages of

the disease, so its use as a screening method is not recommended.<sup>v,ix-xi</sup>

The most frequently reported findings on chest radiographs are similar to those of other viral pneumonias: focal and ground-glass opacities, which can range from very subtle to affecting both lungs, with a characteristic peripheral distribution.<sup>xi-xiv</sup> In initial case series studies in Wuhan, China, where the first cases were documented, they reported that 75 % of patients showed bilateral and 25 % unilateral findings.<sup>xv</sup> Other case series studies, such as that of Wang *et al.* reported that out of a total of 138 patients, 100 % showed bilateral findings.<sup>xvi</sup> In the present study, a lower proportion of bilateral and unilateral findings was found, which could be attributed to temporal and geographic differences in the evolution of the virus and its clinical and imaging manifestations.<sup>xvii</sup>

Chest CT is reported to be the most sensitive and specific method for detecting SARS-CoV-2 infection compared to chest X-ray.<sup>viii</sup> However, CT may be normal on admission, even with confirmed infection by RT-PCR.<sup>vi</sup> Some studies report that 2-56 % of patients may have a normal CT scan between day 0-3 ± 3 from symptom onset, despite a positive RT-PCR.<sup>xviii</sup>

**Table 3.** Diagnostic Thoracic Imaging Findings

Findings	X-Ray		CT	
Types of lesions	Patchy opacities	43 %	Patchy opacities	49 %
	Consolidation	16 %	Consolidation	20 %
	Alveolointerstitial infiltrates	22 %	Alveolointerstitial infiltrates	24 %
	Others	19 %	Others	7 %
Lesion distribution	Unilateral	2 %	Unilateral	0 %
	Bilateral	40 %	Bilateral	14 %
	Peripheral	38 %	Peripheral	59 %
	Central	10 %	Central	12 %
Location	None/other	10 %	None/other	15 %
	Upper third	14 %	Right upper lobe	26.1 %
	Middle third	28 %	Right middle lobe	58.7 %
	Lower third	48 %	Right lower lobe	69.6 %
	No lesions	10 %	Left upper lobe	35.5 %
-	-	Left lower lobe	69.6 %	

**Table 4.** Sensitivity, specificity, positive predictive value, negative predictive value of thoracic imaging for SARS-CoV-2

Diagnostic test	(S)	(S)	(PPV)	(NPV)	(K)	(BF)
Chest X-ray	86 %	52.9 %	92.9 %	34.6 %	0.32	1.8
Chest CT	92.9 %	64 %	92.1 %	66.7 %	0.58	3.6

Findings: (S) Sensitivity. (S) Specificity. (PPV) Positive predictive value. (NPV) Negative predictive value. (K) Kohen Kappa index. (BF) Bayes factor.

In the study, CT showed moderate diagnostic concordance, with high sensitivity and PPV but moderate specificity and NPV; these values are similar to those reported internationally. For example, Sharma *et al.* reported a sensitivity of up to 98 %<sup>xix</sup>, Kim *et al.* 94 % (95 % CI) for chest CT<sup>xx</sup>, and Herpé *et al.* reported a specificity of 88 %, sensitivity of 80 %, PPV 89 % and NPV 79 %.<sup>xxi</sup>

CT shows a higher yield in cases of moderate clinical suspicion, diagnostic discrepancy, or for the detection of complications. Common CT findings include peripherally distributed, bilateral, multifocal ground-glass areas associated with subsegmental patchy consolidations, mainly affecting lower lobes and posterior segments.<sup>xxii-xxiv</sup>

A case series in China reported that "ground glass" was the most common finding at 45-67 %, similar to the data obtained in the investigation.<sup>xv</sup> Consolidative lesions were approximately 30-60 %,<sup>xv</sup> a percentage almost three times higher than that found in the investigation, which could be attributable to differences in the disease at the time of evaluation, circulating strains, and lineages of the virus.

The investigation also documented other specific findings, such as the thickening of interlobular septa and the crazy-paving pattern, findings similar to those reported in Mexican case series.<sup>xxv-xxvii</sup> Because CT can be normal in the initial periods of the disease, it is not recommended as a screening or early diagnostic tool.<sup>xxviii,xxviii,xxix</sup> Although the sensitivity of RT-PCR varies considerably among studies, e.g., Smith *et al.* reported a sensitivity of 30 % to 91 %, when evaluating imaging studies concerning RT-PCR results for SARS-CoV-2, it was found that "positive" categories correlated well with RT-PCR results but categories considered "negative" showed low negative predictive values due to their limited ability to rule out disease in the absence of imaging findings, independent of the study modality analyzed.

Regarding the clinical characterization of the patients, most cases were symptomatic, with fever being the main symptom of SARS-CoV-2 infection, data consistent with international studies that report a high percentage of fever (98.6 %), fatigue (69.6 %) and dry cough (59.4 %) as the main symptoms in the first cases reported in China.<sup>xvi</sup> While, other case series mention that fever (83 %), cough (82 %), and respiratory distress (31 %) were the main symptoms.<sup>xxx</sup>

A limitation of this study was the lack of consistency in the imaging reports, leading to variability in the terminology used by different radiologists. Additionally, two

different groups of professionals interpreted the images based on the imaging method used: radiologist physicians interpreted computed tomography (CT) scans, while radiology resident physicians interpreted chest radiographs (X-rays). This difference in interpretation could have introduced biases related to the experience of the group interpreting the radiographs, potentially affecting the accuracy of the evaluations. Furthermore, since each imaging method has unique characteristics that influence its sensitivity and specificity in detecting disease, the results obtained are not directly comparable with each other, regardless of the interpreter.

It is recommended to standardize the information in reports by adopting institutional templates. Additionally, expanding the use of Picture Archiving Communication Systems (PACS) and Integrated Health Services Networks (RISS) for storing and transmitting diagnostic images is advised. This will enhance the coordination of care services, making it easier for medical specialties to collaborate in order to implement timely treatments based on imaging results.

## Conclusion

Computed tomography showed high sensitivity and positive predictive value, with moderate specificity, negative predictive value, and diagnostic concordance, making it a viable alternative in cases of moderate-high clinical suspicion, diagnostic discrepancy, or to rule out complications. X-rays showed high sensitivity and positive predictive value, but low specificity, negative predictive value, and low diagnostic concordance. They will be useful in cases of high clinical suspicion but need to be complemented with RT-PCR for a definitive diagnosis.

## Funding

No external funds were available.

## References

- i. Organización Panamericana para la Salud. Exceso mundial de mortalidad asociado a la pandemia de COVID-19. Consulted date: August 17, 2023. Available at: <https://www.who.int/es/news-room/questions-and-answers/item/global-excess-deaths-associated-with-the-COVID-19-pandemic>
- ii. Fundaungo. Evolución de casos del COVID-19 en El Salvador, del 14 de marzo al 3 de mayo de 2020. BOLETÍN 1 - 4 de mayo de 2020. Consulted date: August 17, 2023. Available at: <https://observatoriocovid19.sv/>

- [doc/biblioteca/nac/2020\\_05\\_06\\_Boletin\\_COVID\\_FINAL.pdf](#)
- iii. Martínez Chamorro E, Díez Tascón A, Ibáñez Sanz L, *et al.* Diagnóstico radiológico del paciente con COVID-19. Radiología. 2021;63(1):56-73. DOI: [10.1016/j.rx.2020.11.001](#)
  - iv. Villafuerte D, Ojeda L, Valladares M, *et al.* Aspectos imagenológicos útiles en el diagnóstico y seguimiento de pacientes con COVID-19. Medisur vol.18 no.5 °Cienfuegos sept.-oct. 2020. Consulted date: October 2, 2020. Available at: [http://scielo.sld.cu/scielo.php?script=sci\\_arttext&pid=S1727-897X2020000500886](http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1727-897X2020000500886)
  - v. Smith DL, Grenier JP, Batte C, Spieler B. A Characteristic Chest Radiographic Pattern in the Setting of the COVID-19 Pandemic. Radiology: Cardiothoracic Imaging. 2020;2(5):e200280. DOI: [10.1148/ryct.2020200280](#)
  - vi. Choi H, Qi X, Yoon SH, Park SJ, Lee KH, Kim JY, *et al.* Extension of Coronavirus Disease 2019 on Chest CT and Implications for Chest Radiographic Interpretation. Radiol Cardiothorac Imaging. 2020;2(2):e200107. DOI: [10.1148/ryct.2020200107](#)
  - vii. Ippolito, D, Pecorelli, A, Maino, C, Capodaglio, C, *et al.* Diagnostic impact of bedside chest X-ray features of 2019 novel coronavirus in the routine admission at the emergency department: case series from Lombardy region. European Journal of Radiology. 2020.129:109092. DOI: [10.1016/j.ejrad.2020.109092](#)
  - viii. Mayanga-Sausa L, Guerra-Tueros MS, Lira-Villasante A, Pastor-Gutiérrez DK. Utilidad de la radiografía de tórax en el contexto de la pandemia por Sars-Cov-2. Rev. Fac. Med. Hum. 2020;20(4):682-689. DOI: [10.25176/rfmh.v20i4.3034](#)
  - ix. Palleiro Giménez AM, Franquet Casas T. COVID-19. Alteraciones radiológicas en las distintas fases. Medicina respiratoria 2020;13(2):37-49. Consulted date: August 17, 2023. Available at: <http://www.neumologiaysalud.es/descargas/R13/R132-5.pdf>
  - x. Á Nava-Muñoz, S Gómez-Peña, ME Fuentes-Ferrer, B Cabeza, A Victoria, A Bustos. Neumonía COVID-19: relación entre la radiografía de tórax inicial y los datos analíticos. Radiología. 2021;63(6):484-494. DOI: [10.1016/j.rx.2021.06.001](#)
  - xi. Díaz FN, Castro HM, Núñez MM, Furdada JM, *et al.* Hallazgos por imágenes en COVID-19. Actualización y avances en. 2020;40. Rev. Hosp. Ital. B.Aires 2020; 40(3): 144-150. [https://www1.hospitalitaliano.org.ar/multimedia/archivos/noticias\\_attachs/47/documentos/114613\\_144-150-13-26-20-Diaz-A.pdf](https://www1.hospitalitaliano.org.ar/multimedia/archivos/noticias_attachs/47/documentos/114613_144-150-13-26-20-Diaz-A.pdf)
  - xii. B Weinstock M, Echenique A, W Russell J, *et al.* Chest X-Ray Findings in 636 Ambulatory Patients with COVID-19 Presenting to an Urgent Care Center: A Normal Chest X-Ray Is no Guarantee. Journal of Urgent Care Medicine. Consulted date: August 17, 2023. 2020. <https://www.jucm.com/chest-x-ray-findings-in-636-ambulatory-patients-with-COVID-19-presenting-to-an-urgent-care-center-a-normal-chest-x-ray-is-no-guarantee/>
  - xiii. Manna S, Wruble J. COVID-19: A Multimodality Review of Radiologic Techniques, Clinical Utility, and Imaging Features. Radiology: Cardiothoracic Imaging. 2020;2(3):e200210. DOI: [10.1148/ryct.2020200210](#)
  - xiv. Toussie D, Voutsinas N, Finkelstein M, *et al.* Clinical and Chest Radiography Features Determine Patient Outcomes in Young and Middle-aged Adults with COVID-19. Radiology. 2020;297(1):E197-E206. DOI: [10.1148/radiol.2020201754](#)
  - xv. Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513. DOI: [10.1016/S0140-6736\(20\)30211-7](#)
  - xvi. Wang D, Hu B, Hu C, Zhu F, Liu X, *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069. DOI: [10.1001/jama.2020.1585](#)
  - xvii. Organización Panamericana de la Salud / Organización Mundial de la Salud. Actualización epidemiológica: Enfermedad por Coronavirus (COVID-19). 2021. Available at: [https://iris.paho.org/bitstream/handle/10665.2/54283/EpiUpdate18May2021\\_spa.pdf?sequence=2&isAllowed=y](https://iris.paho.org/bitstream/handle/10665.2/54283/EpiUpdate18May2021_spa.pdf?sequence=2&isAllowed=y)
  - xviii. Yang W, Yan F. Patients with RT-PCR-confirmed COVID-19 and Normal Chest CT. Radiology. 2020;295(2):E3. DOI: [10.1148/radiol.2020200702](#)
  - xix. Sharma A, Ahmad Farouk I, Lal SK. COVID-19: A Review on the Novel Coronavirus Disease Evolution, Transmission, Detection, Control and Prevention. Viruses. 2021;13(2):202. DOI: [10.3390/v13020202](#)
  - xx. Kim H, Hong H, Yoon SH. (2020). Diagnostic Performance of CT and Reverse Transcriptase Polymerase Chain Reaction for Coronavirus Disease 2019: A Meta-Analysis. Radiology. 2020;296(3):E145-E155. DOI: [10.1148/radiol.2020201343](#)
  - xxi. Herpe G, Lederlin M, Naudin M, Ohana M, Chaumoitre K, Gregory J, *et al.* Efficacy of Chest CT for COVID-19 Pneumonia Diagnosis in France. Radiology.

- 2021;298(2): E81-E87. [DOI: 10.1148/radiol.2020202568](https://doi.org/10.1148/radiol.2020202568)
- xxii. Caruso D, Zerunian M, Polici M, Pucciarelli F, Polidori T, Rucci C, *et al.* Chest CT Features of COVID-19 in Rome, Italy. *Radiology*. 2020;296(2):E79-E85. [DOI: 10.1148/radiol.2020201237](https://doi.org/10.1148/radiol.2020201237)
- xxiii. Islam N, Ebrahimzadeh S, Salameh JP, Kazi S, Fabiano N, Treanor L, *et al.* Thoracic imaging tests for the diagnosis of COVID-19. *Cochrane Database of Systematic Reviews*. Consulted date: June 25, 2023. Available at: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013639.pub4/full>
- xxiv. Castillo AF, Bazaes ND, Huete GÁ. Radiología en la Pandemia COVID-19: Uso actual, recomendaciones para la estructuración del informe radiológico y experiencia de nuestro departamento. *Revista Chilena de Radiología*. 2020;26(3):88-99. [DOI: 10.4067/S0717-93082020000300088](https://doi.org/10.4067/S0717-93082020000300088)
- xxv. Collado-Chagoya R, *et al.* Hallazgos tomográficos entre sobrevivientes y no-sobrevivientes con COVID-19 y utilidad clínica de una puntuación de tomografía torácica. *Radiología*. 2022;64(1):11-16. [DOI: 10.1016/j.rx.2021.09.010](https://doi.org/10.1016/j.rx.2021.09.010)
- xxvi. Rodríguez OCV, González VC, Figueroa GJ. Hallazgos tomográficos en casos sospechosos de COVID-19 y su asociación con escala CO-RADS en pacientes con prueba RT-PCR negativa. *Acta Med GA*. 2023;21(3):241-246. [DOI: 10.35366/111346](https://doi.org/10.35366/111346)
- xxvii. Ramirez Gutierrez de Velasco Alfredo, Vadillo Santos Adriana, Pérez Ladrón de Guevara Paloma, Quiroz Castro Oscar. COVID-19: historia actual de una pandemia y sus hallazgos clínico-radiológicos, Servicio de Imagenología Diagnóstica y Terapéutica, Hospital Ángeles Pedregal, Ciudad de México, México. *Anales de Radiología México*. 2020;19:175-185 [DOI: 10.24875/ARM.20000063](https://doi.org/10.24875/ARM.20000063)
- xxviii. Filchakova O, Dossym D, Ilyas A, Kuanysheva T, Abdizhamil A, Bukasov R. Review of COVID-19 testing and diagnostic methods. *Talanta*. 2022;244:123409. [DOI: 10.1016/j.talanta.2022.123409](https://doi.org/10.1016/j.talanta.2022.123409)
- xxix. Colombi D, Bodini FC, Petrini M, Maffi G, Morelli N, Milanese G, *et al.* Well-aerated Lung on Admitting Chest CT to Predict Adverse Outcome in COVID-19 Pneumonia. *Radiology*. 2020;296(2):E86-96. [DOI: 10.1148/radiol.2020201433](https://doi.org/10.1148/radiol.2020201433)
- xxx. Kong W, Agarwal PP. Chest Imaging Appearance of COVID-19 Infection. *Radiol Cardiothorac Imaging*. 2020;2(1):e200028. [DOI: 10.1148/ryct.2020200028](https://doi.org/10.1148/ryct.2020200028)



# Use of myo-inositol and other nutritional supplements for the primary prevention of gestational diabetes *mellitus*

DOI: 10.5377/alerta.v7i2.16527

Lorena Guadalupe Menjivar Ponce<sup>1\*</sup>, Andrea Sofia Herrera Orantes<sup>2</sup>, César Gerardo Tario Amaya<sup>3</sup>, Kenny Lissette Abrego de Rodríguez<sup>4</sup>

1-3. Dr. José Matías Delgado University, Antiguo Cuscatlán, La Libertad, El Salvador.  
4. San Rafael National Hospital, Santa Tecla, La Libertad, El Salvador.

\*Correspondence

✉ lorena.menjivar15@gmail.com

1.  0000-0003-3031-2585      2.  0000-0002-6829-7731  
3.  0000-0002-4156-9565      4.  0000-0003-1453-1227

## Abstract

Gestational diabetes *mellitus* is the abnormal carbohydrate tolerance that begins during pregnancy and is considered a risk factor for the development of complications in the mother and fetus during pregnancy. Its prevention is based on lifestyle interventions, glycemia monitoring, and pharmacological and nutritional therapy. Nutritional supplements are presented as a promising alternative to treat and prevent this phenomenon. This literature review aims to determine the efficacy of myo-inositol as a prophylactic supplement to prevent the development of gestational diabetes *mellitus* and its complications, as well as to mention other alternative supplements. A search was conducted in Pubmed, SciELO, Elsevier, and Hinari databases, including original articles published between 2019 and 2023. The evidence found showed that myo-inositol supplementation in pregnancy increases insulin sensitivity, reduces low-density lipoprotein levels, reduces pregnancy-induced hypertension, and reduces the incidence of preterm delivery, fetal macrosomia, episodes of fetal hypoglycemia and neural tube defects, being its implementation safe in pregnancy. However, it is necessary to conduct research with a larger number of participants, with standardized doses that allow for establishing the efficacy of this supplement for its use as an alternative in the prevention of gestational diabetes.

## Keywords

Primary Prevention, Gestational Diabetes, Myo-inositol.

## Resumen

La diabetes *mellitus* gestacional es la tolerancia anormal a los carbohidratos que inicia durante el embarazo y a su vez se considera un factor de riesgo para el desarrollo de complicaciones en la madre y el feto durante el embarazo. Su prevención se basa en intervenciones en el estilo de vida, monitoreo de la glicemia, terapia farmacológica y nutricional. Los suplementos nutricionales se presentan como una alternativa prometedora para tratar y/o prevenir dicho fenómeno. Esta revisión bibliográfica tiene por objetivo determinar la eficacia del mio-inositol como suplemento profiláctico para prevenir el desarrollo de diabetes *mellitus* gestacional y sus complicaciones, así como mencionar otros suplementos alternativos. Se realizó una búsqueda bibliográfica en las bases de datos Pubmed, SciELO, Elsevier e Hinari, incluyendo artículos originales publicados entre el año 2019 hasta 2023. La evidencia encontrada demostró que la suplementación con mio-inositol en el embarazo, aumenta la sensibilidad a la insulina, reduce los niveles de lipoproteínas de baja densidad, disminuye la hipertensión inducida por el embarazo, reduce la incidencia de parto pretérmino, macrosomía fetal, episodios de hipoglicemia fetal y defectos del tubo neural, siendo su implementación segura en el embarazo. Sin embargo, es necesario realizar investigaciones con un mayor número de participantes, con dosis estandarizadas que permitan establecer la eficacia de este suplemento para su uso como alternativa en la prevención de la diabetes gestacional.

## Palabras clave

Prevención primaria, Diabetes gestacional, Mioinositol.

## Introduction

Gestational diabetes *mellitus* (GDM) is defined as abnormal glucose tolerance that begins during pregnancy;<sup>i</sup> it increases the risk of developing preeclampsia, type 2 diabetes *mellitus*,<sup>ii</sup> fetal macrosomia, shoulder dystocia, the threat of preterm delivery; it is estimated that approxi-

mately 10 % of women with GDM will require intensive care.<sup>iii</sup>

GDM has a prevalence of 6 to 13 % worldwide, and in Central and South America, approximately 11 %. Because of this, it is considered a growing public health problem.<sup>iv</sup> Likewise, DGM is one of the main causes of mortality and morbidity in both the mother and the fetus.<sup>v</sup>

## OPEN ACCESS

### Uso de mio-inositol y otros suplementos nutricionales para prevención primaria de la diabetes *mellitus* gestacional

#### Suggested citation:

Menjivar Ponce LG, Herrera Orantes AS, Tario Amaya CG, Abrego de Rodríguez KL. Use of myo-inositol and other nutritional supplements for the primary prevention of gestational diabetes *mellitus*. *Alerta*. 2024;7(2):169-176. DOI: 10.5377/alerta.v7i2.16527

#### Editor:

Nadia Rodríguez.

#### Received:

August 10, 2023.

#### Accepted:

June 27, 2024.

#### Published:

July 24, 2024.

#### Author contribution:

KLAR<sup>2</sup>: study conception. LGMP<sup>1</sup>, ASHO<sup>2</sup>, CGTA<sup>3</sup>: manuscript design. LGMP<sup>1</sup>, ASHO<sup>2</sup>, CGTA<sup>3</sup>: literature search. KLAR<sup>2</sup>: data collection. CGTA<sup>3</sup>: data analysis. LGMP<sup>1</sup>, ASHO<sup>2</sup>, CGTA<sup>3</sup>, KLAR<sup>2</sup>: writing, revising and editing.

#### Conflicts of interest:

The authors declared there are no conflicts of interest.



© 2024 by the authors. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

According to data recorded in the Morbidity, Mortality, and Vital Statistics System, 529 cases of GDM were reported in El Salvador between January and December 2022.<sup>vi</sup>

The prevention of GDM is mainly based on lifestyle interventions, glycemia monitoring, and pharmacological and nutritional therapy.<sup>vii</sup> However, in recent years, the use of nutritional supplements for the prevention of complications derived from GDM has become an object of study of growing interest since it could be a safe, affordable, and effective strategy,<sup>viii</sup> in addition to avoiding certain complications such as the reduction in the incidence of preterm delivery and fetal macrosomia.<sup>ix</sup>

Consequently, the implementation of preventive strategies for GDM offers intergenerational benefits by reducing future chronic diseases in both the mother and her child. Some nutritional supplements represent options with a practical and safe approach for preventing GDM. These include myo-inositol, vitamin D, and fatty acids.<sup>x</sup>

A narrative literature review was carried out, including original articles, narrative reviews, systematic reviews and meta-analyses in English and Spanish, with less than five years of publication. The search was carried out in databases such as PubMed, Elsevier, SciELO and Hinari. The following Boolean operators and search terms were used: "Prevention" AND "Gestational diabetes" AND "Myo-inositol supplementation". This review aims to describe the efficacy of myo-inositol as a prophylactic supplement for the prevention of gestational diabetes *mellitus* and its complications, as well as to mention alternative supplements for the prevention and treatment of gestational diabetes *mellitus*.

## Discussion

Inositol is a cyclic carbohydrate isolated from muscle extracts in 1850 by Johan Joseph Scherer, initially considered an essential nutrient belonging to the vitamin B family.<sup>xi</sup> It has nine structural isomers; myo-inositol and D-chiro-inositol are the most studied; myo-inositol is incorporated within the cell membrane and acts as a secondary messenger in the transduction of endocrine signals, including follicle-stimulating hormone, thyroid-stimulating hormone and insulin.<sup>xii</sup>

In recent years, inositol has played an important role in modulating the pathogenesis of inflammation, oxidative stress, and insulin resistance, acting as a mediator of insulin action and is necessary to activate key enzymes in glucose metabolism.<sup>xiii</sup> There-

fore, abnormalities in its metabolism have been associated with insulin resistance.<sup>xiv</sup>

Myo-inositol is synthesized endogenously from glucose-6-phosphate; the body is capable of producing up to 4 g per day of inositol, with the kidneys and liver being the main producers. Exogenously, it is obtained from cereals, legumes, and seeds from which up to 1 g per day is obtained from these sources.<sup>xv</sup>

Recent research has shown that supplementation with inositols correlates with a healthy pregnancy, achieving adequate glucose levels, and preventing possible maternal/fetal alterations and complications.<sup>xvi</sup> Comparative studies have evaluated the efficacy of different inositol stereoisomers for the prevention of GDM, showing that the greatest benefit is found in the myo-inositol group.<sup>xvii</sup>

## Glycemic control

Guarnotta *et al.* in their study conducted in Italy included 330 women with GDM, 150 supplemented with myo-inositol at a dose of 4 g per day, and the remaining 180 supplemented with placebo, showed that women with GDM supplemented with myo-inositol had better glycemic control and lower insulin requirements, and also had a lower incidence of low birth weight and hypoglycemic events in the newborn, compared to women who did not receive myo-inositol supplementation (Table 1).<sup>xviii</sup>

Likewise, Gambioli *et al.* compared the effectiveness of myo-inositol and metformin in glycemic control and lipid profile. In this study, they demonstrated that myo-inositol was more effective in increasing insulin sensitivity, thus reducing serum insulin levels and low-density lipoprotein levels in women with polycystic ovary syndrome.<sup>xix</sup> Numerous studies have established that a dose of 2 g of myo-inositol twice daily resulted in a decrease in the risk of developing GDM, such as the study by McVay *et al.*, where this administration schedule was associated with a 66 % decrease in the incidence of GDM.<sup>xx</sup>

## Overweight and obesity

Overweight and obesity have become a growing public health problem since their presence before pregnancy increases the risk of complications during that period.<sup>xxi</sup> These complications include preterm delivery, fetal macrosomia, shoulder dystocia, among others.<sup>xxii</sup>

On the other hand, the meta-analysis performed by Sepideh *et al.*, which included overweight and obese pregnant women, indi-

cated that supplementation with myo-inositol showed that it was a new and safe preventive strategy to reduce the incidence of GDM through the regulation of fasting glucose levels and in the oral glucose tolerance test one and two hours postprandially. In addition, a decrease in the development of hypertension during pregnancy was evidenced,<sup>xxiii</sup> as stated by Salvatore G, in his study of 223 women, of whom 110 women were supplemented with myo-inositol and 113 with placebo; the former showed a significant reduction in the overall incidence of pregnancy-induced hypertension (7.3 %), while in the latter group, it was higher (21.2 %).<sup>xxiv</sup>

## Maternal-fetal miscarriages

A study carried out at the University d'Annunzio in Italy with non-obese patients but with elevated fasting glucose in the first and second trimester of pregnancy included a total of 73 women, 35 of whom were supplemented with myo-inositol and 38 with placebo; as a result, a decrease in the incidence of GDM was evidenced in women who received myo-inositol as a supplement, with an absolute risk reduction of 66.3 %. In addition, it was shown that this group required a lower dose of insulin compared to the placebo group (placebo group 21 % versus myo-inositol group 3 %). Likewise, the incidence of preterm delivery, fetal macrosomia, and episodes of neonatal hypoglycemia was significantly lower in the myo-inositol-supplemented group (Table 1). Because of this, the authors concluded that myo-inositol supplementation during pregnancy reduces the incidence of GDM in women at high risk of this disorder.<sup>xxv</sup>

From another perspective, maternal obesity and GDM have been considered risk factors for the development of neural tube defects.<sup>xxvi</sup> Facchinetti *et al.* concluded

that myo-inositol supplementation, initiated in the first trimester in obese pregnant women, appears to reduce the incidence of GDM through a reduction in insulin resistance and also appears to reduce the risk of recurrence of neural tube defects.<sup>xxvii</sup>

In addition, a meta-analysis conducted in February 2023, which included seven studies with 1319 pregnant women, states that the use of myo-inositol can reduce GDM and hypertensive disorders in pregnancy and preterm delivery. However, its use does not generate a reduction in the risk of a large-for-gestational-age newborn. These reviewed studies were performed with small samples, which do not allow the necessary statistical power to evaluate perinatal mortality and severe infant morbidity.<sup>xxviii</sup>

## Safety of myo-inositol

Myo-inositol has been used for decades in many studies related to both polycystic ovary syndrome and insulin resistance.<sup>xxix</sup> Studies in animal models and multiple clinical trials have been conducted to evaluate the safety of the supplement.<sup>xxx</sup> Preclinical data indicate no toxic effects in terms of renal function, cognitive functions or carcinogenesis.<sup>xxxi</sup>

Reyes *et al.* analyzed five randomized clinical studies and found no adverse effects in pregnant patients who consumed myo-inositol at a dose of 2 g twice daily.<sup>xxxii</sup> In addition, in the meta-analysis developed by Vitagliano A and Saccone G, it was concluded that there were no differences in secondary outcomes such as incidence of cesarean section, shoulder dystocia, perineal tears, newborn birth weight, neonatal hypoglycemia and admission to the neonatal intensive care unit with the use of this supplement.<sup>xxxiii</sup> In contrast, Formoso *et al.* observed gastrointestinal adverse effects such as nausea, flatulence, and diarrhea after administration of

**Table 1.** Effects on glycemic control and neonatal and perinatal outcomes in women supplemented with myo-inositol compared to women supplemented with placebo

	Group supplemented with myo-inositol (N=150)	Placebo-supplemented group (N= 180)
<b>Effects on glycemic control</b>		
Fasting glucose (mg/dL)	95.7 ± 9.81	95.1 ± 10.9
1-hour postprandial glycemia (mg/dL)	150.7 ± 36.5	163.5 ± 52.1
2-hour postprandial glycemia (mg/dL)	115.8 ± 30.8	122.4 ± 37.6
<b>Neonatal and perinatal outcomes (in years)</b>		
Birth weight (grams)	3.241 ± 443	3.361 ± 406
Hypoglycemia (%)	11 (7.3 %)	36 (20 %)

**Source:** Adapted from Guarnotta V, Cuva G, Imbergamo MP, Giordano C. Myo-inositol supplementation in the treatment of gestational diabetes mellitus: effects on glycaemic control and maternal-fetal outcomes. *BMC Pregnancy Childbirth.* 2022 Jun 26; 22 (1): 516. <http://creativecommons.org/licenses/by/4.0/>

myo-inositol at doses greater than 12 grams per day from the first trimester of gestation.<sup>xxxiv</sup>

In addition, myo-inositol is part of the list of compounds generally recognized as safe for the general population by the FDA (Food and Drug Administration); however, further studies are still required to confirm its efficacy and safety in pregnancy.<sup>xxxv</sup> On the other hand, the usual pharmacological therapy for reducing the risk of GDM is metformin,<sup>xxxvi</sup> a drug that can positively influence metabolic disorders.<sup>xxxvii</sup> Although it has been extensively studied, more data is still required regarding its long-term safety.<sup>xxxviii</sup> As demonstrated by Shokrpour M *et al.* who conclude that when comparing the risk-benefit ratio of myo-inositol and metformin, myo-inositol represents a valid alternative given its greater safety and tolerability,<sup>xxxix</sup> unlike metformin which has been associated with multiple adverse effects compared to placebo.<sup>xl</sup>

However, the studies neither report on other relevant maternal and newborn outcomes nor provide data on long-term outcomes.<sup>xli</sup>

### Other Nutritional Supplements for the Prevention of GDM

Nutritional supplements are presented as a safe and generally well-tolerated alternative for the treatment and prevention of GDM.<sup>xlii</sup> These supplements include probiotics, vitamin D and polyunsaturated fatty acids, among others. Some of their effects are detailed in Table 2.

#### Vitamin D

Vitamin D deficiency is common during pregnancy due to fetal requirements,

inadequate intake, and limited sun exposure<sup>xliii</sup> and is associated with an increased occurrence of GDM.<sup>xliv</sup>

#### Probiotics

Probiotic supplementation during pregnancy has been associated with improved glucose and lipid metabolism, being beneficial in the prevention or control of GDM.<sup>xlv</sup>

#### Polyunsaturated fatty acids

The antilipidic effects of these fatty acids are of particular interest during pregnancy due to the existence of an increase in total cholesterol, triglycerides, and lipoproteins from week eight of gestation; in addition, it has been seen that women with GDM present even higher levels of these lipids compared to women with normal glucose tolerance.<sup>xlvi</sup>

#### Conclusion

Most studies suggested that using myo-inositol could prevent GDM and its complications in both the mother and the fetus due to the reduction in fasting glucose levels and the oral glucose tolerance test one and two hours postprandial. However, it is unclear whether supplementation is associated with a decrease in the incidence of GDM because the existing studies are small enough to detect differences in maternal-fetal outcomes. Myo-inositol has been associated with a reduction of hypertensive disorders during pregnancy. There are variations in the dosage of the supplement between studies and the characteristics of the pregnant patients, such as ethnicity; most of

**Table 2.** Comparison of the effectiveness of nutritional supplements for the prevention of GDM

Nutritional supplement	Effect on pregnancy
Vitamin D	High-dose vitamin D supplementation decreases insulin resistance and cholesterol levels in patients with GDM. <sup>xlvii</sup> It reduces the risk of GDM, preeclampsia and newborn complications such as low birth weight and preterm delivery. <sup>xlviii</sup>
Probiotics	They modulate the composition of the intestinal flora, benefits the immune system and improves glucose and lipid levels, as well as markers of inflammation and oxidative stress, subsequently reducing the risk of gestational diabetes. <sup>xlix</sup> Supplementation for four to eight weeks in women with GDM reduced insulin resistance, improved HDL cholesterol levels, markers of inflammation and oxidative stress, and decreased the incidence of hyperbilirubinemia in the newborn. <sup>l</sup>
Fish oil and fatty acids	Omega-3 supplementation for six weeks in women with GDM demonstrated benefits in the expression of genes that regulate insulin function, decreased triglyceride levels and increased LDL and HDL cholesterol levels. <sup>li</sup> Potential benefits have been seen in the fetus, reducing preterm delivery and the risk of low birth weight. <sup>lii</sup>

these studies were conducted on the European continent. Being a natural component, synthesized in the body and present in many foods in the regular diet, studies suggest that the component does not pose a risk to the mother or fetus, so its use is considered safe during pregnancy.

The reviewed studies suggest that supplementation with vitamin D, probiotics, fish oil, and fatty acids can reduce insulin resistance and improve cholesterol levels in patients with GDM. However, there is a lack of significant studies comparing the effects of myo-inositol with these supplements. It is necessary to conduct well-designed research with a larger number of participants using standardized doses to establish the efficacy of myo-inositol in preventing GDM. Subsequent research that compares the effectiveness of myo-inositol with other nutritional supplements is also required.

## Acknowledgements

To Karla Margarita Navarrete Gálvez for her support to this work; to the School of Health Sciences of the Dr. Luis Edmundo Vásquez of the Dr. José Matías Delgado University for promoting research.

## Funding

No external funds were received for this work.

## References

- i. Sweeting A, Wong J, Murphy HR, Ross GP. A Clinical Update on Gestational Diabetes Mellitus. *Endocrine Reviews*. 2022;43(5):763-793. DOI: [10.1210/edrv/bnac003](https://doi.org/10.1210/edrv/bnac003)
- ii. Poblete JA, Olmos P. Obesity and Gestational Diabetes in Pregnant Care and Clinical Practice. *Current Vascular Pharmacology*. 2021;19(2):154-164. DOI: [10.2174/1570161118666200628142353](https://doi.org/10.2174/1570161118666200628142353)
- iii. Aburezq M, AlAlban F, Alabdulrazzaq M, Badr H. Risk factors associated with gestational diabetes *mellitus*: The role of pregnancy-induced hypertension and physical inactivity. *Pregnancy Hypertension*. 2020;22:64-70. DOI: [10.1016/j.preghy.2020.07.010](https://doi.org/10.1016/j.preghy.2020.07.010)
- iv. Laburre-Torrealva GT, Martinez S, Luque-Fernandez MA, Sanchez SE, Mascaro PA, Ingar H, *et al*. Prevalence and risk factors of gestational diabetes *mellitus*: findings from a universal screening feasibility program in Lima, Peru. *BMC Pregnancy Childbirth*. 2018; 18 (1): 303. DOI: [10.1186/s12884-018-1904-0](https://doi.org/10.1186/s12884-018-1904-0)

- v. Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, *et al*. Prevalence and risk factors of gestational diabetes *mellitus* in Asia: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2018;18(1):494. DOI: [10.1186/s12884-018-2131-4](https://doi.org/10.1186/s12884-018-2131-4)
- vi. Sistema de Morbi Mortalidad en la Web. Ministerio de Salud. El Salvador. 2020. Consulted date: March 27, 2023. Available at: <https://simmow.salud.gob.sv/>.
- vii. American Diabetes Association. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes - 2022. *Diabetes Care*. 2022;45(1):232-243. DOI: [10.2337/dc22-S015](https://doi.org/10.2337/dc22-S015)
- viii. Plows JF, Reynolds CM, Vickers MH, Baker PN, Stanley JL. Nutritional Supplementation for the Prevention and/or Treatment of Gestational Diabetes Mellitus. *Current Diabetes Reports*. 2019;19(9):73. DOI: [10.1007/s11892-019-1199-1](https://doi.org/10.1007/s11892-019-1199-1)
- ix. D'Anna R, Santamaria A, Alibrandi A, Corrado F, DI Benedetto, Facchinetti F. Myo-Inositol for the Prevention of Gestational Diabetes Mellitus. A Brief Review. *Journal of Nutritional Science and Vitaminology*. 2019;65: 59-61. DOI: [10.3177/jnsv.65.S59](https://doi.org/10.3177/jnsv.65.S59)
- x. Wei J, Yan J, Yang H. Inositol Nutritional Supplementation for the Prevention of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients*. 2022;14(4):2831. DOI: [10.3390/nu14142831](https://doi.org/10.3390/nu14142831)
- xi. Bizzarri M, Fuso A, Dinicola S, Cucina A, Bevilacqua A. Pharmacodynamics and pharmacokinetics of inositol(s) in health and disease. Expert Opinion on Drug Metabolism & Toxicology. 2016;12(10):1181-1196. DOI: [10.1080/17425255.2016.1206887](https://doi.org/10.1080/17425255.2016.1206887)
- xii. Dinicola S, Unfer V, Facchinetti F, Soulage CO, Greene ND, Bizzarri M, *et al*. Inositols: From Established Knowledge to Novel Approaches. *International Journal of Molecular Sciences*. 2021;22(19):10575. DOI: [10.3390/ijms221910575](https://doi.org/10.3390/ijms221910575)
- xiii. Abdali D, Samson SE, Grover AK. How effective are antioxidant supplements in obesity and diabetes? Medical principles and practice: *International Journal of the Kuwait University*. 2015;24(3):201-215. DOI: [10.1159/000375305](https://doi.org/10.1159/000375305)
- xiv. Lerner J, Brautigan DL, Thorner MO. D-chiro-inositol glycans in insulin signaling and insulin resistance. *Molecular Medicine*. 2010;16(11-12):542-552. DOI: [10.2119/molmed.2010.00107](https://doi.org/10.2119/molmed.2010.00107)
- xv. Dinicola S, Minini M, Unfer V, Verna R, Cucina A, Bizzarri M. Nutritional and Acquired Deficiencies in Inositol Bioavailability. Correlations with Metabolic

- Disorders. *International Journal of Molecular Sciences*. 2017;18(10):2187. DOI: [10.3390/ijms18102187](https://doi.org/10.3390/ijms18102187)
- xvi. Reyes-Muñoz E, Guardo FD, Ciebiera M, Kahramanoglu I, Sathyapalan T, Lin LT, *et al*. Diet and Nutritional Interventions with the Special Role of Myo-Inositol in Gestational Diabetes Mellitus Management. An Evidence-Based Critical Appraisal. *Current Pharmaceutical Desing*. 2019;25(22):2467-2473. DOI: [10.2174/1381612825666190722155512](https://doi.org/10.2174/1381612825666190722155512)
- xvii. Celentano C, Matarrelli B, Pavone G, Vitacolonna E, Mattei PA, Berghella V, *et al*. The influence of different inositol stereoisomers supplementation in pregnancy on maternal gestational diabetes *mellitus* and fetal outcomes in high-risk patients: a randomized controlled trial. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2020;33(5):743-751. DOI: [10.1080/14767058.2018.1500545](https://doi.org/10.1080/14767058.2018.1500545)
- xviii. Guarnotta V, Cuva G, Imbergamo MP, Giordano C. . Myo-inositol supplementation in the treatment of gestational diabetes *mellitus*: effects on glycaemic control and maternal-foetal outcomes. *BMC Pregnancy and Childbirth*. 2022;22(1). DOI: [10.1186/s12884-022-04852-3](https://doi.org/10.1186/s12884-022-04852-3)
- xix. Gambioli R, Forte G, Buzzaccarini G, Unfer V, Laganà AS. Myo-Inositol as a Key Supporter of Fertility and Physiological Gestation. *Pharmaceuticals*. 2021;14(6):504. DOI: [10.3390/ph14060504](https://doi.org/10.3390/ph14060504)
- xx. McVay R, Greuel J. Does supplementation with myo-inositol reduce the risk of developing GDM? Evidence-Based Practice. 2021;24(10):20-21. DOI: [10.1097/EBP.0000000000001236](https://doi.org/10.1097/EBP.0000000000001236)
- xxi. Sun Y, Shen Z, Zhan Y, Wang Y, Ma S, Zhang S, *et al*. Effects of pre-pregnancy body mass index and gestational weight gain on maternal and infant complications. *BMC Pregnancy and Childbirth*. 2020;20(1). DOI: [10.1186/s12884-020-03071-y](https://doi.org/10.1186/s12884-020-03071-y)
- xxii. Esmailzadeh S, Ghadimi R, Mashayekhamiri S, Delavar MA, Basirat Z. The effect of myo- inositol supplementation on the prevention of gestational diabetes in overweight pregnant women: a randomized double-blind controlled trial. *Minerva Obstetrics and Gynecology*. 2023;75(4):357-364. DOI: [10.23736/S2724-606X.22.05036-9](https://doi.org/10.23736/S2724-606X.22.05036-9)
- xxiii. Mashayekh-Amiri S, Mohammad-Alizadeh-Charandabi S, Abdolalipour S, Mirghafourvand M. Myo-inositol supplementation for prevention of gestational diabetes *mellitus* in overweight and obese pregnant women: a systematic review and meta- analysis. *Diabetology & Metabolic Syndrome*. 2022;14(1):93. DOI: [10.1186/s13098-022- 00862-5](https://doi.org/10.1186/s13098-022- 00862-5)
- xxiv. Vitale SG, Corrado F, Caruso S, Di Benedetto A, Giunta L, Ciancia A, D'Anna R. Myo-inositol supplementation to prevent gestational diabetes in overweight non-obese women: bioelectrical impedance analysis, metabolic aspects, obstetric and neonatal outcomes - a randomized and open-label, placebo-controlled clinical trial. *International Journal of Food Sciences and Nutrition*. 2021;72(5):670-679. DOI: [10.1080/09637486.2020.1852191](https://doi.org/10.1080/09637486.2020.1852191)
- xxv. Matarrelli B, Vitacolonna E, D'Angelo M, Pavone G, Mattei P, Liberati M, *et al*. Effect of dietary myo-inositol supplementation in pregnancy on the incidence of maternal gestational diabetes *mellitus* and fetal outcomes: a randomized controlled trial. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2013;26(10):967-972. DOI: [10.3109/14767058.2013.766691](https://doi.org/10.3109/14767058.2013.766691)
- xxvi. Rasmussen SA, Chu SY, Kim SY, Schmid CH. Maternal obesity and risk of neural tube defects: a metaanalysis. *American Journal of Obstetrics and Gynecology*. 2008;198(6):611-619. DOI: [10.1016/j.ajog.2008.04.021](https://doi.org/10.1016/j.ajog.2008.04.021)
- xxvii. Facchinetti F, Cavalli P, Copp AJ, D'Anna R, Kandaraki E, Greene N, Unfer V; Experts Group on Inositol in Basic And Clinical Research. An update on the use of inositols in preventing gestational diabetes *mellitus* (GDM) and neural tube defects (NTDs). *Expert Opinion on Drug Metabolism & Toxicology*. 2020;16(12):1187-1198. DOI: [10.1080/17425255.2020.1828344](https://doi.org/10.1080/17425255.2020.1828344)
- xxviii. Motuhifonua SK, Lin L, Alsweller J, Crawford TJ, Crowther CA. Antenatal dietary supplementation with myo-inositol for preventing gestational diabetes. *Cochrane Database of Systematic Reviews*. 2023;2(2). DOI: [10.1002/14651858.CD011507.pub3](https://doi.org/10.1002/14651858.CD011507.pub3)
- xxix. DiNicolantonio J, O'Keefe J. Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. *Open Heart*. 2022;9(1):e001989. DOI: [10.1136/openhrt-2022-001989](https://doi.org/10.1136/openhrt-2022-001989)
- xxx. Greff D, Juhász A, Vancsa S, Váradi A, Sipos Z, *et al*. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Reprod Biol Endocrinol*. 2023;21(1):10. DOI: [10.1186/s12958-023-01055-z](https://doi.org/10.1186/s12958-023-01055-z)
- xxxi. Formoso G, Baldassarre M, Ginestra F, Carlucci M, Bucci I, Consoli A. Inositol and antioxidant supplementation: Safety and efficacy in pregnancy. *Diabetes/Metabolism Research and Reviews*. 2019;35(5):e3154. DOI: [10.1002/dmrr.3154](https://doi.org/10.1002/dmrr.3154)
- xxxii. Reyes-Muñoz E, Sosa S, Flores-Robles CM, Arce-Sánchez L, Martínez-Cruz N, Gutiérrez-Castrellón P. Suplementos nutricionales

- para prevención de diabetes *mellitus* gestacional: lecciones aprendidas basadas en la evidencia. *Gaceta Médica de México*. 2020;156(3):S43-S50. DOI: [10.24875/GMM.M20000437](https://doi.org/10.24875/GMM.M20000437)
- xxxiii. Vitagliano A, Saccone G, Cosmi E, Visentin S, Dessole F, Ambrosini G, *et al.* Inositol for the prevention of gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. *Archives of Gynecology and Obstetrics*. 2019;299(1):55-68. DOI: [10.1007/s00404-018-5005-0](https://doi.org/10.1007/s00404-018-5005-0)
- xxxiv. Formoso G, Baldassarre M, Ginestra F, Assunta M, Bucci I, Consoli A. Inositol and antioxidant supplementation: Safety and efficacy in pregnancy. *Diabetes/Metabolism Research and Reviews*. 2019;35(5):e3154. DOI: [10.1002/dmrr.3154](https://doi.org/10.1002/dmrr.3154)
- xxxv. Facchinetti F, Appetecchia M, Aragona C, Bevilacqua A, Bezerra Espinola MS, Bizzarri M, *et al.* Experts' opinion on inositols in treating polycystic ovary syndrome and non-insulin dependent diabetes *mellitus*: a further help for human reproduction and beyond. *Expert Opinion Drug Metabolism Toxicology*. 2020;16(3):255-74. DOI: [10.1080/17425255.2020.1737675](https://doi.org/10.1080/17425255.2020.1737675)
- xxxvi. Griffith RJ, Alsweller J, Moore AE, Brown S, Middleton P, Shepherd E, *et al.* Interventions to prevent women from developing gestational diabetes *mellitus*: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews*. 2020; 6 (9): CD012394. DOI: [10.1002/14651858.CD012394.pub3](https://doi.org/10.1002/14651858.CD012394.pub3)
- xxxvii. Brand K, Saarelainen L, Sonajal J, *et al.* Metformin in pregnancy and risk of adverse long- term outcomes: a register-based cohort study. *BMJ Open Diabetes Research and Care* 2022;10(1):e002363. DOI: [10.1136/bmjdr-2021-002363](https://doi.org/10.1136/bmjdr-2021-002363)
- xxxviii. Jorquera G, Echiburú B, Crisosto N, Sotomayor-Zárate R, Maliqueo M and Cruz G. Metformin during Pregnancy: Effects on Offspring Development and Metabolic Function. *Frontiers in Pharmacology*. 2020;11:653. DOI: [10.3389/fphar.2020.00653](https://doi.org/10.3389/fphar.2020.00653)
- xxxix. Shokrpour M, Foroozanfar F, Afshar Ebrahimi F, Vahedpoor Z, Aghadavod E, Ghaderi A, *et al.* Comparison of myo-inositol and metformin on glycemic control, lipid profiles, and gene expression related to insulin and lipid metabolism in women with polycystic ovary syndrome: a randomized controlled clinical trial. *Gynecological Endocrinology*. 2019;35(5):406-11. DOI: [10.1080/09513590.2018.1540570](https://doi.org/10.1080/09513590.2018.1540570)
- xl. Syngelaki A, Nicolaidis KH, Balani J, Hyer S, Akolekar M, Kotecha R, *et al.* Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus. *The New England Journal of Medicine*. 2016;374(5):434-443. DOI: [10.1056/NEJMoa1509819](https://doi.org/10.1056/NEJMoa1509819)
- xli. Motuhifonua SK, Lin L, Alsweller J, Crawford TJ, Crowther CA. Antenatal dietary supplementation with myo-inositol for preventing gestational diabetes. *Cochrane Database of Systematic Reviews*. 2023;2(2):CD011507. DOI: [10.1002/14651858.CD011507.pub3](https://doi.org/10.1002/14651858.CD011507.pub3)
- xlii. Ibrahim I, Bashir M, Singh P, Al Khodor S, Abdullahi H. The Impact of Nutritional Supplementation During Pregnancy on the Incidency of Gestational Diabetes and Glycaemia Control. *Frontiers in Nutrition*. 2022;9:867099. DOI: [10.3389/fnut.2022.867099](https://doi.org/10.3389/fnut.2022.867099)
- xliii. Hu L, Zhang Y, Wang X, You L, Xu P, Cui X, *et al.* Maternal Vitamin D Status and Risk of Gestational Diabetes: A Meta-Analysis. *Cellular Physiology and Biochemistry*. 2018;45(1):291-300. DOI: [10.1159/000486810](https://doi.org/10.1159/000486810)
- xliv. Xia J, Song Y, Rawal S, Wu J, Hinkle SN, Tsai MY, *et al.* Vitamin D status during pregnancy and the risk of gestational diabetes *mellitus*: A longitudinal study in a multiracial cohort. *Diabetes, Obesity and Metabolism*. 2019;21(8):1895-1905. DOI: [10.1111/dom.13748](https://doi.org/10.1111/dom.13748)
- xlv. Amabebe E, Robert F, Agbalalah T, Orubu E. Microbial dysbiosis-induced obesity: role of gut microbiota in homeostasis of energy metabolism. *British Journal of Nutrition*. 2020;123(10):1127-1137. DOI: [10.1017/S0007114520000380](https://doi.org/10.1017/S0007114520000380)
- xlvi. Cibickova L, Schovaneck J, Karasek D. Changes in serum lipid levels during pregnancy in women with gestational diabetes. A narrative review. *Biomedical Papers*. 2021;165(1):8-12. DOI: [10.5507/bp.2021.009](https://doi.org/10.5507/bp.2021.009)
- xlvii. Zhang Q, Cheng Y, He M, Li T, Ma Z, Cheng H. Effect of various doses of vitamin D supplementation on pregnant women with gestational diabetes *mellitus*: A randomized controlled trial. *Experimental and Therapeutic Medicine*. 2016;12(3):1889-1895. DOI: [10.3892/etm.2016.3515](https://doi.org/10.3892/etm.2016.3515)
- xlviii. Palacios C, Kostiuik, Peña-Rosas J and Cochrane Pregnancy and Childbirth Group. Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews*. 2019;7(7):CD008873. DOI: [10.1002/14651858.cd008873.pub4](https://doi.org/10.1002/14651858.cd008873.pub4)
- xlix. Mahdizade Ari M, Teymouri S, Fazlalian T, Asadollahi P, Afifrad R, Sabaghan M, *et al.* The effect of probiotics on gestational diabetes and its complication in pregnant mother and newborn: A systematic review and meta-analysis during 2010-2020. *Journal of Clinical and Laboratory Analysis*. 2022;36(4):e24326. DOI: [10.1002/jcla.24326](https://doi.org/10.1002/jcla.24326)
- I. Zhang J, Ma S, Wu S, Guo C, Long S, Tan H. Effects of probiotic supplement in pregnant

- women with gestational diabetes *mellitus*: a systematic review and meta-analysis of randomized controlled trials. *Journal of Diabetes Research*. 2019;2019:5364730. DOI: [10.1155/2019/5364730](https://doi.org/10.1155/2019/5364730)
- li. Jamilyan M, Samimi M, Mirhosseini N, Afshar-Ebrahumi F, Aghadavod E, Asemi Z. A randomized Double-Blinded, Placebo-Controlled Trial Investigating the Effects of Fish Oil Supplementation on Gene Expression Related to Insulin Action, Blood Lipids, and Inflammation in Gestational Diabetes Mellitus-Fish Oil Supplementation and Gestational Diabetes. *Nutrients*. 2018;10(2):163. DOI: [10.3390/nu10020163](https://doi.org/10.3390/nu10020163)
- lii. Middleton P, Gomersall J, Gould J, Shepherd E, Olsen S, Makrides M, Omega-3 fatty acid addition during pregnancy. *Cochrane Database of Systematic Reviews*. 2018;11(11):CD003402. DOI: [10.1002/14651858.CD003402.pub3](https://doi.org/10.1002/14651858.CD003402.pub3)



# Hyperbaric oxygentherapy as an adjuvant in the treatment of diabetic foot



DOI: 10.5377/alerta.v7i2.16810

Fabiola Sofía Ventura Cornejo<sup>1\*</sup>, Finella Nicole Rottmann<sup>2</sup>, Héctor Elías Menjívar Saravia<sup>3</sup>

1-3. Dr. José Matías Delgado University, Antiguo Cuscatlán, El Salvador.

Correspondence

✉ [fabiolaventurac140498@gmail.com](mailto:fabiolaventurac140498@gmail.com)

1.  0009-0006-0073-097X
2.  0000-0003-4504-3875
3.  0000-0002-9461-9204

## Abstract

Diabetic foot ulcers affect about 20 % of patients. They affect the quality of life and increase the risk of mortality, as main complication. Treatment currently includes the use of drugs and surgical debridement of the ulcerated tissue. Among its coadjuvant therapies, the use of hyperbaric oxygen therapy stands out as it reduces the risk of complications. This study seeks to describe the use of hyperbaric oxygen therapy as an adjuvant in the treatment of diabetic foot. A literature review was conducted using databases: PubMed, Elsevier, SciELO, and in Spanish and English languages, published between 2018 and 2023. Hyperbaric oxygen therapy consists of placing the patient in a higher-pressure environment, with oxygen concentrations close to 100 %, resulting in anti-inflammatory effects. The approach to the diabetic foot should be multidisciplinary in order to achieve early recovery, including a pharmacological approach to manage neuropathic pain and cure infections. Hyperbaric oxygen therapy has been considered as a coadjuvant treatment by increasing the percentage of complete healing to 33.3 %, facilitating healing, increasing and reducing the perceived pain. It concluded that there are publications that support the use of hyperbaric oxygen therapy in addition to conventional therapy, because it improves the healing rate and reduces the risk of major amputations.

## Keywords

Hyperbaric Oxygenations, Diabetic Feet, Amputation Surgical, Diabetes *mellitus*, Vascular Disease, Foot Ulcer.

## Resumen

Las úlceras de pie diabético afectan alrededor del 20 % de los pacientes. Estas afectan la calidad de vida e incrementan el riesgo de mortalidad, como principales complicaciones. El tratamiento actual incluye la utilización de medicamentos y la desbridación quirúrgica del tejido ulcerado. Dentro de sus terapias coadyuvantes se destaca el uso de la oxigenoterapia hiperbárica que reduce el riesgo de sus complicaciones. Por esto se busca describir el uso de la oxigenoterapia hiperbárica como coadyuvante en el tratamiento de pie diabético. Por lo tanto, se realizó una revisión bibliográfica utilizando bases de datos: PubMed, Elsevier, SciELO, y en los idiomas español e inglés, publicados entre 2018 y 2023. La oxigenoterapia hiperbárica consiste en colocar al paciente en un entorno de mayor presión, con concentraciones de oxígeno cercanas al 100 %, resultando en efectos antiinflamatorios. El abordaje del pie diabético debe ser multidisciplinario con el fin de lograr una pronta recuperación, incluyendo abordaje farmacológico dando manejo al dolor neuropático y a la curación de las infecciones. La oxigenoterapia hiperbárica se ha considerado como tratamiento coadyuvante al aumentar el porcentaje de curación completa a un 33,3 %, facilitando la curación, aumentando y reduciendo el dolor percibido. Se concluye que efectivamente existen publicaciones que respaldan el uso de la oxigenoterapia hiperbárica adicional a la terapéutica convencional ya que mejora la tasa de curación y reduce el riesgo de amputaciones mayores.

## Palabras clave


Oxigenoterapia hiperbárica, pie diabético, amputación quirúrgica, diabetes *mellitus*, úlcera de pie.

## Introduction

Diabetes *mellitus* has a global impact, affecting nearly 500 million individuals. Among the most serious and prevalent complications is the diabetic foot, which can develop from a range of factors, including diabetic neuropathy, vascular disease, diabetic foot ulcer (DFU), and osteomyelitis.<sup>i,ii</sup>

Diabetic foot disease develops in patients who abandon their treatment or do not attend their medical check-ups,<sup>iii</sup> which usually leads to amputation and disability.<sup>iv</sup>

Approximately 20 % of diabetic patients develop DFU, increases visits to emergency departments and hospitalization, raises the risk of mortality, and elevates the costs of patients with diabetes in the healthcare system by up to 40 %.<sup>v</sup>

 OPEN ACCESS

**Oxigenoterapia hiperbárica como coadyuvante en el tratamiento del pie diabético**

### Suggested citation:

Ventura Cornejo FS, Rottmann FN, Menjívar Saravia HE. Hyperbaric oxygentherapy as an adjuvant in the treatment of diabetic foot. *Alerta*. 2024;7(2):177-183. DOI: 10.5377/alerta.v7i2.16810

### Editor:

Nadia Rodríguez.

### Received:

September 12, 2023.

### Accepted:

April 17, 2024.

### Published:

July 24, 2024.

### Author contribution:

FSVC<sup>1</sup>, FNRD<sup>2</sup>, HEMS<sup>3</sup>: study conception, literature search, data collection. FSVC<sup>1</sup>, FNRD<sup>2</sup>, HEMS<sup>3</sup>: manuscript design, data management and analysis or software, writing, revising and editing.

### Conflict of interests:

The authors declared there was no conflict of interests.



© 2024 by the authors. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Between July 2014 and August 2018, about 26 million people with DFU were registered worldwide, and 130 million were at risk of developing diabetic peripheral neuropathy.<sup>vi</sup> There is evidence that 19 to 35 % of UPDs do not heal, and 10 to 20 % progress to amputation despite careful treatment with conventional therapies.<sup>vii</sup>

Hyperbaric oxygen therapy (HBO) favors the resolution of lesions in diabetic patients by increased tissue oxygenation at the local level and the measurement of transcutaneous oxygen pressure,<sup>viii</sup> through the reduction of the risk of major amputations; consequently, it improves the patient's quality of life and presents a higher healing rate in patients with DFU,<sup>x</sup> because it reduces the surface area of the treated wounds, the pain perceived by the patients,<sup>x</sup> and the healing time of DFU compared to the exclusive use of conventional treatment.<sup>xi</sup> Likewise, HBO has demonstrated a reduction in hospital stays, emergency department visits, and treatment costs.<sup>xii</sup> For this reason, this review aims to describe the use of HBO as an adjuvant in treating diabetic foot.

## Discussion

### Hyperbaric oxygen therapy as an adjuvant in the conventional treatment of diabetic foot

The current treatment of the diabetic foot consists of a multidisciplinary approach using three key steps: identification of diabetic patients at risk, treatment of the affected foot, and measures to prevent recurrence.<sup>xiii</sup> The pharmacological approach to diabetic foot care focuses on the management of neuropathic pain and the prevention or cure of infections, whether localized or systemic, associated with the lesion.<sup>xiv</sup>

In addition to drugs, there are also different techniques in use, such as surgical debridement of the ulcerated tissue to promote healing, the use of wheelchairs, crutches, customized orthopedic footwear, or other devices that allow weight redistribution.<sup>xv</sup>

Among these adjuvant techniques is HBO which, according to Salama *et al.*, can reduce the ulcerated surface from an average of 7.5 cm<sup>2</sup> to 2 cm<sup>2</sup> after 30 sessions of HBO and, in addition, the complete closure of the wounds was 33.3 % greater, compared to the control group.<sup>xvi</sup> With this, an ease in DFU healing and a reduction in the need for additional surgical procedures are described<sup>xvii</sup> and summarized in the patient's quality of life.

In soft tissue infection, HBO has shown to reduce the mortality rate associated with

this condition, with a relative risk of 0.55,<sup>xviii</sup> although it did not represent significant changes in in-hospital stay ( $p = 0.96$ ) or the number of debridement required for healing of the lesion ( $p = 0.17$ ).<sup>xix</sup>

It is described that at least 60 % of non-traumatic amputations occur due to diabetes-related complications.<sup>xx</sup> Hyperbaric oxygen therapy has been shown to have a positive effect in reducing the risk of a major amputation (OR = 0.53, 95 % CI [0.32; 0.90],  $p = 0.02$ ), and has a positive impact on minor amputation when compared to conventional therapy (OR = 0.89, 95 % CI [0.35; 2.24],  $p = 0.80$ ). About the total healing of ulcerated tissue, it is observed that the ulcers of patients who underwent HBO had a complete resolution that was higher at 23 % (OR = 4.00, 95 % CI [1.54; 10.44],  $p = 0.005$ ), compared to the group that received conventional therapy.<sup>xxi</sup>

The effect of HBO is not limited to its impact on DFU but also reduces glycemia levels and increases insulin sensitivity in patients with type 2 diabetes mellitus (DM2).<sup>xxii</sup> Heyboerli *et al.* observed that in 75 % of 1825 HBO sessions, there was a reduction in glycemia levels, with a mean decrease of 25 mg/dL in patients with DM2, while they only observed a 51.5 % reduction in patients with type 1 diabetes mellitus (DM1).<sup>xxiii</sup>

Some absolute counter-indications to the use of HBO include pneumothorax, chemotherapy with cisplatin and doxorubicin, hyperthyroidism, and congestive heart failure with LVEF <30 %.<sup>xxiv</sup> In addition, adverse effects of HBO were reported, including middle ear barotrauma, most frequently described as hyperoxic myopia, claustrophobia, hypoglycemia, pulmonary barotrauma, and oxygen-mediated central nervous system toxicity.<sup>xxv</sup>

### Mechanism of action and application of hyperbaric oxygen therapy (HBO)

HBO consists of placing a patient in a high-pressure environment and boosting an inspiration of 100 % oxygen at the usual minimum acceptable pressure of 1.4 atmospheres absolute (ATA), under specific indications (Table 1),<sup>xxvi</sup> with an average duration of two hours daily, with two ten-minute breaks.<sup>xxvii</sup>

Oxygen dissolves in the plasma and increases oxygen pressure ( $pO_2$ ) from 2.0 to 3.0 ATA to achieve an arterial oxygen pressure ( $PaO_2$ ) between 1200 and 2000 mmHg. This hyper-oxygenation causes therapeutic effects at the molecular level because it triggers functional and structural changes that allow tissue recovery.<sup>xxviii,xxix</sup>

**Table 1.** Specific indications for hyperbaric oxygen therapy

---

Arterial or venous air or gas embolisms.
Severe or symptomatic carbon monoxide poisoning.
Myositis and clostridial myonecrosis ( gaseous gangrene).
Selected crush injuries, compartment syndrome and other acute traumatic ischemia.
Decompression sickness.
Selected arterial insufficiencies, including central retinal artery occlusion and improved healing in selected problematic wounds.
Specific intracranial abscesses.
Chronic refractory osteomyelitis.
Delayed radiation injuries with bone or soft tissue necrosis.
Acute thermal burn injuries.

---

**Source:** Essentials of Hyperbaric Oxygen Therapy: 2019 Review.<sup>xxxv</sup>

Moghadam *et al.* describe that the most relevant effect that HBO allows is the production of free radicals in a therapeutic range for the initiation of cell signaling that induces oxidative stress and generates in the short term, an improvement in oxygen supply; consequently, it produces anti-inflammatory effects and reduces the injury caused by ischemia, while, in the long term, it induces neovascularization, angiogenesis and collagen production.<sup>xxxviii</sup>

The pathology of delayed healing of lesions is associated with a prolonged oxygen deficit explained by hypoxia, which generates an imbalance that delays the appearance of proinflammatory cells causing an expression of growth factors, angiogenesis, and defective extracellular matrix formation. A hyperglycemic state destabilizes the hypoxia-inducible factor, and therefore, dysregulation of the activation of varied factors appears, contributing to the progression of the disease.<sup>xxxix</sup>

Hanley *et al.* described inadequate skin oxygenation as a risk factor triggering complications that lead to amputation. The use of HBO in patients with DFU Wagner classification 3 or higher, who have undergone recent surgical debridement, generates a reduction in the risk of amputation; therefore, the use of this treatment is considered an adjuvant in those patients who have not improved after 30 days of conventional therapies.<sup>xxxix</sup>

According to Menmar *et al.*, HBO increased the frequency of DFU healing, and decreased the need for amputations and debridement, thus decreasing the need for surgical treatment with amputa-

tions and debridement.<sup>xxxiv</sup> Sharma *et al.* identified a significantly lower amputation rate compared to conventional therapy with a significant statistical difference (HBO 27/232 compared to ST 46/23,  $p = 0.02$ );<sup>xxxv</sup> in addition to a decrease in HbA1c levels in Wagner 3-4 patients.<sup>xxxvi</sup>

## Characteristics of the systemic oxygen therapy and local oxygen therapy

HBO represents a therapeutic approach that can be delivered systemically, placing the patient in a completely closed environment, in a pressurized chamber known as a hyperbaric chamber, in which an ambient pressure higher than the conventional atmospheric pressure is administered. During this session, pure oxygen is applied, which generates a significant increase in oxygen pressure ( $pO_2$ ) higher than one atmosphere in the body, and leads to the removal of oxygen in tissues and body fluids.<sup>xxxvii</sup>

The alveolar  $pO_2$  increases significantly and consequently triggers a series of biological reactions, such as an increase in the oxygen content present in the blood plasma, an increase in the metabolic activity of the cells that receive optimized amounts of oxygen, and the positive influence of the HBO that is not limited to the cellular level but extends to the systemic level. Therefore, the elevation of alveolar  $pO_2$  generates a biological environment conducive to counteract tissue hypoxia through regeneration, repair, and reduction of the inflammatory reaction.<sup>xxxviii</sup> The treatment is administered in a monoplane chamber, where only one person is placed at a time, although there are also larger chambers, called multiple, where two or more people can be treated at the same time.<sup>xxxix</sup>

HBO can also be administered locally, called topical oxygen therapy, which consists of the application of 100 %  $pO_2$  directly to the base of an open wound at a pressure above sea level ( $>1$  ATA),<sup>xl</sup> through chambers that fit snugly around a limb using disposable polyethylene bags that facilitate administration in a controlled environment.<sup>xli</sup> Consequently, it increases the amount of oxygen that dissolves in the patient's plasma through the circulatory system; this more efficient and deeper oxygenation of the cells allows them to optimize their metabolic functions.<sup>x</sup>

Pasek *et al.* conducted a study about the use of local oxygen therapy in the treatment of DFU, in which 45 patients with diabetic foot received 30 sessions of local HBO therapy at a pressure of 2.5 ATA. The

outcome presented the progress of wound healing, which was evaluated by computerized planimetry. It showed that wound surface area was significantly reduced with a decrease in mean ulcer area from  $8.54 \pm 3.34 \text{ cm}^2$  before treatment to  $4.23 \pm 3.23 \text{ cm}^2$  ( $p = 1 \times 10^{-6}$ ) after treatment (Table 2).<sup>xliii</sup>

On the other hand, Stoekenbroek *et al.* studied systemic oxygen therapy, highlighting its benefit due to the accelerated healing process of ischemic ulcers at the local level with a reduction in pain intensity, as perceived by the patient.<sup>xliiii</sup> Likewise, Abidia *et al.*, conducted a study with 18 patients who received HBO for one year, in which a significantly greater healing process was evidenced; complete healing was achieved in five out of eight ulcers in the group treated with HBO compared to zero out of eight ulcers in the control group ( $p = 0.026$ ).<sup>xliiv</sup>

In addition, it is worth mentioning that there was evidence of increased healing of grade 3 and 4 ulcers of the Wagner-Merrit Scale classification in persons who received systemic HBO,<sup>xliv</sup> but there has not been a study comparing the classification with local HBO. It is suggested that systemic HBO may be a valuable adjunctive therapy as it has shown a positive evolution in hypoxic skin of lower limb vascular lesions in acute and chronic lesions.<sup>xlvi,xlvii</sup>

Research advances show the benefits of systemic and local oxygen therapy for patients with DFU<sup>xlviii</sup> and continue to clarify the therapeutic effects of these modalities; however, it is recommended that

large-scale randomized controlled trials be conducted to generate more evidence of their effectiveness.

## Conclusion

The use of local and systemic HBO as an adjuvant in the treatment of DFU is effective in reducing the size of the ulcer, with better and faster healing, reduction of local edema, and reduction of local pain; however, it represents an additional cost to the treatment due to the use of instruments and studies that define whether a patient is eligible for this treatment.

## Acknowledgements

To Jacobo Abullarade, for his advice on this work.

## Funding

There was not external financing for this study.

## References

- i. International Diabetes Federation. IDF Diabetes Atlas. 2022. Consulted date: March 16, 2023. Available at: <https://diabetesatlas.org>
- ii. Ministerio de Salud. Diez Primeras Causas frecuentes de Consulta Ambulatoria Año 2020. San Salvador: Ministerio de Salud; 2021. 31 p. Available at: <https://www.salud.gub.ve>

**Table 2.** DFU surface area before and after completion of local HBO procedures

	UPB Surface area (cm <sup>2</sup> )			p
	n (%)	Before treatment	After treatment	
		Media ± DE	Media ± DE	
<b>Total</b>	45 (100 %)	8.54 ± 3.34	4.23 ± 3.23	1 x 10 <sup>-6</sup>
<b>Gender</b>				
<b>Male</b>	24 (53.3 %)	8.98 ± 3.67	4.62 ± 3.39	1.8 x 10 <sup>-5</sup>
<b>Female</b>	21 (46.6 %)	8.03 ± 2.94	3.79 ± 3.05	6 x 10 <sup>-5</sup>
<b>p</b>		0.372438	0.36039	
		Age (years)		
<b>&lt;60</b>	11 (24.4 %)	6.66 ± 2.37	2.79 ± 1.44	3.346 x 10 <sup>-3</sup>
<b>60-70</b>	16 (35.5 %)	8.96 ± 3.58	4.51 ± 3.13	0.438 x 10 <sup>-4</sup>
<b>&gt;70</b>	18 (40 %)	9.31 ± 3.36	4.87 ± 3.9	1.96 x 10 <sup>-4</sup>
<b>p</b>		0.1411	0.4616	
		Foot		
<b>Left</b>	26 (57.7 %)	8.23 ± 3.19	4.13 ± 3.38	8 x 10 <sup>-6</sup>
<b>Right</b>	19 (42.2 %)	8.95 ± 3.6	4.38 ± 3.09	1.32 x 10 <sup>-4</sup>
<b>p</b>		0,690505	0,758774	

**Source:** Local hyperbaric oxygen therapy in the treatment of diabetic foot ulcers<sup>xlix</sup>.

- [gob.sv/causas-frecuentes-y-principales-anos-2020-2015/](http://gob.sv/causas-frecuentes-y-principales-anos-2020-2015/)
- iii. Musuuza J, Sutherland BL, Kurter S, Balasubramanian P, Bartels CM, Brennan MB. A systematic review of multidisciplinary teams to reduce major amputations for patients with diabetic foot ulcers. *J. Vasc. Surg.* 2020;71(4):1433-1446.e3. DOI: [10.1016/j.jvs.2019.08.244](https://doi.org/10.1016/j.jvs.2019.08.244)
  - iv. Lipsky BA, Senneville É, Abbas ZG, Aragón Sánchez J, Diggle M, Embil JM, *et al.* Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab. Res. Rev.* 2020;36(S1):e3280. DOI: [10.1002/dmrr.3280](https://doi.org/10.1002/dmrr.3280)
  - v. Pourkazemi A, Ghanbari A, Khojamli M, Balo H, Hemmati H, Jafaryparvar Z, *et al.* Diabetic foot care: knowledge and practice. *BMC Endocr. Disord.* 2020;20(1):40. DOI: [10.1186/s12902-020-0512-y](https://doi.org/10.1186/s12902-020-0512-y)
  - vi. Lazzarini PA, Jarl G, Gooday C, Viswanathan V, Caravaggi CF, Armstrong DG, *et al.* Effectiveness of offloading interventions to heal foot ulcers in persons with diabetes: a systematic review. *Diabetes Metab. Res. Rev.* 2020;36(S1):e3275. DOI: [10.1002/dmrr.3275](https://doi.org/10.1002/dmrr.3275)
  - vii. Kumar A, Shukla U, Prabhakar T, Srivastava D. Hyperbaric oxygen therapy as an adjuvant to standard therapy in the treatment of diabetic foot ulcers. *J. Anaesthesiol Clin Pharmacol.* 2020;36(2):213-218. DOI: [10.4103/joacp.JOACP\\_94\\_19](https://doi.org/10.4103/joacp.JOACP_94_19)
  - viii. Brouwer RJ, Laliou RC, Hoencamp R, Van Hulst RA, Ubbink DT. A systematic review and meta-analysis of hyperbaric oxygen therapy for diabetic foot ulcers with arterial insufficiency. *J Vasc Surg.* 2020;71(2):682-692.e1. DOI: [10.1016/j.jvs.2019.07.082](https://doi.org/10.1016/j.jvs.2019.07.082)
  - ix. Zhang Z, Zhang W, Xu Y, Liu D. Efficacy of hyperbaric oxygen therapy for diabetic foot ulcers: An updated systematic review and meta-analysis. *Asian J. Surg.* 2022;45(1):68-78. DOI: [10.1016/j.asjsur.2021.07.047](https://doi.org/10.1016/j.asjsur.2021.07.047)
  - x. Piotrowska A, Zych M, Oliwa J. Application of Hyperbaric Oxygen Therapy in the Skin Diseases Treatment. *Rehabil. Med.* 2021;25(1). DOI: [10.5604/01.3001.0015.2526](https://doi.org/10.5604/01.3001.0015.2526)
  - xi. Nik Hisamuddin N, Wan Mohd Zahiruddin W, Mohd Yazid B, Rahmah S. Use of hyperbaric oxygen therapy (HBOT) in chronic diabetic wound - A randomised trial. *Med. J. Malaysia.* 2019;74(5):418-424.
  - xii. Espinel Jara VM, Noboa Proaño FR, Tapia Paguay MX, Chalá Minda MP, Castillo Andrade RE, Reyes López LG, *et al.* Terapia hiperbárica, efectividad en el tratamiento de pie diabético. *Enferm. Investiga.* 2020;5(3):27-31. DOI: [10.31243/ei.uta.v5i3.915.2020](https://doi.org/10.31243/ei.uta.v5i3.915.2020)
  - xiii. Oyebo OA, Jere SW, Houreld NN. Current Therapeutic Modalities for the Management of Chronic Diabetic Wounds of the Foot. *Chattopadhyay M, editor. J. Diabetes Res.* 2023;2023:1-10. DOI: [10.1155/2023/1359537](https://doi.org/10.1155/2023/1359537)
  - xiv. Ministerio de Salud. Lineamientos técnicos para el abordaje integral, multidisciplinario e interinstitucional a las personas con pie diabético. Ministerio de Salud, San Salvador. 2021. 53 p. Available at: <http://asp.salud.gob.sv/regulacion/pdf/lineamientos/lineamiento-ostecnicosabordajeintegralmultidisciplinarioeinterinstitucionalalaspersonasconpiediabetico-Acuerdo-2736.pdf>
  - xv. Ramakrishnan Ramesh D, Ahmed Shaikh F, Ilyas Nadeem M. Current Perspective of Prevention and Management of Diabetic Foot. In: Raghav A, editor. *Diabetic Foot - Recent Advances.* 1st ed. Malaysia: IntechOpen; 2023. 1-14.
  - xvi. Salama SE, Eldeeb AE, Elbarbary AH, Abdelghany SE. Adjuvant Hyperbaric Oxygen Therapy Enhances Healing of Nonischemic Diabetic Foot Ulcers Compared With Standard Wound Care Alone. *Int. J. Low. Extrem. Wounds.* 2019;18(1):75-80. DOI: [10.1177/1534734619829939](https://doi.org/10.1177/1534734619829939)
  - xvii. Aydın F, İncesu M, Özer EE, Kaya A. The Use of Hyperbaric Oxygen Therapy the Following Amputation in Patients with Diabetes. *Anatol. J. Med.* 2023;32(1):73-78. DOI: [10.4274/terh.galenos.2021.64507](https://doi.org/10.4274/terh.galenos.2021.64507)
  - xviii. Huang C, Zhong Y, Yue C, He B, Li Y, Li J. The effect of hyperbaric oxygen therapy on the clinical outcomes of necrotizing soft tissue infections: a systematic review and meta-analysis. *World J. Emerg. Surg.* 2023;18(1):23. DOI: [10.1186/s13017-023-00490-y](https://doi.org/10.1186/s13017-023-00490-y)
  - xix. Raizandha MA, Hidayatullah F, Klopung YP, Rahman IA, Djatisoesanto W, Rizaldi F. The role of hyperbaric oxygen therapy in Fournier's Gangrene: A systematic review and meta-analysis of observational studies. *Int. Braz. J. Urol.* 2022;48(5):771-781. DOI: [10.1590/s1677-5538.ibju.2022.0119](https://doi.org/10.1590/s1677-5538.ibju.2022.0119)
  - xx. Pitocco D, Spanu T, Di Leo M, Vitiello R, Rizzi A, Tartaglione L, *et al.* Diabetic foot infections: a comprehensive overview. *Eur. Rev. Med. Pharmacol. Sci.* 2019;23(2 Suppl):26-37. DOI: [10.26355/eurrev\\_201904\\_17471](https://doi.org/10.26355/eurrev_201904_17471)
  - xxi. Moreira Da Cruz DL, Oliveira Pinto J, Mansilha A. The role of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers: a systematic review with meta-analysis of randomized controlled trials on limb amputation and ulcer healing. *Int. Angiol.* 2022;41(1):63-73. DOI: [10.23736/S0392-9590.21.04722-2](https://doi.org/10.23736/S0392-9590.21.04722-2)
  - xxii. Baitule S, Patel AH, Murthy N, Sankar S, Kyrou I, Ali A, *et al.* A Systematic Review

- to Assess the Impact of Hyperbaric Oxygen Therapy on Glycaemia in People with Diabetes Mellitus. *Medicina*. 2021;57(10):1134. DOI: [10.3390/medicina57101134](https://doi.org/10.3390/medicina57101134)
- xxiii. Heyboer Iii M, Wojcik SM, Swaby J, Boes T. Blood glucose levels in diabetic patients undergoing hyperbaric oxygen therapy. *Undersea Hyperb. Med. J. Undersea Hyperb. Med. Soc. Inc.* 2019;46(4):437-445. Available at: <https://pubmed.ncbi.nlm.nih.gov/31509900/>
- xxiv. Hajhosseini B, Kuehlmann BA, Bonham CA, Kamperman KJ, Gurtner GC. Hyperbaric Oxygen Therapy: Descriptive Review of the Technology and Current Application in Chronic Wounds. *Plast. Reconstr. Surg. - Glob. Open.* 2020;8(9):e3136. DOI: [10.1097/GOX.0000000000003136](https://doi.org/10.1097/GOX.0000000000003136)
- xxv. Heyboer M, Sharma D, Santiago W, McCulloch N. Hyperbaric Oxygen Therapy: Side Effects Defined and Quantified. *Adv. Wound Care.* 2017;6(6):210-224. DOI: [10.1089/wound.2016.0718](https://doi.org/10.1089/wound.2016.0718)
- xxvi. Kirby JP, Snyder J, Schuerer DJE, Peters JS, Bochicchio GV. Essentials of Hyperbaric Oxygen Therapy: 2019. *Mo. Med.* 2019;116(3):176-179.
- xxvii. Jones MW, Cooper JS. Hyperbaric Therapy for Wound Healing. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
- xxviii. Lindenmann J, Kamolz L, Graier W, Smolle J, Smolle Juettner F M. Hyperbaric Oxygen Therapy and Tissue Regeneration: A Literature Survey. *Biomedicines.* 2022;10(12):3145-3163. DOI: [10.3390/biomedicines10123145](https://doi.org/10.3390/biomedicines10123145)
- xxix. Ortega MA, Fraile Martinez O, García Montero C, Callejón Peláez E, Sáez MA, Álvarez Mon MA, *et al.* A General Overview on the Hyperbaric Oxygen Therapy: Applications, Mechanisms and Translational Opportunities. *Medicina (Mex.)*. 2021;57(9):864-889. DOI: [10.3390/medicina57090864](https://doi.org/10.3390/medicina57090864)
- xxx. Moghadam N, Hieda M, Ramey L, Levine BD, Guilliod R. Hyperbaric Oxygen Therapy in Sports Musculoskeletal Injuries. *Med. Sci. Sports Exerc.* 2020;52(6):1420-1426. DOI: [10.1249/MSS.0000000000002257](https://doi.org/10.1249/MSS.0000000000002257)
- xxxi. Dhamodharan U, Karan A, Sireesh D, Vaishnavi A, Somasundar A, Rajesh K, *et al.* Tissue-specific role of Nrf2 in the treatment of diabetic foot ulcers during hyperbaric oxygen therapy. *Free Radic. Biol. Med.* 2019;138:53-62. DOI: [10.1016/j.freeradbiomed.2019.04.031](https://doi.org/10.1016/j.freeradbiomed.2019.04.031)
- xxxii. Venkateshan J, Viswanathan P. Hyperbaric oxygen therapy and chemokine administration - a combination with potential therapeutic value for treating diabetic wounds. *World J. Diabetes.* 2022;13(12):1122-1130. DOI: [10.4239/wjd.v13.i12.1122](https://doi.org/10.4239/wjd.v13.i12.1122)
- xxxiii. Hanley ME, Manna B. Hyperbaric Treatment of Diabetic Foot Ulcer. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
- xxxiv. Memar MY, Yekani M, Alizadeh N, Baghi HB. Hyperbaric oxygen therapy: Antimicrobial mechanisms and clinical application for infections. *Biomed. Pharmacother.* 2019;109:440-447. DOI: [10.1016/j.biopha.2018.10.142](https://doi.org/10.1016/j.biopha.2018.10.142)
- xxxv. Sharma R, Sharma SK, Mudgal SK, Jelly P, Thakur K. Efficacy of hyperbaric oxygen therapy for diabetic foot ulcer, a systematic review and meta-analysis of controlled clinical trials. *Sci. Rep.* 2021;11(1):2189-2201. DOI: [10.1038/s41598-021-81886-1](https://doi.org/10.1038/s41598-021-81886-1)
- xxxvi. Irawan H, Semadi IN, Widiiana IGR. A Pilot Study of Short-Duration Hyperbaric Oxygen Therapy to Improve HbA1c, Leukocyte, and Serum Creatinine in Patients with Diabetic Foot Ulcer Wagner. *Sci. World J.* 2018;2018:1-6. DOI: [10.1155/2018/6425857](https://doi.org/10.1155/2018/6425857)
- xxxvii. Wenhui L, Changgeng F, Lei X, Baozhong Y, Guobin L, Weijing F. Hyperbaric oxygen therapy for chronic diabetic foot ulcers: An overview of systematic reviews. *Diabetes Res. Clin. Pract.* 2021;176:108862. DOI: [10.1016/j.diabres.2021.108862](https://doi.org/10.1016/j.diabres.2021.108862)
- xxxviii. FDA. Cust. Updat. Hyperbaric Oxygen Therapy: Get the Facts. FDA. Consulted date: May 10, 2023. Available at: <https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts>
- xxxix. Zhou D, Fu D, Yan L, Xie L. The Role of Hyperbaric Oxygen Therapy in the Treatment of Surgical Site Infections: A Narrative Review. *Medicina (Mex.)*. 2023;59(4):762-779. DOI: [10.3390/medicina59040762](https://doi.org/10.3390/medicina59040762)
- xl. Bennett MH, Mitchell SJ. Emerging indications for hyperbaric oxygen. *Curr. Opin. Anaesthesiol.* 2019;32(6):792-798. DOI: [10.1097/ACO.0000000000000773](https://doi.org/10.1097/ACO.0000000000000773)
- xli. OHSU Health Services. Hyperbaric Oxygen Therapy/Topical Oxygen Therapy. Portland: OHSU; 2019. 8 p. Available at: <https://www.ohsu.edu/sites/default/files/2020-06/OHSUHealthServices-Hyperbaric-Oxygen-Therapy-June2020.pdf>
- xlii. Pasek J, Szajkowski S, Oleś P, Cieślar G. Local Hyperbaric Oxygen Therapy in the Treatment of Diabetic Foot Ulcers. *Int. J. Environ. Res. Public Health.* 2022;19:10548. DOI: [10.3390/ijerph191710548](https://doi.org/10.3390/ijerph191710548)
- xliii. Stoekenbroek RM, Santema TB, Legemate DA, Ubbink DT, Van Den Brink A, Koelemay MJW. Hyperbaric Oxygen for the Treatment of Diabetic Foot Ulcers: A Systematic Review. *Eur. J. Vasc. Endovasc. Surg.* 2014;47(6):647-655. DOI: [10.1016/j.ejvs.2014.03.005](https://doi.org/10.1016/j.ejvs.2014.03.005)

- xliv. Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, *et al.* The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: A double-blind randomised-controlled trial. *Eur. J. Vasc. Endovasc. Surg.* 2003;25(6):513-518. DOI: [10.1053/ejvs.2002.1911](https://doi.org/10.1053/ejvs.2002.1911)
- xlv. Ennis WJ, Huang ET, Gordon H. Impact of Hyperbaric Oxygen on More Advanced Wagner Grades 3 and 4 Diabetic Foot Ulcers: Matching Therapy to Specific Wound Conditions. *Adv. Wound Care.* 2018;7(12):397-407. DOI: [10.1089/wound.2018.0855](https://doi.org/10.1089/wound.2018.0855)
- xlvi. Kranke P, Bennett MH, Martyn St James M, Schnabel A, Debus SE, *et al.* Hyperbaric oxygen therapy for chronic wounds Cochrane Wounds Group, editor. *Cochrane Database Syst. Rev.* 2015;6:Art. No.: CD004123. DOI: [10.1002/14651858.CD004123.pub4](https://doi.org/10.1002/14651858.CD004123.pub4)
- xlvii. Margolis DJ, Gupta J, Hoffstad O, Papdopoulos M, Glick HA, Thom SR, *et al.* Lack of Effectiveness of Hyperbaric Oxygen Therapy for the Treatment of Diabetic Foot Ulcer and the Prevention of Amputation. *Diabetes Care.* 2013;36(7):1961-1966. DOI: [10.2337/dc12-2160](https://doi.org/10.2337/dc12-2160)
- xlviii. Löndahl M, Boulton AJM. Hyperbaric oxygen therapy in diabetic foot ulceration: Useless or useful? A battle. *Diabetes Metab. Res. Rev.* 2020;36(S1):e3233. DOI: [10.1002/dmrr.3233](https://doi.org/10.1002/dmrr.3233)

# An update on the detection of tuberculosis through molecular testing

DOI: 10.5377/alerta.v7i2.17129

Laura Sofía Sánchez Figueroa<sup>1\*</sup>, Valeria Alexandra Guillén Muñoz<sup>2</sup>, Juan Diego Pérez Pérez<sup>3</sup>, Pablo Alberto Rodríguez Abrego<sup>4</sup>, Claudia María Caprile Mata<sup>5</sup>, Katherine Lisseth Cartagena López<sup>6</sup>

1-6. Dr. Luis Edmundo Vásquez School of Health Sciences, Dr. José Matías Delgado University, Antigua Cuscatlán, El Salvador.

\*Correspondence

✉ laurasanchezco2020@gmail.com

1.  0009-0004-2612-74372.  0009-0005-0670-218X3.  0009-0001-6417-40214.  0009-0009-3616-60815.  0009-0004-2648-205X6.  0009-0006-9503-7990

## OPEN ACCESS

### Actualización en la detección de la tuberculosis a través de pruebas moleculares

#### Suggested citation:

Sánchez Figueroa LS, Guillén Muñoz VA, Pérez Pérez JD, Rodríguez Abrego PA, Caprile Mata CM, Cartagena López KL. An update on the detection of tuberculosis through molecular testing. *Alerta*. 2024;7(2):184-190. DOI: 10.5377/alerta.v7i2.17129

#### Editor:

Nadia Rodríguez.

#### Received:

December 4, 2023.

#### Accepted:

June 27, 2024.

#### Published:

July 24, 2024.

#### Author contribution:

LSSF1, VAGM2, JDPP3, PARA4: study conception, manuscript design, writing, revision and edition. LSSF1, VAGM2, JDPP3, PARA4, CMCM5, KLCL6: literature search and information analysis.

#### Conflicts of interest:

The authors declared there are not conflicts of interest.



© 2024 by the authors. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

### Abstract

Tuberculosis is a respiratory infectious disease that affects one third of the world's population and is a significant threat to global health. Detecting tuberculosis early is crucial for effective treatment and preventing its spread. One solution to improve diagnosis and address antituberculosis drug resistance is the use of high-throughput molecular tests for the identification of *Mycobacterium tuberculosis* and its susceptibility. This narrative review study seeks to describe the generalities, efficacy, sensitivity, advantages and limitations of the main molecular tests: Truenat® MTB, MTB plus and MTB-RIF, Abbott RealTime MTB and MTB RIF/INH on the m2000sp and m2000rt system and FluoroType MTBDR, and to compare them with GeneXpert MTB/RIF or Xpert Ultra, used for the detection of the tuberculosis drug-resistant pathogen. These tests use various techniques for the detection of *Mycobacterium tuberculosis* DNA and quantification of bacterial load with high sensitivity and specificity, rapid results, reduction of human error, as well as early detection of drug-resistant strains.

### Keywords

*Mycobacterium Tuberculosis*, Tuberculosis, Diagnosis, Molecular Tests.

### Resumen

La tuberculosis es una enfermedad infecciosa respiratoria que afecta a un tercio de la población mundial y es una amenaza significativa para la salud global. La detección de la tuberculosis de manera temprana es crucial para un tratamiento eficaz y prevenir su propagación. Una solución para mejorar el diagnóstico y abordar la resistencia a los medicamentos antituberculosos es el uso de pruebas moleculares de alto rendimiento para la identificación del *Mycobacterium tuberculosis* y su susceptibilidad. Este estudio de revisión narrativa busca describir las generalidades, la eficacia, la sensibilidad, las ventajas y las limitaciones de las principales pruebas moleculares; Truenat® MTB, MTB plus y MTB-RIF, Abbott RealTime MTB y MTB RIF/INH en el sistema m2000sp y m2000rt y FluoroType MTBDR, además, de compararlas con GeneXpert MTB/RIF o Xpert Ultra, utilizadas para la detección del patógeno resistente a medicamentos tuberculosos. Estas pruebas utilizan diversas técnicas para la detección del ADN del *Mycobacterium tuberculosis* y la cuantificación de la carga bacteriana con alta sensibilidad y especificidad, resultados rápidos, reducción de los errores humanos, así como la detección temprana de cepas drogo-resistentes. A pesar de que requieren infraestructura especializada y competencias profesionales para su implementación, representan avances significativos con el potencial de mejorar la atención sanitaria y la gestión de la tuberculosis. Estas pruebas moleculares, comparadas con el GeneXpert, son una alternativa viable, aunque esta última tecnología sigue siendo la preferida en áreas con recursos limitados.

### Palabras clave

*Mycobacterium tuberculosis*, tuberculosis, diagnóstico, técnicas de diagnóstico molecular.

## Introduction

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* (MTB) complex that encompasses a group of closely genetically related species, including MTB, the most recognized as it is responsible for infecting more than one-third of the world's human popula-

tion<sup>1</sup>. TB continues to pose a considerable health risk globally, as indicated by figures provided by the World Health Organization (WHO), which estimated 7.5 million cases diagnosed with TB in 2023 and a total of 1.3 million deaths from TB. In addition, it is believed that around three million TB cases went undetected during the same year.<sup>1</sup>



Early diagnosis of TB is critical for effective treatment and prevention of disease spread; likewise, detection of drug resistance is important for effective treatment.<sup>i</sup> A potential solution to close the diagnostic gap for TB and drug resistance lies in using centralized high-throughput platforms to detect MTB through molecular drug susceptibility testing.<sup>ii</sup> Several molecular technologies are available, such as nucleic acid amplification tests, whole genome sequencing, and the GeneXpert system (Xpert MTB/RIF or Xpert MTB/RIF Ultra). These detect the presence of MTB and its antibiotic resistance genes by DNA detection in patient samples.<sup>iii</sup>

The GeneXpert system is a standard and widely used molecular test that rapidly detects MTB and assesses resistance to multiple anti-TB drugs, primarily rifampicin (RIF), the first-line drug for TB. Other molecular tests such as Truenat MTB, Abbott RealTime MTB, and FluoroType MTB are also used in the diagnosis of TB.<sup>iv</sup>

These molecular tests provide greater speed and accuracy compared to traditional methods such as microscopy and culture. In addition, they allow the detection of antibiotic resistance, which facilitates more accurate and effective treatment.<sup>v</sup>

Through this review, the generalities, efficacy, sensitivity, advantages, and limitations of the Truenat MTB, MTB plus and MTB-RIF, Abbott RealTime MTB and MTB RIF/INH tests on m2000sp and m2000rt systems, and FluoroType MTBDR, as well as their comparison with GeneXpert MTB/RIF or Xpert<sup>®</sup> MTB/RIF Ultra, used for the detection of MTB resistant to tuberculous drugs, are described.

## Discussion

### Test Overview

#### Truenat MTB, MTB Plus and & MTB-RIF Dx

The Truenat MTB, MTB Plus and MTB-RIF Dx tests are molecular tests for the detection of MTB and RIF resistance,<sup>vi</sup> developed by Bigtec Labs, Molbio Diagnostics of Goa, India and endorsed by WHO in 2020.<sup>iv</sup>

Truenat testing employs loop-mediated isothermal amplification technology to identify the presence of MTB and assess resistance to RIF. It consists of a technique of nucleic acid amplification at a constant temperature, usually around 65 °C. In addition, it is semi-quantitative; it can indicate the approximate amount of bacteria present directly in sputum samples. The devices for these tests are portable. The tests are capable of performing simultaneously multiple reactions, which facilitates faster and more efficient diagnosis.<sup>vii</sup>

The Truenat MTB test is the basic test used for the identification of the presence of MTB. The Truenat Plus assays, an enhanced version of the Truenat MTB, detect specific genes such as *nrdB*, *nrdZ*, and IS6110.<sup>viii</sup> The *nrdB* gene encodes the beta subunit of ribonucleotide reductase, a crucial enzyme that supplies the precursors necessary for DNA synthesis. It also detects the *nrdZ* gene, which is part of the dormancy-associated gene regulon. In addition, it detects the IS6110 gene, which is used as a specific epidemiological marker for TB and is found exclusively in the MTB complex.<sup>ix,x</sup>

Likewise, Truenat MTB-Rif Dx tests are able to detect mutations in the *rpoβ* gene, which encodes the beta subunit of RNA polymerase in bacteria and is the main target of action of RIF. Mutations in the *rpoβ* gene can alter the structure of RNA polymerase, preventing RIF from efficiently binding to the active site of the enzyme and is ineffective in inhibiting DNA-to-RNA transcription in bacteria with *rpoβ* mutations, leading to resistance to RIF. Test results are obtained in less than one hour.<sup>xi-xiii</sup>

#### Abbott RealTime MTB and MTB RIF/INH

Abbott RealTime MTB is a molecular test launched by Abbott Company in 2015 to detect MTB, endorsed by WHO since its development. This test also identifies RIF and isoniazid (INH)-resistant variants, expanding its utility in diagnosing antibiotic-resistant strains.<sup>xiv</sup> It employs the real-time polymerase chain reaction (PCR-RT) technique, which focuses on identifying the gene encoding the antigen B protein, essential in the synthesis of mycolic acids. These are key components of the bacterial cell wall and are crucial for survival and resistance to host immune responses.<sup>xv</sup> The IS6110 gene is important in the identification of MTB, as a transposon-like element, is mobile within the bacterial genome and with specific characteristics of the bacterial complex; however, the number of copies of the IS6110 element may vary between different strains of the bacterium.<sup>xvi</sup>

The Abbott Realtime MTB RIF/INH test can detect resistance to RIF (*rpoβ* gene) and INH (*katG* and *inhA* genes). Moreover, the *katG* gene encodes catalase-peroxidase enzymes that are necessary to activate INH within the bacteria. If there is a mutation in the *katG* gene, INH will not be activated and will not be able to perform its antimicrobial action.<sup>xvii</sup> On the other hand, the *inhA* gene encodes the enzyme enoyl-ACP reductase, essential for the synthesis of fatty acids in bacteria, including the synthesis of

bacterial cell walls. When there are mutations in the *inhA* gene, the enzyme enoyl-ACP reductase can become less sensitive to inhibition by INH, and consequently generates resistance.<sup>xviii</sup>

The Abbott RealTime MTB and MTB RIF/INH tests differ in technology, sample types and processing time in the m2000sp and m2000rt systems. The m2000sp system uses PCR-RT, while the m2000rt uses PCR-RT with fluorescent probes that are validated for sputum samples. The m2000rt also supports bronchoalveolar lavage and pleural fluid samples. The processing time for m2000sp is approximately two hours, while m2000rt is four hours.<sup>xiv,xvi,xix</sup>

### **FluoroType MTBDR**

Fluorotype MTBDR1.0 and MTBDR2.0 are WHO-approved molecular tests for the detection of MTB, and were developed by the German laboratory Hain Lifescience in 2019. These tests use linear after exponential PCR (LATE-PCR) technology, and special probes with lights-on/lights-off detection. In addition, they incorporate LiquidArray technology, a PCR platform that enables the detection of multiple targets in a single reaction through the use of specific primers. These tests are designed to identify mutations in the *rpoβ*, *inhA* and *katG* genes, which indicate drug resistance in multi-drug-resistant TB cases.<sup>v</sup>

FluoroType MTB VER 1.0 and FluoroType MTB VER 2.0 have key similarities and differences. Version 1.0 focuses on the IS6110 insertion element and can process decontaminated pulmonary and extrapulmonary samples. In contrast, version 2.0 targets the *rpoβ* gene to detect MTB complex and RIF resistance, the *inhA* promoter and the *katG* gene for INH resistance, validated for respiratory samples. Both versions employ LiquidArray technology in PCR amplification, providing results in an average of two hours and 30 minutes. Notably, version 1.0 uses FluoroCycler® 12, while version 2.0 uses FluoroCycler® XT, thermal cyclers designed specifically for this test. The entire process can be completed in an average of two and a half hours.<sup>xx,xxi</sup>

### **Sensitivity and specificity**

#### **Truenat MTB, MTB Plus and MTB-RIF Dx**

In a four-hospital study in Cameroon involving 945 people with TB symptoms, the Truenat MTB Plus test demonstrated a sensitivity of 91 % (228 of 251) in TB patients with bacteriological confirmation of disease by culture. The overall specificity of the Truenat

MTB Plus test was 96 %; 31 of the 694 participants with culture-negative TB results were positive for MTB with the Truenat MTB Plus test. Therefore, they concluded that these results support the effectiveness of the Truenat tests as they demonstrate their ability to adequately identify this disease in the majority of cases.<sup>xxii</sup>

#### **Abbott RealTime MTB and MTB RIF/INH**

Abbott Realtime MTB has a high specificity (97 %) and sensitivity (93 %), according to information provided by the company.<sup>xxiii</sup> In terms of sensitivity, a study conducted in Africa showed that the Abbott Realtime MTB test has a sensitivity of 92.4 %.<sup>xvi</sup> This study performed such a test on people who already have a confirmed TB diagnosis: in them, the test detected MTB in 73 out of 79 people. In addition, it showed that the test has a specificity of 95.4 %.<sup>xvi</sup> These findings indicate that the Abbott RealTime MTB and MTB RIF/INH tests are highly effective diagnostic resources for TB, with the ability to identify accurately in most clinical situations.<sup>xvi</sup>

#### **FluoroType MTBDR**

The FluoroType MTB and MTBDR VER 2.0 tests were evaluated for accuracy in detecting drug-resistant TB in a study conducted at the National Reference Laboratory for Mycobacteria in Borstel, Germany. Of the 610 patients, 360 samples tested positive for MTB on Xpert Ultra, and 250 samples tested negative for MTB on Xpert Ultra. Therefore, FluoroType MTB VER 2.0 showed a sensitivity for manual DNA extraction of 91.6 % and a sensitivity of 89.8 % for automated extraction. Automated DNA extraction had a sensitivity of 92.1 % in contrast to non-automated extraction with 87.7 %. Consequently, the sensitivity for INH was 91.7 %, and for RIF, 98.9 %.<sup>xxiv</sup>

Studies were conducted in South Africa to evaluate the specificity of the FluoroType MTBDR test for the detection of MTB and resistance to RIF and INH. Sputum samples from patients who had a previous evaluation with Xpert MTB/RIF were used, and the results showed a specificity of 100 % for both MTB detection and RIF and INH resistance.<sup>xxv,xxvi</sup>

### **Advantages**

#### **Truenat MTB, MTB Plus and MTB-RIF Dx**

Truenat MTB, MTB Plus, and MTB-RIF Dx tests offer several significant advantages over other TB diagnostic methods. They provide

rapid results in less than one hour, allowing immediate initiation of TB treatment. Additionally, they are highly sensitive and specific, enabling the differentiation of TB from other diseases with similar symptoms. Their portability and ease of use make them suitable for primary care settings. These combined advantages make Truenat tests an effective, rapid, and accurate tool for TB diagnosis.<sup>xxv</sup>

### **Abbott RealTime MTB and MTB RIF/INH**

One of the advantages offered by Abbott Realtime MTB and MTB RIF/INH is the ability to process a variability of samples including sputum, bronchoalveolar lavage and already extracted MTB DNA samples.<sup>xxvi</sup>

The m2000sp/m2000rt systems offer complete automation for MTB amplification and detection. These systems allow adjustment of sample volume and number of samples, reduce reagent waste and optimize throughput. In addition, they can process up to 96 samples with reduced turnaround time, most useful in antibiotic resistance testing such as RIF/INH. The capacity is 96 samples in eight hours and the inactivation reagent reduces the risk of contagion during sample handling. The test is noted for its accuracy, with the presence or absence of infection in processed samples.<sup>xxvi-xxviii</sup>

### **FluoroType MTBDR**

FluoroType MTBDR has several significant advantages. It processes sputum samples, which are minimally invasive and easy to obtain. The automated system can analyze up to 94 samples in three hours. Results are automatically generated. This system is characterized by detecting INH resistance and provides crucial information for treatment strategy. Automation reduces the risk of contamination, with a preparation time of 30 minutes. In summary, FluoroType MTBDR offers a fast and accurate assay for drug resistance detection in MTB.<sup>xxvi,xxvii</sup>

### **Limitations**

#### **Truenat MTB, MTB Plus and MTB-RIF Dx**

The Truenat MTB, MTB Plus, and MTB-RIF Dx tests, while valuable tools in the diagnosis of TB, have certain limitations to consider, including the possibility of providing false negative results in cases of RIF-resistant TB, because the Truenat MTB-RIF Dx test focuses exclusively on identifying genetic changes in the *rpoβ* gene. Similarly, in cases of low bacterial load, the tests can yield false negatives because they require a minimal

amount of MTB DNA to obtain a positive result (five copies of MTB genome and 131 CFU/mL in expectoration samples).<sup>xxii</sup>

### **Abbott RealTime MTB and MTB RIF/INH**

Less common MTB strains may give false negative results due to the difficulty of detection. Also, amplification reagents have a limited shelf life of 90 days from the date of manufacture or 60 days from the date of shipment, which may result in the loss of unused reagents. In addition, maintenance of the units must be performed through contracts with Abbott, which limits the ability to reduce operating costs by performing maintenance through third parties. Finally, the m200sp and m200rt systems do not have a USB port, so data must be manually exported or digitized.<sup>xxviii</sup>

Also, training on using the m200sp and m200rt systems is more complex compared to other TB diagnostic platforms. Training lasts at least five days and includes both theoretical and practical aspects. In addition, the implementation of these platforms requires a robust infrastructure, including isolated spaces for sample preparation.<sup>xxviii</sup>

### **FluoroType MTBDR**

The FluoroType MTBDR has several limitations. Its accuracy in diagnosing TB in low bacterial load samples is limited, as its detection range of 10 398 copies is three times greater than Xpert MTB/RIF. In addition, it does not detect certain mutations related to INH resistance, such as *katG* S315N. Although it has a high detection capability for RIF and INH resistance mutations, there are other tests with even higher sensitivity percentages. Finally, its sensitivity in the diagnosis of extrapulmonary tuberculosis is significantly lower than for sputum samples; because of this, it is not recommended for this type of tuberculosis.<sup>xxi,xxvii,xxviii</sup>

### **Comparison with GeneXpert**

#### **Truenat MTB, MTB Plus and MTB-RIF Dx**

The Truenat MTB and MTB PLUS test has lower sensitivity and higher specificity than the Xpert MTB/RIF for TB, especially in smear-negative and HIV-positive subjects. Truenat has a higher specificity than Xpert MTB/RIF in subjects with a history of TB. In terms of identifying RIF resistance, Xpert MTB/RIF has superior sensitivity and specificity compared to Xpert MTB/RIF. Positive results at the trace level are common with the Truenat MTB and MTB PLUS. The Truenat MTB, MTB Plus and MTB-RIF Dx

tests are effective molecular diagnostic tests for tuberculosis and are noted for their rapidity, sensitivity and specificity. These tests are accessible and inexpensive, suitable for primary care settings. Although the GeneXpert MTB/RIF test is more sensitive in detecting mutations in the *rpoβ* gene, it is a more expensive option and requires a specific PCR-RT system.<sup>xxix</sup>

### **Abbott RealTime MTB and MTB RIF/INH**

Although GeneXpert provides faster results than Abbott's RealTime tests, these are more useful for large workflows because they allow processing of a large number of samples. However, this represents a paradox, as the RealTime test would be beneficial in regions where TB is endemic for fast and accurate results, but requires adjustments in laboratory infrastructure, trained personnel, and is more difficult to implement; these features limit its use.<sup>xxviii,xxix</sup>

Abbott MTB detects MTB, MTB RIF/INH identifies MTB and resistance to RIF and INH, while GeneXpert detects MTB with some models able to identify resistance to RIF and uses a second cartridge that detects resistance to INH, quinolones, kanamycin, capreomycin, among others. In addition, GeneXpert is easier to use in resource-limited settings and requires less technical training. Both tests are highly sensitive for MTB detection, however, GeneXpert has a sensitivity of about 98 % while Abbott has a sensitivity of 92-97 %. For RIF and INH resistance, GeneXpert exhibits a high specificity (between 94 and 98 %), while Abbott has a lower specificity. In addition, the detection limit of GeneXpert is 18 CFU/mL, while Abbott RealTime requires only 17 CFU/mL, giving Abbott RealTime a slight advantage over GeneXpert.<sup>xxx</sup>

### **FluoroType MTBDR**

Although Xpert MTB/RIF remains the standard for molecular diagnostic testing for pulmonary tuberculosis, FluoroType MTBDR tests perform similarly. In terms of sensitivity, both tests are quite similar to Xpert, with a sensitivity of 98 % to MTB and FluoroType MTBDR of 97.9 %. In terms of resistance to RIF, Xpert has a percentage of 95 % and FluoroType 96.9 %. On the other hand, the main difference between the two tests is the detection limits. Xpert MTB/RIF can detect MTB in samples with a minimum load of 3781 copies, whereas FluoroType MTBDR has a minimum load limit of 10 398 copies. Therefore, Xpert MTB/RIF is more useful for detection of tuberculosis in tests with low bacterial load.<sup>xxv,xxvii,xxx</sup>

## **Conclusion**

The Truenat MTB, Abbott RealTime MTB, and FluoroType MTBDR diagnostic tests provide effective and reliable methods for the detection of *Mycobacterium Tuberculosis* and anti-tuberculosis drug resistance. Each of these tests has unique advantages, allowing the most appropriate test to be chosen based on the specific needs of the testing context. Truenat MTB uses chip-based nucleic acid amplification that can detect MTB in clinical sputum samples with a sensitivity of 91 % and specificity of 96 %. Abbott RealTime MTB employs *in vitro* polymerase chain reaction (PCR) for qualitative DNA detection, with a sensitivity of 92.4 % and specificity of 95.4 %, enabling high-throughput testing. FluoroType MTBDR is a new molecular test that diagnoses TB and RIF drug resistance. It has a sensitivity of 91.7 % for INH, 98.9 % for RIF, and a specificity of 100 %. Currently, GeneXpert is the preferred choice for molecular testing for tuberculosis, and its preference is justified. However, with the continued emergence of new technologies, such as these molecular tests, significant advances in TB detection and management are represented, and their implementation could improve healthcare for confirmed or suspected TB cases. Truenat MTB, Abbott RealTime MTB, and FluoroType MTBDR have provided a more comprehensive perspective and have shown promise for the global fight against TB because of their ability to accurately detect MTB and resistance to certain anti-TB drugs such as RIF and INH.

## **Acknowledgements**

To Gloria Patricia de Cativo, for her invaluable orientation, advice and guidance throughout the development of this work. Her experience and dedication have been fundamental for the development of the research. Her commitment and support have significantly enriched our work, and we are grateful for her valuable contribution to this project.

## **Funding**

No external funds were received for this work.

## **References**

- i. World Health Organization. Global tuberculosis report. Geneva. WHO. 2023. 57 p. Available at: <https://iris.who.int/bitstream/handle/10665/373828/9789240083851-eng.pdf?sequence=1>

- ii. MacLean E, Kohli M, Weber SF, Suresh A, Schumacher SG, Denkinger CM, *et al.* Advances in Molecular Diagnosis of Tuberculosis Suzanne Kraft C, editor. J Clin Microbiol. 2020;58(10):e01582-19. DOI: [10.1128/JCM.01582-19](https://doi.org/10.1128/JCM.01582-19)
- iii. Osei Sekyere J, Maphalala N, Malinga LA, Mbelle NM, Maningi NE. A Comparative Evaluation of the New Genexpert MTB/RIF Ultra and other Rapid Diagnostic Assays for Detecting Tuberculosis in Pulmonary and Extra Pulmonary Specimens. Sci Rep. 2019;9(1):16587. DOI: [10.1038/s41598-019-53086-5](https://doi.org/10.1038/s41598-019-53086-5)
- iv. Organización Panamericana de la Salud. Comunicación rápida: Análisis moleculares como pruebas diagnósticas iniciales de la tuberculosis y la resistencia a la rifampicina. Washington. 2020. OPS. 9 p. Available at: <https://iris.paho.org/handle/10665.2/52078>
- v. Nurwidya F, Handayani D, Burhan E, Yunus F. Molecular Diagnosis of Tuberculosis. Chonnam Med J. 2018;54(1):1. DOI: [10.4068/cmj.2018.54.1.1](https://doi.org/10.4068/cmj.2018.54.1.1)
- vi. Meaza A, Tesfaye E, Mohamed Z, Zerihun B, Seid G, Eshetu K, *et al.* Diagnostic accuracy of Truenat Tuberculosis and Rifampicin-Resistance assays in Addis Ababa, Ethiopia Kumar P, editor. PLoS ONE. 2021;16(12):e0261084. DOI: [10.1371/journal.pone.0261084](https://doi.org/10.1371/journal.pone.0261084)
- vii. Shete PB, Farr K, Strnad L, Gray CM, Cattamanchi A. Diagnostic accuracy of TB-LAMP for pulmonary tuberculosis: a systematic review and meta-analysis. BMC Infect Dis. 2019;19(1):268. DOI: [10.1186/s12879-019-3881-y](https://doi.org/10.1186/s12879-019-3881-y)
- viii. Singh UB, Singh M, Sharma S, Mahajan N, Bala K, Srivastav A, *et al.* Expedited diagnosis of pediatric tuberculosis using Truenat MTB-Rif Dx and GeneXpert MTB/RIF. Sci Rep. 2023;13(1):6976. DOI: [10.1038/s41598-023-32810-2](https://doi.org/10.1038/s41598-023-32810-2)
- ix. Kyaw SP, Hanthamrongwit J, Jangpatarapongsa K, Khaenam P, Leepiyasakulchai C. Sensitive detection of the IS 6110 sequence of *Mycobacterium tuberculosis* complex based on PCR-magnetic bead ELISA. RSC Adv. 2018;8(59):33674-33680. DOI: [10.1039/C8RA06599C](https://doi.org/10.1039/C8RA06599C)
- x. Soto ME, Del Carmen Ávila-Casado M, Huesca-Gómez C, Alarcon GV, Castrejon V, Soto V, *et al.* Detection of IS6110 and HupB gene sequences of *Mycobacterium tuberculosis* and bovisin the aortic tissue of patients with Takayasu's arteritis. BMC Infect Dis. 2012;12(1):194. DOI: [10.1186/1471-2334-12-194](https://doi.org/10.1186/1471-2334-12-194)
- xi. Vijayalakshmi J, Surekha A, Devi AR, Devi SU. Truenat - A Novel Diagnostic Tool for Rapid Detection of *Mycobacterium Tuberculosis* and Rifampicin Resistance in Pulmonary Samples. Int.J.Curr.Microbiol.App.Sci. 2019;8(10):1260-1267. DOI: [10.20546/ijcmas.2019.810.148](https://doi.org/10.20546/ijcmas.2019.810.148)
- xii. Ullah I, Shah AA, Basit A, Ali M, Khan A, Ullah U, *et al.* Rifampicin resistance mutations in the 81 bp RRDR of rpoB gene in *Mycobacterium tuberculosis* clinical isolates using Xpert MTB/RIF in Khyber Pakhtunkhwa, Pakistan: a retrospective study. BMC Infect Dis. 2016;16(1):413. DOI: [10.1186/s12879-016-1745-2](https://doi.org/10.1186/s12879-016-1745-2)
- xiii. Sinha P, Srivastava GN, Tripathi R, Mishra MN, Anupurba S. Detection of mutations in the rpoB gene of rifampicin-resistant *Mycobacterium tuberculosis* strains inhibiting wild type probe hybridization in the MTBDR plus assay by DNA sequencing directly from clinical specimens. BMC Microbiol. 2020;20(1):284. DOI: [10.1186/s12866-020-01967-5](https://doi.org/10.1186/s12866-020-01967-5)
- xiv. Wang M-G, Xue M, Wu S-Q, Zhang M-M, Wang Y, Liu Q, *et al.* Abbott RealTime MTB and MTB RIF/INH assays for the diagnosis of tuberculosis and rifampicin/isoniazid resistance. Infection, Genetics and Evolution. 2019;71:54-59. DOI: [10.1016/j.meegid.2019.03.012](https://doi.org/10.1016/j.meegid.2019.03.012)
- xv. Andersen AB, Hansen EB. Structure and mapping of antigenic domains of protein antigen b, a 38,000-molecular-weight protein of *Mycobacterium tuberculosis*. Infect Immun. 1989;57(8):2481-2488. DOI: [10.1128/iai.57.8.2481-2488.1989](https://doi.org/10.1128/iai.57.8.2481-2488.1989)
- xvi. Araya BT, Ali KE, Geleta DA, Tekele SG, Tulu KD. Performance of the Abbott RealTime MTB and RIF/INH resistance assays for the detection of *Mycobacterium Tuberculosis* and resistance markers in sputum specimens Quinn F, editor. PLoS ONE. 2021;16(5):e0251602. DOI: [10.1371/journal.pone.0251602](https://doi.org/10.1371/journal.pone.0251602)
- xvii. Jaber M, Rattan A, Kumar R. Presence of *katG* gene in resistant *Mycobacterium tuberculosis*. Journal of Clinical Pathology. 1996;49(11):945-947. DOI: [10.1136/jcp.49.11.945](https://doi.org/10.1136/jcp.49.11.945)
- xviii. De Maio F, Cingolani A, Bianco DM, Salustri A, Palucci I, Sanguinetti M, *et al.* First description of the *katG* gene deletion in a *Mycobacterium tuberculosis* clinical isolate and its impact on the mycobacterial fitness. International Journal of Medical Microbiology. 2021;311(4):151506. DOI: [10.1016/j.ijmm.2021.151506](https://doi.org/10.1016/j.ijmm.2021.151506)
- xix. Gomathi N, Singh M, Singh U, Myneedu V, Chauhan D, Sarin R, *et al.* Multicentric validation of indigenous molecular test TruenatTM MTB for detection of *Mycobacterium tuberculosis* in sputum samples from presumptive pulmonary tuberculosis patients in comparison with reference standards. Indian J Med

- Res. 2020;152(4):378. DOI: [10.4103/ijmr.ijmr\\_2539\\_19](https://doi.org/10.4103/ijmr.ijmr_2539_19)
- xx. Merker M, Kohl TA, Barilar I, Andres S, Fowler PW, Chryssanthou E, *et al.* Phylogenetically informative mutations in genes implicated in antibiotic resistance in *Mycobacterium tuberculosis* complex. *Genome Med.* 2020;12(1):27. DOI: [10.1186/s13073-020-00726-5](https://doi.org/10.1186/s13073-020-00726-5)
- xxi. Svensson E, Folkvardsen DB, Rasmussen EM, Lillebaek T. Detection of *Mycobacterium tuberculosis* complex in pulmonary and extrapulmonary samples with the FluoroType MTBDR assay. *Clinical Microbiology and Infection.* 2021;27(10):1514.e1-1514.e4. DOI: [10.1016/j.cmi.2020.12.020](https://doi.org/10.1016/j.cmi.2020.12.020)
- xxii. Ngangue YR, Mbuli C, Neh A, Nshom E, Koudjou A, Palmer D, *et al.* Diagnostic Accuracy of the Truenat MTB Plus Assay and Comparison with the Xpert MTB/RIF Assay to Detect Tuberculosis among Hospital Outpatients in Cameroon Turenne CY, editor. *J Clin Microbiol.* 2022;60(8):e00155-22. DOI: [10.1128/jcm.00155-22](https://doi.org/10.1128/jcm.00155-22)
- xxiii. Realtime MTB. Illinois, U.S.A.: Abbott; 2024. p. 1. Available at: <https://www.molecular.abbott/int/en/products/infectious-disease/realtime-mtb>
- xxiv. Hillemann D, Haasis C, Andres S, Behn T, Kranzer K. Validation of the FluoroType MTBDR Assay for Detection of Rifampin and Isoniazid Resistance in *Mycobacterium tuberculosis* Complex Isolates Land GA, editor. *J Clin Microbiol.* 2018;56(6):e00072-18. DOI: [10.1128/JCM.00072-18](https://doi.org/10.1128/JCM.00072-18)
- xxv. De Vos M, Scott L, David A, Trollip A, Hoffmann H, Georghiou S, *et al.* Comparative Analytical Evaluation of Four Centralized Platforms for the Detection of *Mycobacterium tuberculosis* Complex and Resistance to Rifampicin and Isoniazid Miller MB, editor. *J Clin Microbiol.* 2021;59(3):e02168-20. DOI: [10.1128/JCM.02168-20](https://doi.org/10.1128/JCM.02168-20)
- xxvi. Zabost A, Filipczak D, Kupis W, Szturmowicz M, Olendrzyński Ł, Winiarska A, *et al.* Use of a FluoroType® System for the Rapid Detection of Patients with Multidrug-Resistant Tuberculosis-State of the Art Case Presentations. *Diagnostics.* 2022;12(3):711. DOI: [10.3390/diagnostics12030711](https://doi.org/10.3390/diagnostics12030711)
- xxvii. Bielsa S, Bernet A, Civit C, Acosta C, Manonelles A, Porcel JM. FluoroType® MTB in pleural fluid for diagnosing tuberculosis. *Revista Clínica Española (English Edition).* 2021;221(3):139-144. DOI: [10.1016/j.rceng.2020.04.010](https://doi.org/10.1016/j.rceng.2020.04.010)
- xxviii. Kohli M, MacLean E, Pai M, Schumacher SG, Denkinger CM. Diagnostic accuracy of centralised assays for TB detection and detection of resistance to rifampicin and isoniazid: a systematic review and meta-analysis. *Eur Respir J.* 2021;57(2):2000747. DOI: [10.1183/13993003.00747-2020](https://doi.org/10.1183/13993003.00747-2020)
- xxix. Penn-Nicholson A, Gomathi SN, Ugarte-Gil C, Meaza A, Lavu E, Patel P, *et al.* A prospective multicentre diagnostic accuracy study for the Truenat tuberculosis assays. *Eur Respir J.* 2021;58(5):2100526. DOI: [10.1183/13993003.00526-2021](https://doi.org/10.1183/13993003.00526-2021)
- xxx. Arend SM, Van Soolingen D. Performance of Xpert MTB/RIF Ultra: a matter of dead or alive. *The Lancet Infectious Diseases.* 2018;18(1):8-10. DOI: [10.1016/S1473-3099\(17\)30695-3](https://doi.org/10.1016/S1473-3099(17)30695-3)

# Importance of childhood nutritional status in their cognitive development

DOI: 10.5377/alerta.v7i2.17862

Luz Olivia Bernal Regalado

Department of Physiology and Medical Pharmacology, Alberto Masferrer Salvadorean University (USAM), San Salvador, El Salvador.

Correspondence

✉ luzoliviab68@outlook.es

1.  0009-0004-5294-8896

## Abstract

The nutritional status of children is a priority issue for many national and international institutions. Despite efforts to improve their condition, there are still cases of malnutrition, due to excess and deficit of macro and micronutrients. Diseases associated with this condition, whether communicable or not, have a direct impact on the physical and psychological health of infants. This article presents the relationship between appropriate nutrition and optimal cognitive development during the early life stages. For this purpose, information was consulted from various sources such as SciELO, PubMed, Scopus, Hinari, university repositories, and reports from the Food and Agriculture Organization of the United Nations, the World Food Program and the World Health Organization. These sources state that malnutrition and hidden hunger in children is the cause of alterations in cognitive processes, since the daily diet provides the substances necessary for brain metabolic processes.

## Keywords

*Diet, Food, Nutrition, Cognition, Child.*

## Resumen

El estado nutricional de los niños es un tema prioritario para numerosas instituciones nacionales e internacionales. A pesar de los esfuerzos por mejorar su condición, aún persisten casos de malnutrición, tanto por exceso como por déficit de macro y micronutrientes. Las enfermedades asociadas a esta condición transmisibles o no, tienen un impacto directo en la salud física y psicológica de los infantes. Este artículo presenta la relación entre una nutrición adecuada y el desarrollo cognitivo óptimo durante las primeras etapas de la vida. Para ello, se consultó información de diversas fuentes como SciELO, PubMed, Scopus, Hinari, repositorios universitarios, e informes de la Organización de las Naciones Unidas para la Alimentación y la Agricultura, del Programa Mundial de Alimentos y de la Organización Mundial de la Salud. Estas fuentes afirman que la malnutrición y el hambre oculta en los niños son causas de alteraciones en los procesos cognitivos, ya que la dieta diaria provee las sustancias necesarias para los procesos metabólicos cerebrales.

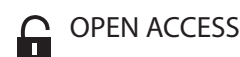
## Palabras clave

*Nutrición, Alimentación y Dieta, Cognición, Niño.*

## Introduction

Globally, there is enormous concern about the nutritional status of children, especially in middle and low-income countries. According to reports from the World Health Organization (WHO), eight million children under five years old present some degree of malnutrition, which is of significance because of its repercussions on health from the first years of life to adulthood.<sup>i,ii,iii</sup>

Malnutrition is an abnormal condition caused by a deficit or excess of nutrients, either macronutrients or micronutrients, manifesting as loss (undernutrition), excessive weight gain (overweight and obesity), age-related short stature, and inadequate intake of vitamins and minerals (hidden hunger). It is multifactorial and includes socioeconomic, biological, and cultural factors.<sup>iii,iv,v</sup>



OPEN ACCESS

**Importancia del estado nutricional de la niñez en su desarrollo cognitivo**

**Suggested citation:**

Bernal Regalado LO. Importance of childhood nutritional status in their cognitive development. *Alerta*. 2024;7(2):191-197. DOI: 10.5377/alerta.v7i2.17862

**Editor:**

Nadia Rodríguez.

**Received:**

November 21, 2023.

**Accepted:**

July 5, 2024.

**Published:**

July 24, 2024.

**Author contribution:**

LOBR: study conception, manuscript design, literature search, data collection, data or software management, data analysis, writing, revising and editing.

**Conflicts of interest:**

The author declared there are not conflicts of interest.



© 2024 by the author. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Proper nutrition is crucial to maintain homeostasis in brain functions, since nutrients act as cofactors or neurotransmitters, i.e., they are chemical substances necessary to perform cognitive activities such as information processing, memory, motor skills, and language, among other key elements of learning and academic performance.<sup>ii,iii,iv,v</sup>

The study of this subject is relevant because the first stages of life are fundamental for brain development. The classification of cognitive development stages by Jean Piaget emphasized that children's learning process is qualitative and quantitative since, as they advance through the stages, their way of thinking is modified due to the assimilation and accommodation of the learning process.<sup>vi</sup>

Therefore, it is essential to ensure an adequate diet from pregnancy, during breastfeeding, until the first five years of life, a crucial period to provide nutrients in appropriate quantity and prevent the different manifestations of malnutrition.<sup>iii</sup>

This review aims to report on the relationship between adequate nutrition and cognitive development in early childhood. A documental search was conducted in scientific databases such as PubMed, Google Scholar, Research Gate, Cochrane, SciELO, Redalyc, and the National Library of Medicine. The search also included university repositories and official documents of the WHO, World Food Program (WFP), and the Food and Agriculture Organization of the United Nations (FAO). Articles published in Spanish, English, and Portuguese with publication dates of less than five years (2019-2023) were considered.

## Discussion

### Nutritional status of children

Proper nutrition in the first years of life is crucial for the development of children. However, worldwide, the production and consumption of foods that lack the necessary nutrients for optimal growth are predominant, which raises concerns about the high rates of malnutrition reported in the children population.<sup>i,ii,iii,iv,v</sup>

In 2022, the WHO estimated that 149 million children under five years old were stunted, 45 million were wasted, and 37 million were overweight or obese, and that about half of all deaths of children under five were related to undernutrition.<sup>i</sup>

The United Nations Agenda 2030 (UN) and the WHO Global Nutrition Targets 2025 established targets for the health of children and mothers, recognizing that child nutri-

tion begins before pregnancy and continues through the first five years of life. These goals aim to reduce stunting, maternal anemia, overweight rate, low birth weight, and wasting, as well as to increase the breastfeeding rate up to six months of age.<sup>vii,viii</sup>

Children are constantly exposed to unrestricted advertising of fast foods. This situation implies an increase in the frequent consumption of processed and ultra-processed foods, which are modified from their natural state to prolong their consumption time, change their consistency, and improve their taste at the expense of adding high contents of fat, sugar, salt or other additives.<sup>vii,ix</sup>

According to the Food Systems Summit 2021 of the United Nations, in El Salvador, the diet is based mainly on bread, corn tortillas, sugary drinks, and sweet bread, with an increase in the consumption of simple carbohydrates, carbonated beverages, foods with excess fat and sodium, such as fast foods.<sup>vii</sup>

In addition, the report mentions a lower consumption of fruits, vegetables, and foods of animal origin because the Salvadoran population is influenced by the mass media and globalization, which induces the incorporation of fast food into the daily diet. In addition, there is insufficient water consumption of less than two liters per day.<sup>x</sup>

According to the United Nations Children's Fund (UNICEF), globally for 2019, one in three children under five years old is undernourished or overweight, and half of them present hidden hunger, which negatively affects their physical and cognitive development.<sup>viii</sup> This was evidenced in El Salvador's National Health Survey 2021, which showed that children under two years old in urban areas mainly ingest packaged juices and carbonated beverages, while in rural areas, chocolate or coffee drinks predominate in that age group.<sup>xi</sup>

This survey also reveals that in El Salvador, chronic malnutrition mainly affects children under five months old, living in rural areas (5.9 %) and that the percentage of stunting is also higher in these areas (11 %) compared to 9.3 % in urban areas. This contrasts with the percentage of children under five years old, who are overweight (8.3 %) and obese (3 %), predominantly in the urban areas.<sup>vii,xii</sup>

### Cerebral cortex and cognitive functions

Understanding the physiological processes involved in brain metabolism and cognitive functions is crucial for discerning the importance of maintaining a balanced



nutrient intake through a healthy diet. It helps in establishing the connection between proper nutrition and the cognitive processes.<sup>iii,xii,xiii</sup>

The cerebral cortex is formed by millions of neurons and glial cells, which receive environmental stimuli, generating nerve impulses that cause sensory or motor responses. Neurotransmitters and chemical receptors are involved in nerve impulse transmission through the synaptic space.<sup>xiii</sup>

The function of glial cells is to maintain brain homeostasis, and support and produce the myelin sheath, contributing to the transmission of nerve impulses to the central and peripheral nervous system to generate a response.<sup>xii,xiii</sup>

Neurotransmitters are chemical messengers that send inhibitory or excitatory signals to neurons to trigger nerve impulses. Major neurotransmitters include acetylcholine, noradrenaline, gamma amino butyric acid (GABA), glutamate, serotonin, glycine, and histamine.<sup>xii,xiii</sup>

This entire system is necessary for cognitive processes, which comprise the set of actions related to the intellectual activity of knowing and reasoning, including memory, perception, language, thought, and imagination, influenced both by the biopsychosocial environment and by the nutrition received, which provides essential micro and macronutrients for the synthesis of neurotransmitters and the energy necessary for brain metabolism.<sup>xiv,xv,xvi</sup>

These cognitive processes are shaped in the brain through thousands of synapses, forming neural networks that store or discard information according to the child's needs. These neural networks begin to form in the first five years of life and last into adulthood.<sup>xvii,xviii,xix</sup>

Jean Piaget described that cognitive development includes several stages and that learning, as well as the assimilation of information, is both qualitative and quantitative, i.e., accumulating knowledge and reorganizing it. The stages proposed by Piaget are: sensorimotor (0-2 years), preoperational (2-7 years), concrete operations (7-11 years), and formal operations (11 years and older).<sup>vi,xx</sup>

## Balanced diet and hidden hunger

The term diet refers to all prepared foods and beverages that people consume daily, whose preparation habits and practices are influenced by geographic location, culture, and socioeconomic status.<sup>xviii,xix</sup>

Proper nutrition begins with good maternal nutrition during pregnancy and continues with breastfeeding, contrib-

uting to healthy growth, optimal cognitive development, and a strengthened immune system. Similarly, adequate nutrition in the first five years of life helps to avoid the risk of communicable and non-communicable diseases and the different expressions of malnutrition described above.<sup>xix,xx</sup>

A balanced diet should consider the appropriate amount of food, with rations adjusted to age and metabolic needs, and the nutrients necessary to support the proper functioning of the body without causing harm while respecting the dietary habits according to the culture of each region. Transculturization has altered local diets.<sup>xx,xxi</sup>

It is advisable to use a combination of foods that provide both macronutrients and micronutrients and to avoid processed or ultra-processed foods that contain high levels of fat, salt, or sugar, which make them more appealing, but increase the rates of obesity and heart disease, among other risks.<sup>xix,xx,xxi</sup>

The Food and Nutrition Board of the United States suggests that the recommended daily intake for children from zero to eight years old should include carbohydrates, total fiber, lipids, linoleic acid, alpha-linolenic acid, proteins, as well as vitamins A, B, E, K, C, B6, B12, thiamine, riboflavin, niacin, folate, pantothenic acid, biotin, choline, and minerals such as calcium, iodine, iron, zinc, fluorine, magnesium, phosphorus, among others.<sup>xx,xxi</sup>

Micronutrient deficiency is known as "Hidden Hunger". Micronutrients such as iron, vitamins A, D, B complex, zinc, and calcium are responsible for multiple functions in the body and both their deficiency and excess consumption can alter cognitive development and growth in childhood.<sup>xxii,xxiii</sup>

The impact of hidden hunger during pregnancy is of particular concern, as it could affect the fetus and be reflected in the newborn's health up to five years of life. McCoy argues that hidden hunger at this stage of life has consequences on the functional capacity of the developing brain, which is crucial for the assimilation of information.<sup>xxii,xxiii</sup>

## Malnutrition and cognitive development

In the early stages of life, the brain undergoes accelerated development and maturation, where neural connections occur enabling children to adapt to their surrounding environment and to use the information assimilated. These connections are more evident in the stages of concrete and formal operations.<sup>xii,xiv,xxiv</sup>

Brain metabolism involving neurons and glial cells requires cofactors to synthesize neurotransmitters and Adenosine Triphosphate (ATP), the main energy source for electrophysiological functions, obtained from glucose and oxygen.<sup>xxv,xxvi</sup>

Research has shown that children with a balanced diet have better cognitive development. Breastfeeding alone is a necessary and sufficient source of nutrients, vitamins, carbohydrates, and other bioactives in appropriate amounts that provide the substrates required for infant development.<sup>xxvi,xxvii,xxviii</sup>

Children who lack these nutrients may present deficits in analytical processes, classification of ideas and images, organization of ideas and symbols transmitted mainly through language, or the performance of everyday tasks such as playing, solving problems, and even learning a melody, among other activities.<sup>xx,xxii</sup>

Martin *et al.* conducted studies on children with obesity to assess cognitive development and reported that compared to children of normal weight, they presented lower scores in mathematics, reading, and spelling; in addition, they detected decreased perceptual reasoning and memory reflected in emotional problems, lower motivation, and reduced participation in academic activities.<sup>xx,xxii</sup>

Malnutrition also contributes to a decrease in the number of neurons and nerve connections, damage to the myelin sheath and dendritic branches, manifesting in a thin cerebral cortex, and slow brain growth, affecting motor function and memory. This damage may be irreversible if it persists beyond four years of age.<sup>iii,xxii</sup>

Poor micronutrient intake is not physically visible, and it manifests itself in children's cognitive deficits, including grade repetition, shorter schooling, and poor performance in academic assessments, due to their essential role in the neurotransmitters synthesis and cofactors that promote biochemical reactions.<sup>xxiii,xxiv</sup>

The brain demands a large amount of energy, mainly from glucose obtained from daily carbohydrate intake. However, carbohydrates with high sugar content and low nutritional value tend to decrease cognitive and psychomotor functions in children under five.<sup>xxv,xxvi,xxvii</sup>

Neurotransmitters derived from protein metabolism are mainly obtained from the diet and are essential for cognitive functions. Glial cells are structurally composed of lipids and underline the importance of a healthy diet in adequate portions.<sup>xxiv,xxv,xxviii</sup>

Neurotransmitters such as serotonin, adrenaline, and dopamine are synthesized from the amino acids tryptophan and

tyrosine, which are present in dairy products, red and white meats, nuts, and some vegetables. These compounds participate in cognitive processes such as learning, reasoning, and memory.<sup>xxix,xxx,xxxi</sup>

Acetylcholine is related to memory and neurodevelopment; it is synthesized from the amino acid L-tyrosine, obtained from the daily diet. In addition, its synthesis depends on vitamin B12 and folate. Deficiency of pyridoxal phosphate, thiamine pyrophosphate, and vitamin B12 leads to marked neurological dysfunction.<sup>xxxii,xxxiii</sup>

Two-thirds of the neurons in the cerebral cortex use glutamic acid as a neurotransmitter and contain zinc in their synaptic vesicles. Zinc deficiency has been linked to cognitive delay in children since these neurons are responsible for long-term memory and the learning process.<sup>xxxiv,xxxv</sup>

Iron is a necessary cofactor for several enzymatic reactions, given that it intervenes in the conduction of the nervous impulse. It is a required nutrient in the diet of children under five years old, where most neuronal connections are built.<sup>xxxvi,xxxvii</sup>

Docosahexaenoic acid (DHA) is a phospholipid that is part of the cell membrane and is involved in the transmission of nerve impulses, neuronal growth, learning processes, neurogenesis, memory and visual function. It is mainly found in breast milk, fish and seafood, soybeans and nuts.<sup>xxxvi,xxxvii,xxxviii</sup>

Iodine present in fish, seafood, and dairy products is essential for thyroid hormone synthesis. These hormones are crucial for the development and proper functioning of the brain. Iodine deficiency leads to intellectual deficits. It is recommended to fortify salt with iodine.<sup>xxxvii,xxxix</sup>

It is worth noting that although a balanced diet is a determining factor in the cognitive development of children, physical exercise and the environmental conditions in which they develop also play a significant role.<sup>xl,xli</sup>

In cases of obese children, cognitive impairment is associated with neuroinflammation and neurodegeneration. Adipose tissue releases adipokines such as leptin and interleukin 6, which have proinflammatory functions, causing chronic inflammation. This inflammation leads to a weakening of the blood-brain barrier and may cause damage at the microglial level.<sup>xlii,xliii</sup>

The insulin resistance present in obesity, combined with the leptin effect, decreases the function of this hormone, altering synaptic plasticity. Research in children with obesity has shown difficulties in sustained attention, memory, and other motor skills.<sup>xliii,xliv</sup>

## Conclusion

There is a scientific consensus that connects proper nutrition to optimal cognitive development in the early stages of life. During this period, children assimilate and process the information they receive from their environment, which enables higher development. On the contrary, malnourished children have high rates of school repetition, school dropout, or low schooling.

For this reason, it is necessary to ensure the intake of an appropriate diet, balancing macro and micronutrients. Lack of this balance results in cognitive deficits at early age and may even cause irreversible brain damage. The mother's prenatal diet and exclusive breastfeeding until six months of life are essential, followed by the progressive introduction of foods with all the necessary nutrients.

In contrast, excessive consumption of processed and ultra-processed food containing excess sodium, fat, and sugars, contributes negatively to children's neurodevelopment. These products generate nutritional imbalances and do not provide essential substrates for brain development.

It is essential to provide nutritional guidance at home and school since adults are directly responsible for children's nutrition. Likewise, there must be permanent nutritional surveillance, allowing the evaluation of the child in all areas of his life and ensuring adequate cognitive development, providing more possibilities for a better future.

## Funding

Funding by Alberto Masferrer Salvadorean University.

## References

- i. OMS, Malnutrición. Organización Mundial para la Salud. 2024. Consulted date: July 11, 2024. Available at: <https://www.who.int/es/news-room/fact-sheets/detail/malnutrition>
- ii. Prost M, Martínez R. El costo de la doble carga de la malnutrición. Impacto social y económico en El Salvador. El Salvador. Programa Mundial de Alimentos. 2019. 56p. Available at: <https://es.wfp.org/publicaciones/el-coste-de-la-doble-carga-de-la-malnutricion-el-salvador>
- iii. Dipasquale V, Cucinotta U, Romano C. Acute Malnutrition in Children: Pathophysiology, Clinical Effects and Treatment. *Nutrients*. 2020;12(8):2413. DOI: [10.3390/nu12082413](https://doi.org/10.3390/nu12082413)
- iv. Katoch O. Determinants of malnutrition among children: A systematic review. *Nutrition*. 2022;96:111565. DOI: [10.1016/j.nut.2021.111565](https://doi.org/10.1016/j.nut.2021.111565)
- v. Fonseca Z, Quesada A, Meireles M, Cabrera E, Boada A. La malnutrición; problema de salud pública de escala mundial. *Multimed*. 2020;24(1):237-246. Available at: [http://scielo.sld.cu/scielo.php?script=sci\\_arttext&id=S1028-48182020000100237](http://scielo.sld.cu/scielo.php?script=sci_arttext&id=S1028-48182020000100237)
- vi. Bálsamo M. Teoría Psicogenética de Jean Piaget. Aportes para comprender al niño de hoy que será el adulto del mañana. 1a.ed. Paraná. Centro de Investigación Interdisciplinar en Valores, Integración y Desarrollo Social, 2022.42p.
- vii. Castro, D. El consumo de comida preparada fuera de casa. San Salvador, Defensoría del Consumidor.2019. 80p. Available at: <https://www.defensoria.gob.sv/wp-content/uploads/2015/04/DEFENSORIA-DIGITAL-ok.pdf>
- viii. Keeley B, Little C, Diniz J, Zuehlke E, Sclama G, Vrolijk K, *et al*. Informe sobre estado mundial de la infancia 2019. New York. Fondo de las Naciones Unidas para la Infancia. 2019. 258p. Available at: <https://www.unicef.org/media/62486/file/Estado-mundial-de-la-infancia-2019.pdf>
- ix. Popkin, B. El impacto de los alimentos ultraprocesados en la salud. 2030. Alimentación, agricultura y desarrollo rural en América Latina y el Caribe. Santiago de Chile. Organización de las Naciones Unidas para la Alimentación y la Agricultura. 2020. 29p. Available at: <https://www.fao.org/3/ca7349es/CA7349ES.pdf>
- x. Gobierno de El Salvador. Modelo de sistemas alimentarios sostenibles El Salvador. Hoja de ruta de un país en el marco de Cumbre de Sistemas Alimentarios 2021. San Salvador. Dirección Ejecutiva del Consejo Nacional de Seguridad Alimentaria y Nutricional. 2021. 28p. Available at: <https://summitdialogues.org/wp-content/uploads/2021/11/SAS-Documento-Sistemas-Alimentarios-Sostenibles-El-Salvador-2021.-Noviembre.pdf>
- xi. Encuesta Nacional de Salud (ENS) -2021. Instituto Nacional de Salud. San Salvador, El Salvador. 2021. Available at: <https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1372915>
- xii. Ascencio C. Fisiología de la Nutrición. 2ª. Edición, México. Editorial Manual Moderno. 2018. 392p.
- xiii. Lema E. La educación alimentaria y su incidencia en el desarrollo cognitivo en niños de 4 a 5 años de Educación Inicial. Tesis de maestría. Ecuador. Universidad Técnica de Cotopaxi. 2022. 198p.
- xiv. Yepes T. Dieta saludable. *Rev. Perspectivas en Nutrición Humana*. 2019. 21(1).e0124-4108. DOI: [10.17533/udea.penh.v21n1a01](https://doi.org/10.17533/udea.penh.v21n1a01)

- xv. Merino M, Toro D, Mendez M. Impacto de la anemia y deficiencia de hierro en el desarrollo cognitivo en la primera infancia en el Ecuador: revisión bibliográfica de la literatura. *Mikarimin*. 2022; 8(3):71-84. Available at: <https://revista.uniandes.edu.ec/ojs/index.php/mikarimin/article/view/2717>
- xvi. Pinto J, Carbajal A. Nutrición y Salud. La dieta equilibrada prudente o saludable. 1ª. Edición. Madrid. Dirección General de Salud Pública y Alimentación. 2003. 84p.
- xvii. Guía alimentaria para las familias salvadoreñas. Ministerio de Salud de El Salvador, San Salvador. 2012. Available at: <https://www.fao.org/3/as867s/as867s.pdf>
- xviii. World Health Organization. Saturated fatty acid and trans-fatty acid intake for adults and children: WHO guideline. Geneva. World Health Organization. 2023. 134p. Available at: <https://www.who.int/publications/i/item/9789240073630>
- xix. Polanco I. Alimentación del niño en edad pre-escolar y escolar. *Rev. Anales de Pediatría*. 2005.3(1):54-63. Available at: <https://www.analesdepediatria.org/es-alimentacion-del-nino-edad-preescolar-articulo-13081721>
- xx. Ala A. Conjunto de recomendaciones sobre la promoción de alimentos y bebidas no alcohólicas dirigida a los niños. Organización Mundial para la Salud, Ginebra. 2010.16p. Available at: <https://www.paho.org/es/documentos/conjunto-recomendaciones-sobre-promocion-alimentos-bebidas-no-alcoholicas-dirigida-ninos>
- xxi. Berón C, Toledo C, Köncke F, Klaczko I, Carriquiry A, Cediel G, *et al*. Productos procesados y ultraprocesados y su relación con la calidad de la dieta en niños. *Rev Panam Salud Pública*, 2022;46: e67. DOI: [10.26633/RPSP.2022.67](https://doi.org/10.26633/RPSP.2022.67)
- xxii. Bernaebu-Mestre J, Tormo-Santamaría M. La perspectiva histórica y el análisis crítico en el abordaje del desafío alimentario y social del hambre oculta. *Anales Venezolanos de Nutrición*. 2020.33(2):149-153. Available at: [https://ve.SciELO.org/SciELO.php?script=sci\\_arttext&pid=S079807522020000200149&lng=e](https://ve.SciELO.org/SciELO.php?script=sci_arttext&pid=S079807522020000200149&lng=e)
- xxiii. Cárdenas L, Carrillo M, Mazuera R, Hernández Y. Primera infancia desde las neurociencias: una apuesta para la construcción de paz. *Revista Virtual Universidad Católica del Norte*. 2018;(55):159-172. Available at: <https://revistavirtual.ucn.edu.co/index.php/RevistaUCN/article/view/1002/1451>
- xxiv. Paolini C, Oiberman A, Mansilla M. Desarrollo cognitivo en la primera infancia: influencia de los factores de riesgo biológicos y ambientales. *Subjetividad y Procesos Cognitivos*. 2017;21(2):162-183. Available at: <https://www.redalyc.org/articulo.oa?id=339655686008>
- xxv. Pulido L. Aprendizaje y Cognición. 1ª. edición. Bogotá. Fundación Universitaria del área andina. 2018. 92p.
- xxvi. Calceto-Garavito L, Garzón S, Bonilla J, Cala-Martínez D. Relación del Estado Nutricional con el Desarrollo Cognitivo y Psicomotor de los Niños en la Primera Infancia. *Rev. Ecuat. Neurol*. 2019;28(2):e1019-8113. Available at: [https://revecuatneurol.com/magazine\\_issue\\_article/relacion-estado-nutricional-desarrollo-cognitivo-psicomotor-ninos-primera-infancia-relationship-between-nutritional-status-cognitive-psychomotor-development-children-early-childhood/](https://revecuatneurol.com/magazine_issue_article/relacion-estado-nutricional-desarrollo-cognitivo-psicomotor-ninos-primera-infancia-relationship-between-nutritional-status-cognitive-psychomotor-development-children-early-childhood/)
- xxvii. Larson L, Young M, Bauer P, Mehta R, Girard A, Ramakrishnan F, *et al*. Effectiveness of a home fortification programme with multiple micronutrients on infant and young child development: a cluster-randomised trial in rural Bihar, India. *Br J Nutr*. 2018;120(2):176-187. DOI: [10.1017/S000711451800140X](https://doi.org/10.1017/S000711451800140X)
- xxviii. Champoñan A, Hernández K. Asociación entre la suplementación con Vitamina A, Hierro y Micronutrientes con el Desarrollo Psicomotor Adecuado en niños de 9 a 36 meses a nivel nacional en Perú: Análisis Secundario de la Encuesta Demográfica y de Salud Familiar - ENDES 2018 al 2020. Tesis de Doctorado. Lima. Universidad Peruana de Ciencias Aplicadas. 2020.57p.
- xxix. Feitosa J, Moura M, Sousa A, Pereira D. A importância dos micronutrientes no desenvolvimento neurocognitivo da gestação a infância. *Revista UNINGÁ*. 2019.56(4).e2318-0579. DOI: [10.46311/2318-0579.56.eUJ2985](https://doi.org/10.46311/2318-0579.56.eUJ2985)
- xxx. Fernández A, Andrés R, Carrasco I, Palma A. Impacto social y económico de la doble carga de la malnutrición: modelo de análisis y estudio piloto en Chile, el Ecuador y México. Editorial CEPAL, 2017. 191p. Available at: <https://www.cepal.org/es/publicaciones/42535-impacto-social-economico-la-doble-carga-la-malnutricion-modelo-analisis-estudio>
- xxxi. Organización de las Naciones Unidas para la Alimentación y la Agricultura. Organización Mundial de la Salud. Declaración Roma sobre la desnutrición. Roma. 2014. 7p. Available at: <https://www.fao.org/about/meetings/icn2/background/es/>
- xxxii. Organización de las Naciones Unidas. Informe de los Objetivos de Desarrollo Sostenible 2023. New York.2023. 80p. Available at: <https://www.un.org/sustainabledevelopment/es/hunger/>
- xxxiii. Jaramillo J. Metabolismo Cerebral. *Revista Mexicana de Anestesiología*. Vol. 36. Supl. 1 abril-junio 2013.pp S183-S185.

- xxxiv. Lieberman M, Marks A. Bioquímica Médica Básica. Un enfoque clínico. 4a. edición. España. Editorial Lippincott Williams & Wilkins. 2013. Capítulo 48. Metabolismo del sistema nervioso. 903-925p.
- xxxv. García O, Massieu L. Interacción entre las células gliales y neuronales y su papel en la muerte y sobrevivencia neuronal. Arch Neurocién 2004;9(1):e1028-5938. Available at: [https://www.SciELO.org.mx/SciELO.php?script=sci\\_arttext&pid=S0187-47052004000100008&lng=es&nrm=iso&tln g=es](https://www.SciELO.org.mx/SciELO.php?script=sci_arttext&pid=S0187-47052004000100008&lng=es&nrm=iso&tln g=es)
- xxxvi. López A, Lorenzo A, Salas M, Peral A, Aránzazu A, Ortega R. Importancia de la colina en la función cognitiva. Nutr Hosp 2020;37(Nº Extra 2):18-23. e1699-5198. DOI: [10.20960/nh.03351](https://doi.org/10.20960/nh.03351)
- xxxvii. Rincón D, Tejada J, Rodríguez J, Chaves J. Flujo sanguíneo cerebral y actividad metabólica cerebral. Una mirada desde la anestesiología. Revista Chilena de Anestesia. 2021. Vol.50. Nº6.912-917. e0716-4076. DOI: [10.25237/revchilanestv5008101043](https://doi.org/10.25237/revchilanestv5008101043)
- xxxviii. Restrepo C, Coronell M, Arrollo J, Martínez, Majana L, Sarmiento L. La deficiencia de zinc: un problema global que afecta la salud y el desarrollo cognitivo. 2016. Archivos Latinoamericanos de Nutrición. 66(3). e0004-0622. Available at: [https://ve.SciELO.org/SciELO.php?pid=S000406222016000300002&script=sci\\_abstract&tln g=es](https://ve.SciELO.org/SciELO.php?pid=S000406222016000300002&script=sci_abstract&tln g=es)
- xxxix. Martin A, Booth J, Laird Y, Sproule J, Reilly JJ, Saunders DH. Physical activity, diet and other behavioural interventions for improving cognition and school achievement in children and adolescents with obesity or overweight. Cochrane Database Syst Rev. 2018;1(1):CD009728. DOI: [10.1002/14651858.CD009728.pub3](https://doi.org/10.1002/14651858.CD009728.pub3)
- xl. Ocaña-Noriega J, Sagñay-Llinin G. La malnutrición y su relación en el desarrollo cognitivo en niños de la primera infancia. Rev. Pol. Con.2020;5(12):e2550-682X. DOI: [10.23857/pc.v5i12.2044](https://doi.org/10.23857/pc.v5i12.2044)
- xli. Vargas K, Jara M, Lozada M, Dume M. Influencia de la neurociencia en el aprendizaje de la lectoescritura. Rev. Universidad Ciencia y Tecnología. 2022. Nº esp. (02):33-38. DOI: [10.29344/0717621x.45.2212](https://doi.org/10.29344/0717621x.45.2212)
- xlii. Martínez R, Jiménez A, López A, Ortega R. Nutrition strategies that improve cognitive function. Nutr. Hosp. 2018;35(6):16-19. DOI: [10.20960/nh.2281](https://doi.org/10.20960/nh.2281)
- xliii. Zavala, J. Comportamiento sedentario y su relación con la estructura del cerebro, cognición y rendimiento académico en niños con sobrepeso/obesidad. Doctoral thesis. España. Universidad de Granada. 2021.185p.
- xliv. García A, Hernández M, L Gamiz A, Incontri-Abraham D, Ibarra A. Effect of overweight and obesity on cognitive function in children from 8 to 12 years of age: a descriptive study with a cross-sectional design. Nutr Hosp. 2021.29;38(4):690-696. DOI: [10.20960/nh.03474](https://doi.org/10.20960/nh.03474)

# CORB65 scale as an alternative to assess community-acquired pneumonia in primary health care

DOI: 10.5377/alerta.v7i2.15603

Hugo Daniel Parrales López

Alberto Masferrer Salvadorean University (USAM), San Salvador, El Salvador.

Correspondence

✉ Dr.hugoparrales@outlook.com

ORCID: 0000-0003-2336-5662

## OPEN ACCESS

**Escala CORB65 para valorar Neumonía Adquirida en la comunidad en el primer nivel de atención**

### Suggested citation:

Parrales López HD. CORB65 scale as an alternative to assess community-acquired pneumonia in primary health care. *Alerta*. 2024;7(2):198-204. DOI: 10.5377/alerta.v7i2.15603

### Editor:

Nadia Rodríguez.

### Received:

July 20, 2023.

### Accepted:

July 15, 2024.

### Published:

July 24, 2024.

### Author contribution:

HDPL: study conception, manuscript design, literature search, data collection and management, writing, revising, and editing.

### Conflicts of interest:

The author declared there are not conflicts of interest.



© 2024 by the author. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## Abstract

Community-acquired pneumonia is a frequent cause of consultation and has a high mortality, which implies that health professionals must have the necessary tools to evaluate and refer promptly. Most of the severity assessment scales for community-acquired pneumonia use laboratory values, which represents a problem for the first level of care where these are usually not available. This study aims to propose the CORB-65 scale (Confusion, Oxygenation, Respiratory Rate, Blood Pressure, Age over 65 years) as an alternative to the classic scales used, such as Pneumonia Severity Index (PSI), CURB-65 (Confusion, Urea, Respiratory Rate, Blood Pressure, Age over 65 years) and qSOFA (quick Sequential Organ Failure Assessment), among others. Documentary research was carried out through a search in databases such as PubMed, Scopus, and Google Scholar, in which different studies were compared, showing that the CORB-65 scale maintains similar or higher levels of sensitivity and specificity than the aforementioned scales and given that it does not require laboratory tests for its scoring, it becomes an ideal alternative for the assessment of community-acquired pneumonia at the first level of care.

## Keywords

Pneumonia, Primary Health Care, Health, Sensitivity and Specificity.

## Resumen

La neumonía adquirida en la comunidad es una causa frecuente de consulta y tiene una mortalidad elevada, lo que implica que los profesionales de salud deben contar con las herramientas necesarias para evaluar y derivar oportunamente. La mayoría de las escalas de valoración de la severidad para la neumonía adquirida en la comunidad utilizan valores de laboratorio, esto representa un problema para el primer nivel de atención donde usualmente no se cuenta con estos. El objetivo del estudio es proponer la escala CORB-65 (Confusión, Oxigenación, Frecuencia Respiratoria, Presión Arterial, Edad mayor de 65 años) como una alternativa a las escalas clásicas utilizadas como Pneumonia Severity Index (PSI), CURB-65 (Confusión, Urea, Frecuencia Respiratoria, Presión Arterial, Edad mayor de 65 años) y qSOFA (*quick Sequential Organ Failure Assessment*), entre otras. Se realizó una investigación documental mediante una búsqueda en bases de datos como PubMed, Scopus y Google Scholar, en la que se compararon diferentes estudios que demuestran que la escala CORB-65 mantiene niveles de sensibilidad y especificidad similares o superiores a las escalas ya mencionadas y dado que no requiere pruebas de laboratorio para su puntaje, la convierte en una alternativa ideal para la valoración de la neumonía adquirida en la comunidad en el primer nivel de atención.

## Palabras clave

Neumonía, Atención Primaria de Salud, Salud, Sensibilidad y Especificidad.

## Introduction

Community-acquired pneumonia is an acute respiratory infection that affects the lungs and represents one of the leading causes of morbidity and mortality worldwide. Early diagnosis and adequate risk stratification are essen-

tial to make appropriate treatment and referral decisions.<sup>1</sup> In the context of the first level of care, where the aim is to promote, prevent and solve the most frequent health needs of the population using simple technologies, the capacity for resolution can be limited. Therefore, having a simple and effective assessment tool is crucial.

The CORB-65 scale (Confusion, Oxygenation, Respiratory Rate, Blood Pressure, Age over 65 years) is presented as an alternative to other pneumonia assessment scales in adult and elderly patients in terms of early referral of the patient and determination of the most appropriate place for management. Unlike other scales, such as CURB-65 and SMART-COP, the CORB-65 is suitable for the first level of care, but laboratory testing is not always available. The CORB-65 scale is based on easily identifiable clinical criteria: mental confusion, oxygenation ( $\text{SatO}_2 < 90\%$ ), respiratory rate ( $\geq 30$  breaths per minute), and systolic ( $\leq 90$  mmHg) or diastolic ( $\leq 60$  mmHg) blood pressure, in addition to the patient's age.<sup>i</sup>

Unlike other scales, the CORB-65 is easy to apply and does not require invasive laboratory tests or chest X-rays. These criteria, which can be assessed at the point of care, allow for rapid stratification of patients into categories: low, moderate, and high risk, facilitating clinical decision-making and identification of those requiring referral to a higher level of care.

This article is based on a literature review that was conducted through an exhaustive search of electronic databases, such as PubMed, Scopus and the Google Scholar search engine, for relevant scientific literature. The search terms used included "pneumonia" "pneumonia scale", "CORB-65", "pneumonia assessment", "first level of care", "lung" and combinations of these terms. Original scientific articles, systematic reviews, case reports and clinical guidelines published in English or Spanish were included. Studies that did not focus on pneumonia assessment or did not specifically address the use of any pneumonia rating scale were excluded. After an initial screening based on titles and abstracts, a thorough reading of the selected articles was performed to assess their relevance and quality. Relevant data were extracted, such as the results of clinical studies, the effectiveness of the CORB-65 scale in pneumonia risk stratification and the need for referral, as well as any other important information on the topic.

Therefore, the aim of this study was to propose the CORB-65 scale as an alternative to the classic scales used, such as: Pneumonia Severity Index, CURB-65, SMART-COP, NEWS2 and qSOFA.

## Discussion

Among the scales used for the assessment and referral of patients with community-acquired pneumonia at different levels

of care such as outpatient management, hospital or intensive care unit, are the Pneumonia Severity Index (PSI), SMART-COP, CURB-65, CRB-65 and CORB-65 scales.<sup>i</sup> The main problem with these scales is that they all require at least one laboratory test for a complete assessment and subsequent decision making.

The CURB-65 scale is one of the most widely used worldwide.<sup>ii,iii,iv</sup> However, one of the elements of analysis in this scale is the value of urea or urea nitrogen, which may not be a viable option in many primary care units or rural areas.

Despite the availability of more intricate scales, studies indicate that the CURB-65 scale demonstrates the highest performance in predicting mortality,<sup>v</sup> with greater specificity than the PSI scale. However, the latter proves to be more sensitive<sup>vi</sup> than the expanded CURB-65 scale.<sup>iv</sup>

Alternative methods have been sought that allow reliable assessment with sensitivity and specificity indices similar to those of the CURB-65 scale. Some authors have investigated the usefulness of the qSOFA criteria, normally used in sepsis, as an assessment scale for patients with community-acquired pneumonia.<sup>vii</sup> This proposal has gained increasing relevance, especially when seeking its direct application for the admission of patients to intensive care units (ICU).

A study conducted between 2017 and 2019 at Beijing Chao-Yang Hospital compared qSOFA plus lactate, qSOFA, PSI, CURB-65, and CRB-65 methods, where the cutoff value for lactate was  $> 2.0$  mmol/L. In this study, qSOFA plus lactate was superior in predicting the need for ICU admission, mechanical ventilation, and 28-day mortality.<sup>viii</sup>

Some authors have explored the possibility of shortening the CURB-65 scale by eliminating the urea or urea nitrogen value, resulting in the CRB-65 scale.<sup>v</sup> These two proposals have been compared in retrospective studies, and it has been shown that the modified CRB-65 scale provides more sensitive and specific results than the qSOFA scale<sup>vii</sup> but is inferior to CURB-65.<sup>ix</sup> The CRB-65 scale has been validated in studies and is considered a reliable method for evaluating patients with community-acquired pneumonia. Its application stands out in primary health care since it does not require additional laboratory tests.<sup>x,xi</sup>

The official American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) guidelines for the diagnosis and treatment of community-acquired pneumonia recommend the use of the IDSA/ATS criteria.<sup>xii</sup> However, these criteria

include urea nitrogen, leukocyte, and platelet values as minor criteria.<sup>xii,xiii</sup>

In 2017, the National Early Warning Score 2 (NEWS2) was introduced as a new alternative method to predict severity in patients with community-acquired pneumonia (CAP). This method uses parameters such as respiratory rate, and oxygen saturation in two scenarios (room air and with the need for supplemental oxygen due to hypercapnic respiratory failure), temperature, systolic blood pressure, pulse, and patient's state of consciousness.<sup>xiv</sup>

A prospective cohort study conducted at Chiang Mai University Hospital between October 2020 and December 2021 compared the CURB-65 scale, IDSA/ATS criteria, and NEWS2. The study showed that NEWS2 offers higher sensitivity in predicting progression to severe pneumonia compared to IDSA/ATS but has lower sensitivity than CURB-65 and IDSA/ATS in predicting mortality in patients with CAP.<sup>xiii</sup>

This study also compared NEWS2 plus albumin < 3 g/dL plus urea nitrogen  $\geq$  30 mg/dL, demonstrating a higher sensitivity in predicting mortality compared to CURB65 and IDSA/ATS.<sup>xiii</sup> However, albumin and urea nitrogen values are not available in most primary care clinics.

The Colombian Association of Pneumology recommends applying the CURB-65 or CRB-65 scale and adding the measurement of oxygen saturation level by pulse oximetry in the evaluation. The Australian guidelines for the management of pneumonia recommend using the SMARTCOP or CORB scale for decision making.<sup>i</sup>

A study performed in 272 patients with COVID-19-associated pneumonia in Istanbul, Turkey, showed that the noninvasive parameter  $SpO_2/FiO_2$  correlates with  $PaO_2/FiO_2$  obtained by arterial blood gas analysis and has been widely used as an early predictor of the need for mechanical ventilation.<sup>xvi</sup> Another study carried out in three Spanish hospitals concluded that there is a good relationship between the  $SpO_2/FiO_2$  parameter and  $PaO_2/FiO_2$ .<sup>xvii</sup>

The Istanbul study showed that a  $SpO_2$  value of less than 90 % or a  $SpO_2/FiO_2$  index of less than 300 has a predictive value of 30-day mortality for pneumonia. The CRB-65 scale shows a sensitivity of 51 % and a specificity of 80 %, but when the  $SpO_2/FiO_2$  value is added, these values increase to 81 % and 72 %.<sup>xvi</sup>

The inclusion of hypoxemia in the CURB-65 scale has already been explored. In Valencia, between 2003 and 2004, a study was carried out using hypoxemia as an added value to the predictor of severity,

which increased the predictive capacity in patients with severe CAP.<sup>xviii</sup>

Hypoxemia is an individual poor prognostic marker used in the assessment of pneumonia, including that caused by COVID-19.<sup>xix</sup> Pulse oximetry is a reliable method to determine hypoxemia. A study conducted by the Bangladesh National Childhood Illness Care Program (NCCIP) between 2020 and 2021 showed that pulse oximetry could detect up to 97 % of hypoxemia cases, whether by doctors, nurses, or paramedical staff.<sup>xx</sup>

Based on the evidence from previous studies, it is recommended to modify an element of the CURB-65 scale with the oxygen saturation value, resulting in the CORB-65 scale. The CORB-65 scale assesses five aspects: confusion, oxygen (pulse oximetry), respiratory rate, blood pressure, and age over 65 years.<sup>xxi</sup> Parameters and scores are in Table 1.

The interpretation of the score obtained is performed similarly to the CURB-65 scale. Values between zero and one are classified as "ambulatory or home treatment"; score two should be considered "hospital treatment"; and score three or higher are classified as patients who require mandatory "hospital management" and should be considered for referral to ICU.<sup>i</sup>

The CORB-65 scale has been tested in several studies that have proven its clinical utility in risk assessment in patients with community-acquired pneumonia. A prospective observational study compared different scales for the assessment of community-acquired pneumonia in 618 Australian patients. The investigation concluded that the CURB-65 and CORB-65 scales had the highest specificity for CAP with values of 93 % and 94 %, with CORB-65 being superior.<sup>i</sup>

A case-control study compared both scales in 60 patients in the hospital-at-home modality and 54 patients in the hospital control group. In both study groups, no differences were found between the CURB-65 and CORB-65 scale.<sup>xxii</sup>

In 2014, a prospective analytical observational prospective study was conducted that included a total of 120 patients who attended the Hospital General Provincial Docente "Dr. Antonio Luaces Iraola" in Cuba, with a diagnosis of CAP.<sup>xxiii</sup> The study proposed a standardized care protocol for patients with CAP using the CORB-65 scale. At the end of the study, it was concluded that the scale was useful for assessing patient severity and prognosis.

The study showed that the majority of patients who were discharged without



complications belonged to group one. These are patients who can be managed on an outpatient basis. Conversely, most of the patients who died were classified in group three, which consists of those requiring ICU management.<sup>xxiii</sup>

At the "Hospital Universitario de Los Andes" (UANDES) an open study was carried out with a first cross-sectional phase and a subsequent follow-up phase, in which a total of 54 patients were studied, comparing the classification of the different groups between both scales. The results are shown in Table 2.

In this study, it was found that the CORB-65 scale showed greater sensitivity for the classification of patients with CAP into groups two and three, which are the groups requiring hospital care.

A retrospective study performed with patient data from January 2012 to February 2020 at La Sabana University Hospital in Colombia evaluated 1811 patients and compared the results obtained on the CURB-65 and CORB-65 scales.<sup>xxi</sup> The cut-off value for oxygen saturation obtained by pulse oximetry was 90%.<sup>xxi</sup>

The study showed that the CORB65 scale had a higher predictive value for patients who required mechanical ventilation or vasopressor support, i.e., those patients who had to be admitted to an Intensive Care Unit.

The parameter is even higher when SpO<sub>2</sub> less than 90% is replaced by SpO<sub>2</sub>/FiO<sub>2</sub> less than 300.<sup>xxi</sup> The 2007 IDSA/ATS criteria mention a PaO<sub>2</sub>/FiO<sub>2</sub> value of less than 250.<sup>xii</sup> However, the study demonstrated that the CORB-65 scale did not show a higher

predictive value for mortality compared to the CURB-65 scale.<sup>xxi</sup>

Another retrospective study conducted between 2017 and 2019 at the "Metropolitan Hospital Center" in New York, USA, compared the CURB-65 scale and the CORB-65 scale in 100 patients admitted to the Emergency Department. The study showed that the CORB-65 scale has a higher predictive value about patients requiring ICU admission compared to the CURB-65 scale. In addition, it also found that the CORB-65 scale is more accurate in determining patients requiring mechanical ventilation.<sup>xxiv</sup> Both scales showed similarity in predicting the length of in-hospital stay of patients, and neither showed greater utility compared to patient mortality.<sup>xxiv</sup>

Pneumonia is a dynamic process and multiple variables can complicate the patient's condition, including associated or added comorbidities. The CURB-65 scale is considered more specific than more complex scales, such as the PSI or SMARTCOP; however, the predictive value of the PSI scale is superior to that of CURB-65 according to other authors.<sup>!</sup>

The CORB-65 scale is a valid method for risk assessment and stratification in patients with community-acquired pneumonia and has a specificity similar to that of the CURB-65 scale<sup>i,xv,xxi,xxiv</sup>, or even higher.<sup>xxv</sup> However, it should be considered that multiple studies mention that the sensitivity of the CORB-65 scale may be slightly lower than that of CURB-65, especially in patients classified in category one or requiring outpa-

**Table 1.** Parameters evaluated by the CORB-65 Scale

Modified CORB-65 scale		
Parameter	Value	Score
Confusion	Present	1
Pulse oximetry	Less than 90 %	1
Respiratory rate	Greater than 30 rpm	1
Blood pressure	Less than or equal to 90/60 mmHg	1
Age	Older than 65 years	1

**Source:** Performance of the CORB (Confusion, Oxygenation, Respiratory Rate, and Blood Pressure) Scale for the Prediction of Clinical Outcomes in Pneumonia<sup>xxi</sup>.

**Table 2.** Comparison between CURB-65 and CORB-65 scales

CURB-65 scale	n (%)	CORB-65 scale	n (%)
Group 1	26 (48.1 %)	Group 1	14 (25.9 %)
Group 2	11 (20.4 %)	Group 2	19 (35.2 %)
Group 3	17 (31.5 %)	Group 3	21 (38.9 %)

**Source:** Utility of the CURB65 Score for the Evaluation of Severity of Community Acquired Pneumonia in Adults of the Emergency Setting<sup>vi</sup>.

tient management.<sup>i</sup> This situation is reversed in those patients classified in categories two or three.<sup>i,xv,xxi,xxiii,xxiv</sup>

It is important to emphasize that the CORB-65 scale does not have a defined oxygen saturation value taken by pulse oximetry to add to the overall score. Some authors have performed studies using the SpO<sub>2</sub> cut-off value of 92 %, <sup>xv</sup> while others have the SpO<sub>2</sub> value of 90 %.<sup>xxi</sup> However, given that the SpO<sub>2</sub> parameter of less than 90 % is equivalent to a PaO<sub>2</sub> of less than 60 mmHg,<sup>xvii,xxvi</sup> a value that is also shared as a parameter within the PSI4 and SMART-COP<sup>xxvii,xxviii</sup> scale criteria, it is logical to use this as the cut-off point. On this same point, some studies recommend the inclusion of the variable SpO<sub>2</sub>/FiO<sub>2</sub> less than 300 as a criterion of the scale for the summation of the respective point.<sup>xxi</sup>

It is important to consider that some diseases, such as chronic obstructive pulmonary disease, can generate SpO<sub>2</sub> values lower than those found in a patient without such pathologies. These comorbidities, added to community-acquired pneumonia, require modified scales such as BAP-65 or adjustments in the parameters of the classic scales, such as CURB-65,<sup>xxix</sup> so the CORB-65 scale should be included.

In addition, it is imperative to mention that the scales should not replace at any time the integral and complete study of the patient together with his or her clinical history. The CURB-65, qSOFA or CRB-65 scales have been shown in multiple studies to be ineffective tools on their own for predicting mortality and admission to the ICU,<sup>v</sup> so they should be used in conjunction with all patient data.<sup>xxi</sup>

## Conclusion

The CORB-65 scale is an alternative for the evaluation of patients presenting with community-acquired pneumonia and presents levels of specificity comparable to the CURB-65 scale. It is a useful tool in the first level of care, given that the measurement of oxygen saturation value by pulse oximetry is a more accessible resource compared to the resources, equipment, and personnel necessary for taking urea or urea nitrogen or other laboratory data required by the CURB-65 scale and other scales.

The available evidence suggests that CORB-65 can provide accurate assessment without the need for invasive laboratory testing, making it suitable for resource-limited settings. However, further studies are recommended to confirm these findings and optimize their use in diverse patient populations.

## Funding

No external funds were received for this work.

## References

- i. Williams JM, Greenslade JH, Chu KH, Brown AF, Lipman J. Utility of community-acquired pneumonia severity scores in guiding disposition from the emergency department: Intensive care or short-stay unit? *Emerg Med Australas*. 2018;30(4):538-546. DOI: [10.1111/1742-6723.12947](https://doi.org/10.1111/1742-6723.12947).
- ii. Alonso R, Barletta MS, Rodríguez CL, Mainero FA, Oliva V, Vénica DP, *et al*. Neumonía adquirida en la comunidad en pacientes que requirieron hospitalización. *Medicina Buenos Aires*. 2022;82(1):40-50. Available at: <https://www.medicinabuenaosaires.com/PMID/33611243.pdf>
- iii. Bradley J, Sbaih N, Chandler TR, Furmanek S, Ramirez JA, Cavallazzi R. Pneumonia Severity Index and CURB-65 score are good predictors of mortality in hospitalized patients with SARS-CoV-2 community-acquired pneumonia. *Chest*. 2022;161(4):927-36. DOI: [10.1016/j.chest.2021.10.031](https://doi.org/10.1016/j.chest.2021.10.031)
- iv. Oliva A, Borrazzo C, Mascellino MT, Curtolo A, Al Ismail D, Cancelli F, *et al*. CURB-65 plus hypoalbuminemia: a new score system for prediction of the in-hospital mortality risk in patients with SARS-CoV-2 pneumonia. *Infez Med*. 2021;29(3):408-15. DOI: [10.53854/liim-2903-12](https://doi.org/10.53854/liim-2903-12)
- v. Hincapié C, Ascuntar J, León A, Jaimes F. Community-acquired pneumonia: comparison of three mortality prediction scores in the emergency department. *Colomb Med*. 2021;52(4). Available at: [http://www.scielo.org.co/pdf/cm/v52n4/es\\_1657-9534-cm-52-04-e2044287.pdf](http://www.scielo.org.co/pdf/cm/v52n4/es_1657-9534-cm-52-04-e2044287.pdf)
- vi. Lozada C, Berrera M, Chacín AM, Chirinos M, Albers AJ. Neumonía adquirida en la comunidad mediante las escalas Salus. *Edu. ve*. 2022;26(1):40-50. Available at: <http://servicio.bc.uc.edu.ve/fcs/vol26n1/art03.pdf>
- vii. Kesselmeier M, Pletz MW, Blankenstein AL, Scherag A, Bauer T, Ewig S, *et al*. Validation of the qSOFA score compared to the CRB-65 score for risk prediction in community-acquired pneumonia. *Clin Microbiol Infect*. 2021;27(9):1345.e1-1345.e6. DOI: [10.1016/j.cmi.2020.10.008](https://doi.org/10.1016/j.cmi.2020.10.008)
- viii. Zhou H, Lan T, Guo S. Prognostic prediction value of qSOFA, SOFA and admission lactate in septic patients with community-acquired pneumonia in emergency department. *Emerg Med Int*. 2020;2020:7979353. DOI: [10.1155/2020/7979353](https://doi.org/10.1155/2020/7979353)

- ix. Khari S, Salimi Akin Abadi A, Pazokian M, Youseffard M. CURB-65, qSOFA, and SIRS criteria in predicting in-hospital mortality of critically ill COVID-19 patients; A prognostic accuracy study. *Arch Acad Emerg Med.* 2022;10(1). DOI: [10.22037/aaem.v10i1.1565](https://doi.org/10.22037/aaem.v10i1.1565)
- x. Womack J, Kropa J. Community-acquired pneumonia in adults: Rapid evidence review. *Am Fam Physician.* 2022;105(6):625-630. Available at: <https://www.aafp.org/pubs/afp/issues/2022/0600/p625.html>
- xi. Kolditz M, Ewig S. Community-acquired pneumonia in adults. *Dtsch Arztebl Int.* 2017;114(49):838-848. DOI: [10.3238/arztebl.2017.0838](https://doi.org/10.3238/arztebl.2017.0838)
- xii. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, *et al.* Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019;200(7). DOI: [10.1164/rccm.201908-1581ST](https://doi.org/10.1164/rccm.201908-1581ST)
- xiii. Tajarerntmuang P, Sanwirat P, Inchai J, Phinyo P, Limsukon A. The National Early Warning Score 2 (NEWS2) to predict early progression to severe community-acquired pneumonia. *Trop Med Infect Dis.* 2023;8(2). DOI: [10.3390/tropicalmed8020068](https://doi.org/10.3390/tropicalmed8020068)
- xiv. Smith GB, Redfern OC, Pimentel MA, Gerry S, Collins GS, Malycha J, *et al.* The national early warning score 2 (NEWS2). *Clin Med.* 2019;19(3):260. DOI: [10.7861/clinmedicine.19-3-260](https://doi.org/10.7861/clinmedicine.19-3-260)
- xv. Infectio. Recomendaciones para el diagnóstico, tratamiento y prevención de la neumonía adquirida en la comunidad en adultos inmunocompetentes. 2013;17:1-38. Available at: <https://www.elsevier.es/es-revista-infectio-351-articulo-recomendaciones-el-diagnostico-tratamiento-prevencion-S0123939213700195>
- xvi. Satici MO, Islam MM, Satici C, Uygun CN, Ademoglu E, Altunok I, *et al.* The role of a noninvasive index "SpO2/FiO2" in predicting mortality among patients with COVID-19 pneumonia. *Am J Emerg Med.* 2022;57:54-9. DOI: [10.1016/j.ajem.2022.04.036](https://doi.org/10.1016/j.ajem.2022.04.036)
- xvii. Cinesi-Gómez C, García-García P, López-Pelayo I, Giménez JI, González-Torres LM, Bernal-Morell E. Correlación entre la saturación de oxihemoglobina por pulsioximetría y la presión arterial de oxígeno en pacientes con insuficiencia respiratoria aguda. *Rev Clin Esp.* 2017;217(9):522-5. DOI: [10.1016/j.rce.2017.08.006](https://doi.org/10.1016/j.rce.2017.08.006)
- xviii. Sanz F, Restrepo MI, Fernández E, Mortensen EM, Aguar MC, Cervera A, *et al.* Hypoxemia adds to the CURB-65 pneumonia severity score in hospitalized patients with mild pneumonia. *Respir Care.* 2011;56(5):612-618. DOI: [10.4187/respcare.00853](https://doi.org/10.4187/respcare.00853)
- xix. Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, *et al.* Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PLoS One.* 2020;15(11). DOI: [10.1371/journal.pone.0241955](https://doi.org/10.1371/journal.pone.0241955)
- xx. Rahman AE, Ameen S, Hossain AT, Perkins J, Jabeen S, Majid T, *et al.* Introducing pulse oximetry for outpatient management of childhood pneumonia: An implementation research adopting a district implementation model in selected rural facilities in Bangladesh. *EclinicalMedicine.* 2022;50(101511):101511. DOI: [10.1016/j.eclinm.2022.101511](https://doi.org/10.1016/j.eclinm.2022.101511)
- xxi. Reyes LF, Bastidas AR, Quintero ET, Frías JS, Aguilar AF, Pedreros KD, *et al.* Performance of the CORB (confusion, oxygenation, respiratory rate and blood pressure) scale for the prediction of clinical outcomes in pneumonia. *Can Respir J.* 2022;2022:4493777. DOI: [10.1155/2022/4493777](https://doi.org/10.1155/2022/4493777)
- xxii. Montalto M, Chu MY, Ratnam I, Spelman T, Thursky K. The treatment of nursing home-acquired pneumonia using a medically intensive Hospital in the Home service. *Med J Aust.* 2015;203(11):441-442. DOI: [10.5694/mja15.00672](https://doi.org/10.5694/mja15.00672)
- xxiii. Santos Y, Moyano I, Carlos J, Sánchez M, Hernández D. Protocolo para el manejo de la neumonía adquirida en la comunidad en el Servicio de Urgencias. *Medigraphic.com.* 2018. Available at: <https://www.medigraphic.com/pdfs/mediciego/mdc-2018/mdc182b.pdf>
- xxiv. Arumairaj AJ, Boktor H, Cosico J, Newman T. Comparison of CORB and CURB-65 scores for predicting the severity of community-acquired pneumonia. *Am J Respir Crit Care Med.* 2020;201(1). DOI: [10.1164/ajrccm-conference.2020.201.1.MeetingAbstracts.A2140](https://doi.org/10.1164/ajrccm-conference.2020.201.1.MeetingAbstracts.A2140)
- xxv. Williams E, Williams E, Girdwood J, Janus E, Karunajeewa H. CORB is the best pneumonia severity score for elderly hospitalised patients with suspected pneumonia: Brief Communications. *Intern Med J.* 2014;44(6):613-5. DOI: [10.1111/imj.12445](https://doi.org/10.1111/imj.12445)
- xxvi. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, *et al.* An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. *Am J Respir Crit Care Med.* 2019;199(11):1368-76. DOI: [10.1164/rccm.201803-0589OC](https://doi.org/10.1164/rccm.201803-0589OC)

- xxvii. Nair GB, Niederman MS. Updates on community acquired pneumonia management in the ICU. *Pharmacol Ther.* 2021;217(107663):107663. DOI: [10.1016/j.pharmthera.2020.107663](https://doi.org/10.1016/j.pharmthera.2020.107663)
- xxviii. Robins-Browne KL, Cheng AC, Thomas KAS, Palmer DJ, Currie BJ, Davis JS. The SMART-COP score performs well for pneumonia risk stratification in Australia's Tropical Northern Territory: a prospective cohort study: The SMART-COP score in Tropical Australia. *Trop Med Int Health.* 2012;17(7):914-919. DOI: [10.1111/j.1365-3156.2012.03006.x](https://doi.org/10.1111/j.1365-3156.2012.03006.x)
- xxix. Chen L, Zheng H, Wu S, Wang S. Emergency admission parameters for predicting in-hospital mortality in patients with acute exacerbations of chronic obstructive pulmonary disease with hypercapnic respiratory failure. *BMC Pulm Med.* 2021;21(1):258. DOI: [10.1186/s12890-021-01624-1](https://doi.org/10.1186/s12890-021-01624-1)

# Effect of chemotherapy on sexual function in patients with non-metastatic cancer

DOI: 10.5377/alerta.v7i2.17381

Daniela Carolina Iraheta Lara<sup>1\*</sup>, William Alberto Menjívar Palacios<sup>2</sup>, Vilma Elizabeth Vásquez Castillo<sup>3</sup>, Emilio Jacobo Abullarade Navarrete<sup>4</sup>

1-4. School of Health Sciences Dr. Luis Edmundo Vásquez. Dr. José Matías Delgado University. San Salvador, El Salvador.

\*Correspondence

✉ [daca\\_96@hotmail.com](mailto:daca_96@hotmail.com)

1.  0000-0001-9687-9037

2.  0000-0002-4445-5918

3.  0000-0002-3228-8278

4.  0000-0003-4898-032X

## Abstract

Non-metastatic breast cancer is defined as breast cancer that has not spread from the primary site. More than 90 % of people that received a breast cancer diagnosis is non-metastatic. Chemotherapy reduces the mortality rate by up to 40 %, but it also causes physical, psychological, sexual and social effects. Therefore, we aimed to identify changes in sexual function caused by chemotherapy in patients with non-metastatic breast cancer. Chemotherapy includes four groups of drugs: anthracyclines, alkylating agents, antimetabolites, and taxanes. These cause local ischemia and depletion of primordial follicles, resulting in early menopause and physiological changes that affect physical, sexual and psychological function. A review of the literature was carried out using indexes or databases such as PubMed, SciELO, Elsevier, as well as the journals The Lancet and Nature. Original and peer-reviewed articles in English and Spanish that were published between 2019 and 2023 were included. One of the best treatment options for non-metastatic breast cancer currently is chemotherapy, but it has been shown to cause early menopause, alterations in sex hormones and alterations in sexual function.

## Keywords

Breast Cancer, Chemotherapy, Sexuality, Physiological Sexual Dysfunction.

## Resumen

El cáncer de mama no metastásico es aquel que no se ha diseminado desde el sitio primario. Más del 90 % de las personas que reciben un diagnóstico de cáncer de mama son no metastásicos. La quimioterapia reduce la tasa de mortalidad hasta un 40 %, pero también causa efectos físicos, psicológicos, sexuales y sociales. Por lo tanto, el objetivo fue identificar los cambios en la función sexual causados por la quimioterapia en pacientes con cáncer de mama no metastásico. La quimioterapia incluye cuatro grupos de fármacos: antraciclinas, alquilantes, antimetabolitos y taxanos. Estos provocan la isquemia local y el agotamiento de los folículos primordiales, lo que resulta en una menopausia temprana y cambios fisiológicos que afectan la función física, sexual y psicológica. Se llevó a cabo una revisión de la bibliografía utilizando índices o bases de datos como PubMed, SciELO, Elsevier, así como las revistas The Lancet y Nature. Se incluyeron artículos originales y revisados en inglés y español que se publicaron entre 2019 y 2023. Una de las mejores opciones de tratamiento para el cáncer de mama no metastásico actualmente es la quimioterapia, pero se ha demostrado que provoca una menopausia temprana, alteraciones en las hormonas sexuales y alteraciones en la función sexual.

## Palabras clave

Cáncer de Mama, Quimioterapia, Sexualidad, Disfunciones Sexuales Fisiológicas.

## Introduction

Breast cancer is the most common type of cancer in women worldwide and at present one of the most frequent causes of death.<sup>i</sup> The World Health Organization (WHO)

reports that one in 12 women will develop breast cancer at any stage of life. Although chemotherapy treatment can reduce the mortality rate by up to 40 %, the prevalence of physical, psychological, sexual, and social consequences is increased.<sup>ii</sup>

## OPEN ACCESS

**Efecto de quimioterapia en la función sexual de pacientes con cáncer de mama no metastásico**

### Suggested citation:

Iraheta Lara DC, Menjívar Palacios WA, Vásquez Castillo VE, Abullarade Navarrete EJ. Effect of chemotherapy on sexual function in patients with non-metastatic cancer. 2024;7(2):205-211. DOI: 10.5377/alerta.v7i2.17381

### Editor:

Nadia Rodríguez.

### Received:

July 21, 2023.

### Accepted:

July 16, 2024.

### Published:

July 24, 2024.

### Author contribution:

DCIL<sup>1</sup>, WAMP<sup>2</sup>, VEVC<sup>3</sup>: study conception, literature search, data collection. DCIL<sup>1</sup>, WAMP<sup>2</sup>, VEVC<sup>3</sup>, EJAN<sup>4</sup>: manuscript design, data analysis, writing, revising, and editing.

### Conflicts of interest:

The authors declared there are no conflicts of interest.



© 2024 by the authors. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

More than 90 % of women who are diagnosed with breast cancer for the first time have non-metastatic breast cancer,<sup>iii</sup> which does not spread beyond the milk ducts or lobules of the breast and does not invade normal tissues inside or outside the breast.<sup>iv</sup> The most common noninvasive tumor is ductal carcinoma *in situ*, which is typified by the presence of malignant cells within the breast ducts without rupturing them.<sup>v</sup>

In the early stages, a breast cancer diagnosis is based on breast self-examination, a complete physical examination, and a combination of imaging, including mammography, ultrasound, and MRI, as the gold standard. The mammography and data retrieval system (BI-RADS), which is standardized, establishes categories for guidelines for action and is one of the main benefits of mammography.<sup>vi</sup>

The side effects of treatment in women receiving chemotherapy for this cancer primarily affected sexual function. These effects increase the cognitive, emotional, and behavioral burnout of patients.<sup>vii</sup> In a study of 201 breast cancer patients, Aiyng Qi *et al.* found that 83.08 % of patients experienced sexual dysfunction after starting chemotherapy.<sup>viii</sup>

Early and periodic detection can facilitate the development of an optimal and timely treatment plan, avoiding the progression of problems in women under treatment for breast cancer, since sexual function in cancer patients treated with chemotherapy is a topic that health personnel are unaware of for various reasons, such as lack of time, knowledge or experience to address it.<sup>ix</sup>

Currently, as the survival rate from chemotherapy increases in women with breast cancer, the physical, psychological, sexual, and social effects are increased.<sup>x</sup> In a study of 174 breast cancer patients with chemotherapy, Ospino *et al.* found a five-year relapse-free survival of 88.8 %, disease-free survival of 63.3 %, and an overall survival of 84.4 %.<sup>xi</sup>

It is important to ensure that women who receive a breast cancer diagnosis are informed about the potential effects of chemotherapy treatment on their mental and sexual health. To ascertain this, a review of the literature, as well as indexes or databases such as PubMed, SciELO, Elsevier, and journals such as The Lancet and Nature, was conducted. Additionally, the official websites of the World Health Organization/Pan American Health Organization (WHO/PAHO) and the Ministry of Health (MINSAL) of El Salvador were consulted. Original and peer-reviewed articles in English and Spanish published between 2019 and 2023 were included. The MeSH descriptors:

“breast cancer,” “Chemotherapy,” “Sexuality,” and “Physiological, Sexual Dysfunctions” were used employing the Boolean operator “AND”.

This research aims to identify the alterations caused by chemotherapy in the sexuality of patients with non-metastatic breast cancer and to promote early detection and a multidisciplinary approach.

## Discussion

### Overview and Chemotherapy schemes in non-metastatic breast cancer

Breast cancer is the most common type of cancer in women worldwide and is considered a heterogeneous disease with multiple causes. The Pan American Health Organization (PAHO) indicates it represents 22.7 % of female cancers worldwide. In the Americas, more than 462 000 women are diagnosed with breast cancer each year, and almost 100 000 died as result of this disease.<sup>xii</sup> By 2021, a total of 3509 new cases of breast cancer were registered in El Salvador.<sup>xiii</sup>

Breast cancer is a condition characterized by the rapid multiplication of cells due to changes in the mechanisms of cell division and cell death, leading to the development of tumors or abnormal masses.<sup>xiv</sup> The presence of highly penetrant dominant hereditary genes such as BRCA1 and BRCA2 is present in this disease, and one-third of patients have mutations of these tumor suppressor genes, which are related to alterations in DNA repair.<sup>xv</sup> Although more common in women, this condition can also manifest in less than 1 % of men, making diagnosis difficult due to lack of awareness.<sup>xvi</sup>

Breast cancer is divided into three main subtypes according to the presence or absence of molecular markers for human epidermal growth factor receptor 2 (ERBB2/HER2 neu), estrogen, or progesterone.<sup>xvii</sup> They are classified as follows: hormone receptor-positive/HER2 negative (70 % of patients), HER2 positive (15 %-20 %), and triple-negative (tumors lacking all three molecular markers) 15 %.<sup>xviii</sup>

Eighty percent of non-metastatic breast tumors are ductal carcinoma *in situ*.<sup>xix</sup> There has been an increase in diagnosis by annual mammography screening in recent years,<sup>xx</sup> which results in early detection of 20 % of ductal carcinoma *in situ*<sup>xxi</sup>; leading to an overall survival of 95.1 % at five years and a disease-free survival of 97.6 % at five years due to timely diagnosis and treatment.<sup>xxii</sup>

The mammography report is standardized by the use of the BI-RADS system and mammograms. Seven categories are estab-

lished that determine guidelines for action. BI-RADS 0 suggests a complementary study, BI-RADS 1 suggests a normal study; BI-RADS 2 suggests a benign finding, and category 3, probably benign findings; BI-RADS 5 suggests findings highly suggestive of malignancy, and BI-RADS 6 suggests a malignant finding already proven by histological study.<sup>xxxiii</sup>

After mastectomy, adjuvant chemotherapy is often used in non-metastatic breast cancer to eliminate any remaining cancer cells, reducing the likelihood of recurrence.<sup>xxxiv</sup> Adjuvant chemotherapy is a set of drugs taken in regular doses that may last from three to six months or longer than six months.<sup>xxxv</sup>

Anthracyclines (doxorubicin and epirubicin), alkylating agents (cyclophosphamide), antimetabolites (methotrexate and 5-fluorouracil), and taxanes are the first-line drug groups used in chemotherapy for non-metastatic breast cancer. The most popular drug combinations include AC (doxorubicin and cyclophosphamide) with or without docetaxel, TC (docetaxel and cyclophosphamide), and CMF (cyclophosphamide, methotrexate and 5-fluorouracil).<sup>xxxvi</sup>

Low specificity is a characteristic of the mechanisms of action of the drugs used in chemotherapy for breast cancer, which means that they affect both tumor cells and healthy cells with a high turnover rate.<sup>xxxvii</sup> The most studied pharmacological group of anthracyclines has a mechanism of action that inhibits DNA synthesis and transcription by intercalating between molecules. This inhibits topoisomerase II, which produces a DNA cleavage complex that increases double-strand breaks and causes cardiomyocyte deaths.<sup>xxxviii</sup>

Alkylating agents are one of the anti-neoplastic pharmacological groups that inhibit cell replication by preventing DNA transcription.<sup>xxxix</sup> Antimetabolites stop DNA synthesis by inhibiting the enzyme thymidylate synthase, which is responsible for converting uracil to thymine in the S phase.<sup>xxx</sup> Taxanes act by assembling microtubules, which prevent their depolymerization and disrupt cell mitosis.<sup>xxxi</sup>

## Physiological changes caused by chemotherapy

Women with breast cancer frequently describe problems with sexual dysfunction, especially during the first year after diagnosis.<sup>xxxii</sup> Up to 60 % of the population suffers from sexual dysfunction as a result of chemotherapy. Chemotherapy has been described to cause early menopause and painful dermatitis in the genital

region, which decreases sexual desire. Symptoms of early menopause include dyspareunia, decreased libido, and vaginal dryness, among others.<sup>xxxiii</sup>

Chemotherapy causes lesions due to vascular damage and cortical fibrosis of the ovaries, resulting in local ischemia and depletion of primordial follicles,<sup>xxxiv</sup> affecting sex hormones, which reduces estrogen levels. It has been shown that anatomical areas such as the vulva, vestibule, labia majora and labia minora, and vagina have a high concentration of estrogen receptors that diminished levels of this hormone may cause a decrease in vaginal lubrication and dyspareunia.<sup>xxxv</sup>

Cobo Cuenca A *et al.* found significant differences with a p value < 0.001 in the presence of sexual dysfunction both before (32.1 %) and after (91.2 %) the initiation of chemotherapy as a treatment for breast cancer. Penetration pain (50.6 %), lubrication (50.6 %), sexual desire (44.6 %), and dysfunctional arousal (44.6 %) were the main causes of sexual dysfunction.<sup>xxxvi</sup> Treatment has worsened sexual relations among 61.1 % of women with breast cancer.<sup>xxxvii</sup>

Decreased testosterone is one of the main regulators of central arousal, leading to a directly proportional relationship between the concentration of this hormone and sexual desire.<sup>xxxviii</sup> In addition, sex hormones contribute to neurological functions therefore, a low level of these hormones increases the risk of anxiety, depression, and neuro-cognitive dysfunctions, which are common in patients with non-metastatic breast cancer treated with chemotherapy.<sup>xxxix</sup>

In a study of 110 patients, Widiani MO *et al.* found a significant positive correlation between chemotherapy side effect variants and sexual desire, with a p value = 0.003 and R = 0.518<sup>xl</sup>. It demonstrated that chemotherapy has an impact on skeletal muscle, one of the symptoms is cachexia, which exerts negative impact on their body image and is one of the most influential factors for sexual desire.<sup>xli</sup>

## Chemotherapy and psychological aspects associated with sexual function

Women's sexual function is affected by the decrease in estrogen and progesterone levels caused by chemotherapy. The change in physical appearance, post-treatment infertility, communication problems between partners, and physical changes such as fatigue, which predisposes to episodes of anxiety and depression, are some of the main concerns or affectations of these patients.<sup>xlii</sup>

Breast cancer patients experience depression and anxiety after diagnosis as they come to understand the significance of the disease. Perez M. *et al.* found 97 % depression and 85 % anxiety.<sup>xiii</sup> Before the first cycle of chemotherapy anxiety increases and leads to a decrease in the ability to tolerate side effects, which increases symptoms such as nausea, vomiting, fatigue, and general physical deterioration, reducing the quality of life.<sup>xiv</sup>

Amado E. *et al.* found a significant relationship between sexual dysfunction and depressive disorders in women with breast cancer after chemotherapy treatment. Sexual dysfunction was found to be common in 61 % of the women, depression in 33 %, and anxiety in 69 %.<sup>xv</sup> After chemotherapy treatment,<sup>xvi</sup> an increase in physical affectations such as anxiety symptoms has been associated with varying prevalence from 12 % to 60 % and depression between 8 % to 66 %.

According to Hernández-Blanquisset *et al.*, both the diagnosis and chemotherapy cause changes in physical, mental, and sexual health with hypoactive sexual desire in 83 % of patients.<sup>xvii</sup> In a study that included 154 patients with breast cancer who received chemotherapy, the degree of emotional distress was found to be severe in 9.1 %, moderate in 29.9, and mild in 61 %.<sup>xviii</sup>

Chemotherapy treatment reduces physical activity, and increases fatigue, need for more sleep, sexual dysfunction, persistent pain, and quality of life.<sup>xix</sup> As emotional distress increases, physical and social functioning and quality of life decrease. In a study involving 41 women with non-metastatic breast cancer receiving chemotherapy and administered the EORTC QLQ C-30 and QLQ-BR23 scales, sexual functioning, sexual pleasure, concern for the future, and body image were shown to be the most affected areas.<sup>1</sup>

## Conclusion

Chemotherapy causes multiple physiological, physical, psychological, sexual, and social alterations as it affects both cancerous and non-cancerous cells. The scientific community is in constant study to evaluate the onset and severity of these complications suffered by patients after chemotherapy and to identify the symptomatology associated with the treatments to address them early and prevent complications.

Due to its various causes, including the cancer itself, different treatments, and patient idiosyncrasies, sexual dysfunction is a frequent problem. Chemotherapy has demonstrated local ovarian ischemia, leading

to early menopause, and altered sex hormone concentrations, resulting in dyspareunia, decreased libido, and vaginal dryness. Breast cancer diagnoses and the reduction of sex hormones caused by chemotherapy increase the risk of psychological disturbances, such as depression and anxiety, which reduce quality of life and sexual function during treatment. The diagnosis and treatment of breast cancer have a psychological effect on patients' lives, affecting their sexual and physical activity. Therefore, it is crucial to use a multifactorial approach from the time of diagnosis to prevent the onset of physical, mental, and sexual disorders.

## Acknowledgements

To the Dr. Luis Edmundo Vásquez School of Health Sciences of the Dr. José Matías Delgado University for supporting this process and for allowing its publication.

## Funding

The authors declared there were not external funds for this project.

## References

- i. Mina J, Paredes Y. Prevalencia de cáncer de mama y utilidad clínica de biomarcadores para el diagnóstico. Tesis para Licenciatura de laboratorio clínico. Manabí-Ecuador: Jipijapa-Unesum. 2023. Consulted date: June 10, 2023. Available at: <http://repositorio.unesum.edu.ec/bitstream/53000/4961/1/Paredes%20Y%c3%a1nez%20Wilson%20Augusto.pdf>
- ii. World Health Organization (WHO). Cáncer de mama. 2021. Consulted date: February 25, 2023. Available at: <https://www.who.int/es/news-room/fact-sheets/detail/breast-cancer#:~:text=El%20cáncer%20de%20mama%20es,de%20mortalidad%20en%20las%20mujeres>
- iii. Waks AG, Winer EP. Breast cancer treatment: A review. *JAMA*. 2019. Consulted date: May 12, 2023. 2019;321(3):288-300. DOI: 10.1001/jama.2018.19323
- iv. García Ruiz A, Baldeon Campos F, Fiero Guznay AM, Santillán Coello CE. Cáncer de mama. Editorial: Saber es del Conocimiento Revista: Reciamuc. 2022. P 521-534. Available at: <https://reciamuc.com/index.php/RECIAMUC/article/view/942/1358>
- v. Stebbing J, Delaney G, Thompson A. Breast cancer (non-metastatic). *BMJ clinical evidence*. 2011;2011:0102. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC29437>



- vi. Jaramillo D, Moya K. Descriptores BI-RADS para la clasificación de las lesiones mamarias y su aplicación para las lesiones mamarias no palpables. *Rev. Cienc. Salud*. 2020. Consulted date: June 10, 2023. DOI: [10.47606/ACVEN/MV0036](https://doi.org/10.47606/ACVEN/MV0036)
- vii. Martínez-Basurto AE, Lozano-Arrazola A, Rodríguez-Velázquez AL, Galindo-Vázquez Y, Alvarado-Aguilar S. Impacto psicológico del cáncer de mama y la mastectomía. *Gac Mex Oncol*. 2014. Consulted date: February 28, 2023. 2013;13(1):53-58. Available at: <https://biblat.unam.mx/hevila/Gacetamexicanadeoncologia/2014/vol13/no1/7.pdf>
- viii. Qi A, Li Y, Sun H, Jiao H, Liu Y, Chen Y. Incidence and risk factors of sexual dysfunction in young breast cancer survivors. *Ann Palliat Med*. 2021;10(4):4428-4434. Available at: <https://apm.amegroups.org/article/view/67921/html>
- ix. Villanueva García JE., Delgado Carrillo AM, Hernández Delgado AO y López Robles G. Funcionamiento sexual e imagen corporal en mujeres con cáncer de mama en tratamiento médico o quirúrgico. 2021 Consulted date: February 27, 2023. Available at: <http://repositorio.udem.edu.mx/handle/61000/3491>
- x. Den Ouden MEM, Pelgrum-Keurhorst MN, Uitdehaag MJ, De Vocht HM. Intimacy and sexuality in women with breast cancer: professional guidance needed. *Breast Cancer*. 2019;26(3):326-332. DOI: [10.1007/s12282-018-0927-8](https://doi.org/10.1007/s12282-018-0927-8)
- xi. Ospino R, Cendales R, Cifuentes J, Sánchez Z, Galvis J, Bobadilla I. 2010. Supervivencia en pacientes con cáncer de mama localmente avanzado tratadas con radioterapia posterior a mastectomía en el Instituto Nacional de Cancerología. *Revista Colombiana de Cancerología*. 2010;14(4):210-224. Available at: <https://www.revistacancercol.org/index.php/cancer/article/view/438>
- xii. Valderrama N. Factores controlables y no controlables en la detección temprana de cáncer de mama. Universidad ECCI; trabajo de grado de la Facultad de Ingeniería Programa de Ingeniería Biomédica Bogotá, D.C. 2022. Available at: <https://repositorio.ecci.edu.co/bitstream/handle/001/2972/Trabajo%20de%20grado.pdf?sequence=1&isAllowed=y>
- xiii. Ministerio de Salud de El Salvador. Cáncer de mama. 2021. Consulted date: February 25, 2023. Available at: <https://observadsdr.org/wp-content/uploads/2021/10/Cancer-a-julio-2021-1.pdf>
- xiv. Mera-Mamián AY, Villarreal-Garza C, Segura-Cardona AM, Muñoz-Rodríguez DI, Rodríguez-Villamizar LA, Iván García-García H. Exposición a material particulado y su relación con el cáncer de mama. *Mecanismos fisiopatológicos*. *Med. Lab*. 2023. Consulted date: May 12, 2023. 2023;27(1):13-24. Available at: <https://dialnet.unirioja.es/descarga/articulo/8740114.pdf>
- xv. Osorio BN, Bello HC, Vega BL. Factores de riesgo asociados al cáncer de mama. *Rev cubana Med Gen Integr*. 2020;36(2):1-13. Available at: <https://www.medigraphic.com/pdfs/revcubmedgenint/cmi-2020/cmi202i.pdf>
- xvi. Morales Lazcano DA. Cáncer de mama en hombre: estudio de caso. *Atención Familiar*. 2022. Consulted date: July 18, 2024. 2022;29(2):119-123. DOI: [10.22201/fm.14058871p.2022.2.82037](https://doi.org/10.22201/fm.14058871p.2022.2.82037)
- xvii. Da Silva JL, Cardoso Nunes NC, Izetti P, de Mesquita GG, de Melo AC. Triple negative breast cancer: A thorough review of biomarkers. *Crit Rev Oncol Hematol*. 2020;145:102855. DOI: [10.1016/j.critrevonc.2019.102855](https://doi.org/10.1016/j.critrevonc.2019.102855)
- xviii. Chavarría Campos GF, Blanco Naranjo EG, Garita Fallas YM. Cáncer de mama asociado a mutación en genes BRCA-1 y BRCA-2. *Rev. méd.sinerg*. 2021. Consulted date: July 18, 2024. 2021;6(3):e650. DOI: [10.31434/rms.v6i3.650](https://doi.org/10.31434/rms.v6i3.650)
- xix. Van Seijen M, Lips EH, Thompson AM, Nik-Zainal S, Futreal A, Hwang ES, *et al*. Ductal carcinoma in situ: to treat or not to treat, that is the question. *Br J Cáncer*. 2019. Consulted date: June 8, 2023. 2019;121(4):285-292. DOI: [10.1038/s41416-019-0478-6](https://doi.org/10.1038/s41416-019-0478-6)
- xx. Montagné-Bonilla N, Soto-Harvey N, Huete-Echandi F. Carcinoma ductal in situ de mama. *Rev.méd.sinerg*. 2024. Consulted date: July 18, 2024. 2024;9(2):e1138. DOI: [10.31434/rms.v9i2.1138](https://doi.org/10.31434/rms.v9i2.1138)
- xxi. Labios EH, Kumar T, Megalios A, Visser LL, Sheinman M, Fortunato A, *et al*. Genomic analysis defines clonal relationships of ductal carcinoma in situ and recurrent invasive breast cancer. 2022;54(6):850-860. DOI: [10.1038/s41588-022-01082-3](https://doi.org/10.1038/s41588-022-01082-3)
- xxii. Víctor AM, Víctor AF, Ana RC, Carmen MM, Alberto CS, Jorge PF, *et al*. carcinoma ductal in situ con microinvasión ¿necesaria biopsia del ganglio centinela? 2022. Consulted date: June 9, 2023. Available at: <https://www.redalyc.org/journal/3756/375670062003/375670062003.pdf>
- xxiii. Cajamarca T. Mamografía como método de screening en el cáncer de mama, revisión bibliográfica. Tesis doctoral. Cuenca-Ecuador: Unidad académica de salud y bienestar; 2020. Consulted date: June 10, 2023. Available at: <https://dspace.ucacue.edu.ec/handle/ucacue/8496>

- xxiv. American Cancer Society. Cáncer de seno: Tipos de tratamiento. Cancer.net. 2022. Consulted date: May 12, 2023. Available at: <https://www.cancer.net/es/tipos-de-c%C3%A1ncer/c%C3%A1ncer-de-mama/tipos-de-tratamiento>
- xxv. Memorial Sloan Kettering Cancer Center. Terapia adyuvante para el cáncer de mama: qué es, cómo hacer frente a los efectos secundarios y respuestas a las preguntas comunes. 2023. Consulted date: May 11, 2023. Available at: <https://www.mskcc.org/es/cancer-care/patient-education/adjuvant-therapy-breast>
- xxvi. De Polo J. Medicamentos y tratamiento de quimioterapia. BREASTCANCER.ORG 2022. Consulted date: May 17, 2023. Available at: <https://www.breastcancer.org/es/tratamiento/quimioterapia/medicamentos>
- xxvii. García Chías B. Prevalencia de los efectos orales secundarios a la quimioterapia en un hospital de Madrid y factores asociados. Universidad Complutense de Madrid; 2019. Available at: <https://eprints.ucm.es/id/eprint/56878/>
- xxviii. Carballo Torres D, Soriano García JL, Bazán Milián M. Mecanismos de acción de la cardiotoxicidad inducida por terapias antineoplásicas. Rev Cub Oncol. 2021. Consulted date: May 12, 2023. 2021;19(3). Available at: <https://revoncologia.sld.cu/index.php/onc/article/view/150>
- xxix. García Ruiz de Terry M, Sánchez Bursón JL. Estudio de nuevos medicamentos en oncohematología. Universidad de Sevilla, Facultad de farmacia. 2021. Consulted date: May 14, 2023. Available at: <https://hdl.handle.net/11441/133398>
- xxx. Gómez A, Parma G, Soto E, Torighelli R, Amarillo D, Boada M, *et al.* Recomendaciones para el manejo de la cardiotoxicidad relacionada con el tratamiento del cáncer. Primera parte. Rev.Urug.Cardiol. 2021. Consulted date: May 13, 2023. 2021; 36(1):e404. DOI: [10.29277/cardio.36.1.7](https://doi.org/10.29277/cardio.36.1.7)
- xxxi. Álvarez-Fernández D, Cubillas-Martín M, Álvarez-Suárez ML, Viesca-Fernández MJ, Medina-Mejías MR, Rodríguez-Balsera C. Edema macular asociado a taxanos: presentación de un caso y revisión de la literatura. Arch Soc Esp Oftalmol. 2020;95(10):485-495. DOI: [10.1016/j.oftal.2020.05.030](https://doi.org/10.1016/j.oftal.2020.05.030)
- xxxii. Costa M, Maltagliatti D, Maginera S, Volpini A, Pizarro G, Maldonado M, *et al.* Disfunción sexual en cáncer de mama: Efecto colateral. 2021. Consulted date: June 11, 2023. Rev. argent. mastología. 2021;40(148):80-100. Available at: <https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1417879>
- xxxiii. Chon SJ, Umair Z, Yoon MS. Insuficiencia ovárica prematura: pasado, presente y futuro. Front Cell Dev Biol. Consulted date: June 11, 2023. 2021;9:672890. DOI: [10.3389/fcell.2021.672890](https://doi.org/10.3389/fcell.2021.672890)
- xxxiv. Sodeifian F, Mokhlesi A, Allameh F. Chemotherapy and Related Female Sexual Dysfunction: A Review of Literature. Int J Cancer Manag. 2022;15(4):e120549. DOI: [10.5812/ijcm-120549](https://doi.org/10.5812/ijcm-120549)
- xxxv. Marrocco J, McEwen BS. Sex in the brain: hormones and sex differences. Dialogues Clin Neurosci. 2016;18(4):373-383. DOI: [10.31887/DCNS.2016.18.4/jmarrocco](https://doi.org/10.31887/DCNS.2016.18.4/jmarrocco)
- xxxvi. Cobo-Cuenca AI, Martín-Espinosa NM, Sampietro-Crespo A, Rodríguez-Borrego MA, Carmona-Torres JM. Sexual dysfunction in Spanish women with breast cancer. PLoS One. 2018;13(8):e0203151. DOI: [10.1371/journal.pone.0203151](https://doi.org/10.1371/journal.pone.0203151)
- xxxvii. Maleki M, Mardani A, Ghafourifard M, Vaismoradi M. Qualitative exploration of sexual life among breast cancer survivors at reproductive age. BMC Womens Health. 2021;21(1):56. DOI: [10.1186/s12905-021-01212-9](https://doi.org/10.1186/s12905-021-01212-9)
- xxxviii. Ljungman L, Ahlgren J, Petersson L-M, Flynn KE, Weinfurt K, Gorman JR, *et al.* Sexual dysfunction and reproductive concerns in young women with breast cancer: Type, prevalence, and predictors of problems. Psychooncology. 2018;27(12):2770-2777. DOI: [10.1002/pon.4886](https://doi.org/10.1002/pon.4886)
- xxxix. Carreira H, William R, Muller M, Harewood R, Stanway S, Bhaskaran K. Associations Between Breast Cancer Survivorship and Adverse Mental Health Outcomes: A Systematic Review Journal of the National Cancer Institute 2018;110(12): 1311-1327. DOI: [10.1093/jnci/djy177](https://doi.org/10.1093/jnci/djy177)
- xl. Widiandi MO, Yona S, Waluyo A. Body image, social support, effects of chemotherapy, and sexual desire in breast cancer patients. 2019. Consulted date: May 10, 2023. 2019;12(1):323-330. Available at: <https://www.semanticscholar.org/paper/Body-Image-%2C-Social-Support-%2C-Effects-of-%2C-and-in-Widiandi-Yona/201e6d5c2f1fdd2278ff6aec6f1f2277c8677fd6>
- xli. Guigni BA, Callahan DM, Tourville TW, Miller MS, Fiske B, Voigt T, *et al.* Skeletal muscle atrophy and dysfunction in breast cancer patients: role for chemotherapy-derived oxidant stress. Am J Physiol Cell Physiol. 2018;315(5):C744-56. DOI: [10.1152/ajpcell.00002.2018](https://doi.org/10.1152/ajpcell.00002.2018)
- xl.ii. Pérez M, Gómez J, Diéguez R, *et al.* Determinación del perfil psicológico de pacientes con cáncer de mama del Policlínico. Correo Científico Médico. Consulted date: May 12, 2023. 2020;24(4):1175-1190. Available at: <https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=98399>

- xliii. Gallego A, García C. Reducir la ansiedad en mujeres con cáncer de mama con quimioterapia a través del reiki. Facultad de ciencias de la salud Manresa. 2022. Consulted date: May 12, 2023. BS thesis. Salut-UVic, 2022. Available at: <http://repositori.umanresa.cat/handle/1/1192>
- xliv. Izci F, Özdem G, Ilgün A, Agacayak F, Duymaz T, Erdogan Z, Alco G, Elbüken F, Öztürk A, Ordu C. Niveles de ansiedad, depresión, sueño y función sexual antes y después del tratamiento en pacientes con cáncer de mama. *Eur J Breast Health*. 2020;16(3):219-225. Consulted date: May 8, 2023. DOI: [10.5152/ejbh.2020.5259](https://doi.org/10.5152/ejbh.2020.5259)
- xlv. Amado E, Escorcia R, López N, Ricardo J. Prevalencia de trastornos de ansiedad y depresión en mujeres con cáncer de mama que requieren tratamiento oncológico. Baranquilla-Colombia: Universidad del Norte. 2020. Consulted date: May 8, 2023. Available at: <http://manglar.uninorte.edu.co/handle/10584/10920#page=1>
- xlvi. Ramírez Orozco M, Galindo Vázquez O, Rojas Russell ME, Costas-Muñiz R, Robles García R, Meneses García A, *et al*. Afectaciones psicológicas en supervivientes de cáncer de mama. Una revisión narrativa. *Medicina Conductual*. 2020. Consulted date: July 18, 2024. 2020;10(2):48-59. Available at: <https://www.revistas.unam.mx/index.php/rilmc/article/view/79746>
- xlvii. Hernández-Blanquisset A, Quintero-Carreño V, Álvarez-Londoño A, Martínez-Ávila MC, Díaz-Cáceres R. La disfunción sexual como desafío en el cáncer de mama tratado: análisis en profundidad y evaluación de riesgos para mejorar los resultados individuales. *Frente Oncol*. 2022. Consulted date: May 10, 2023. 2022;12:955057. Available at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.955057/full#B26> DOI: [10.3389/fonc.2022.955057](https://doi.org/10.3389/fonc.2022.955057)
- xlviii. Aliaga J, Vásquez S. Influencia de factores psicosociales en la calidad de vida de pacientes con diagnóstico de cáncer de mama en tratamiento con quimioterapia en el Hospital Regional Cayetano Heredia. Piura-Perú: Universidad Privada Antenor Orrego; 2020. Consulted date: May 9, 2023. Available at: <https://repositorio.upao.edu.pe/handle/20.500.12759/6311>
- xlix. Gil F, Lleras M, Casellas-Grau A. Calidad de vida en supervivientes de cáncer de mama inicial. *Rev cáncer*. 2022. Consulted date: May 10, 2023. 2022;36(5):255-262. Available at: <https://dialnet.unirioja.es/servlet/articulo?codigo=9435351>
- l. Salas-Rivas P, Pousa-Benavente J, Astudillo-Astudillo J. Relación entre satisfacción usuaria y calidad de vida en mujeres con cáncer de mama en quimioterapia. *Rev. chil. obstet. gineco*. 2019. Consulted date: May 16, 2023. 2019;84(4):277-287. DOI: [10.4067/S0717-75262019000400277](https://doi.org/10.4067/S0717-75262019000400277)

# The prelacrimal approach in maxillary sinus pathologies

DOI: 10.5377/alerta.v7i2.17569

Javier Isaac Molina Velásquez

Specialities Consulting Services, Otorhinolaryngology. Salvadoran Social Security Institute (ISSS). San Salvador, El Salvador.

Correspondence

✉ javier\_molina100@hotmail.com

© 0000-0002-0520-2707

## OPEN ACCESS

### Abordaje prelacrimal en las patologías del seno maxilar

#### Suggested citation:

Molina Velásquez JI. The prelacrimal approach in maxillary sinus pathologies. *Alerta*. 2024;7(2):212-213. DOI: 10.5377/alerta.v7i2.17569

#### Editor:

Nadia Rodríguez.

#### Received:

January 19, 2024.

#### Accepted:

June 27, 2024.

#### Published:

July 24, 2024.

#### Author contribution:

JIMV: study conception, manuscript design, literature search, data collection, data analysis writing, revising and editing.

#### Conflicts of interest:

The author declared there are not conflicts of interest.



© 2024 by the author. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Dear Editor.

The knowledge of different techniques for the management of pathologies in medical specialties is essential. Such is the case of maxillary sinus pathology, which is very frequent in the field of otorhinolaryngology, and in the area of endoscopic nasosinus surgery, it is essential to perform an uncinectomy and maxillary antrostomy. Conventional endoscopic sinus surgery can effectively treat maxillary sinus pathologies; however, some conditions may be difficult to address. It is essential to develop the relevant needed skills to employ various approaches for treating these diseases.

The prelacrimal endoscopic approach to the maxillary sinus is a recent proposal. Access to the maxillary sinus through this technique is easily achieved, without modifying the anatomy of the inferior turbinate and the nasolacrimal duct.<sup>i</sup>

It is relevant to remember the anatomy of the floor of the maxillary sinus, which is formed by the alveolar process of the maxilla; this close anatomical relationship forms an interface for therapeutic management with the collaboration of rhinologists, maxillofacial surgeons and dentists.<sup>i</sup> The development of nasal endoscopy and high-resolution imaging techniques enabled nasal endoscopic surgery to become the most widely used and most effective treatment for many disorders of the maxillary sinus; however, for anatomical reasons, such as the positions of the anterior and medial walls and the alveolar process of the maxillary sinus, many pathologies are not easily visible and manageable, thus making

resection through the traditional endoscopic approach difficult.<sup>ii</sup>

Through the pre-lacrimal approach, access to the maxillary sinus is achieved anterior to the nasolacrimal duct in an oblique way, and through this, adequate control of the anterior and lateral walls is achieved, with optics of 0 and 45 degrees. This innovative rhinological technique has demonstrated advantages over traditional external and endoscopic methods, providing optimal surgical access to the anterior maxillary sinus.<sup>i</sup>

The pre-lacrimal recess is an area with boundaries defined by the inner wall of the maxillary sinus, the front wall of the maxillary sinus, the infraorbital region, and the level of the nasolacrimal duct.<sup>iii</sup> From the above, it is clear that the pre-lacrimal approach involves the removal of 2 to 3 mm of anterior lacrimal duct bone with retraction and careful displacement of the medial maxillary wall during surgery.<sup>iii</sup>

Simmen *et al.* proposed that a distance of > 7 mm (Type 3) allows the pre-lacrimal approach to be performed with little difficulty, a distance of > 3 - 7 mm (Type 2) allows the pre-lacrimal approach to be performed with partial dislocation of the lacrimal duct, and a distance of 0 - 3 mm (Type 1) will require a significant amount of bone removal, dislocation of the lacrimal sac, and a smaller pre-lacrimal window, making this approach less feasible.<sup>iii</sup>

The technique involves performing a curvilinear incision in the lateral nasal wall, anterior to the head of the inferior turbinate, then entering the maxillary sinus through a bony cut anterior to the lacrimal duct with

a chisel, preserving the lacrimal duct. The mucosa medial to the bone and the lateral nasal wall is dissected subperiosteally until reaching the head of the inferior turbinate and the anterior border of the maxillary sinus ostium. The bony canal of the lacrimal duct is removed with this dissected bony lateral nasal wall. The bony remnant of the lateral nasal wall resulting from the connection of the anterior and medial portion of the maxillary sinus is excised using Kerrison forceps. The medial retraction of the tear duct and the remaining lateral nasal wall remnant containing the inferior turbinate allows direct visualization and surgical access to the anterior wall and floor of the maxillary sinus.<sup>iii</sup>

The pre-lacrimal approach is recommended for treating severe pathologies of the maxillary sinus, particularly those originating in the anterior wall, lateral wall, or floor of the maxillary sinus. This approach has exhibited a lower recurrence rate when compared to maxillary antrostomy.<sup>iv</sup>

A relevant consideration to keep in mind is to avoid removing the adherent mucosa when performing a pre-lacrimal approach in cases of inflammation or infectious diseases, such as odontogenic sinusitis, fungal sinusitis, chronic sinusitis, and nasal polyps.

About the above, it is inferred that the pre-lacrimal approach to the maxillary sinus is a minimally invasive, safe, and effective procedure for pathologies of the maxillary sinus, such as tumors located in the anteroinferior or inferolateral wall or multiple sites of the maxillary sinus junction, including benign tumors originating in the sinonasal cavity, inverted nasal papilloma, hemangioma, fibrous dysplasia, and angiofibroma.<sup>ii,v</sup>

---

## References

- i. Ananthapadmanabhan S, Noor A, Sritharan N. Prelacrimal Window Approach in the Management of Odontogenic Maxillary Sinusitis from Dental Foreign Body. Mergoni G, editor. *Case Rep. Dent.* 2022;1-6. DOI: [10.1155/2022/1730656](https://doi.org/10.1155/2022/1730656)
- ii. Yu QQ, Guan G, Zhang NK, Zhang XW, Jiang Y, Lian YY, *et al.* Intranasal endoscopic prelacrimal recess approach for maxillary sinus inverted papilloma. *Eur. Arch. Otorhinolaryngol.* 2018;275(9):2297-2302. DOI: [10.1007/s00405-018-5078-1](https://doi.org/10.1007/s00405-018-5078-1)
- iii. Lock PSX, Siow GW, Karandikar A, Goh JPN, Siow JK. Anterior maxillary wall and lacrimal duct relationship in Orientals: CT analysis for prelacrimal access to the maxillary sinus. *Eur. Arch. Otorhinolaryngol.* 2019;276(8):2237-2241. DOI: [10.1007/s00405-019-05446-0](https://doi.org/10.1007/s00405-019-05446-0)
- iv. Mohankumar V, Kannan DS, Narendrakumar V, Kuppuswamy S, Baby AN. A Comparative Study between Endoscopic Prelacrimal Approach and Middle Meatal Antrostomy for Maxillary Sinus Pathologies. *Indian J. Otolaryngol. Head Neck Surg.* 2022;74(1):90-95. DOI: [10.1007/s12070-021-02703-9](https://doi.org/10.1007/s12070-021-02703-9)
- v. Lee JJ, Ahmad ZAM, Kim D, Ryu G, Kim HY, Dhong HJ, *et al.* Comparison Between Endoscopic Prelacrimal Medial Maxillectomy and Caldwell-Luc Approach for Benign Maxillary Sinus Tumors. *Clin. Exp. Otorhinolaryngol.* 2019;12(3):287-293. DOI: [10.21053/ceo.2018.01165](https://doi.org/10.21053/ceo.2018.01165)

# Food and Nutritional Security, a Vital and Imprecise Concept

DOI: 10.5377/alerta.v7i2.17857

Adolfo Martín Hurtado Díaz<sup>1</sup>, Julio Alberto Carpio Cerna<sup>2\*</sup>, Ingrid Odette Sanabria Solchaga<sup>3</sup>

1. Independent consultant and trainer in Right to Food and Food and Nutrition Security. Björnsby, Finland.

2. Retired ES teacher in community nutrition education. San Salvador, El Salvador.

3. Ministry of Public Health and Social Assistance, Temporary Hospital /Covid-19. Guatemala, Guatemala.

\*Correspondence

✉ juliancerna65@gmail.com

1.  0000-0003-0238-6405

2.  0000-0002-3022-3606

3.  0000-0001-6923-2131

## OPEN ACCESS

**La seguridad alimentaria y nutricional, un concepto vital e impreciso**

### Suggested citation:

Hurtado Díaz AM, Carpio Cerna JA, Sanabria Solchaga IO. Food and Nutritional Security, a Vital and Imprecise Concept. *Alerta*. 2024;7(2):214-216. DOI: 10.5377/alerta.v7i2.17857

### Editor:

Veralís Morán.

### Received:

January 15, 2024.

### Accepted:

July 17, 2024.

### Published:

July 22, 2024.

### Author contribution:

AMHD<sup>1</sup>, JACC<sup>2</sup>, IOSS<sup>3</sup>: manuscript conception and design, literature search, data collection and analysis, writing, revising and editing.

### Conflicts of interest:

The authors declared there are not conflicts of interest.



© 2024 by the authors. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

*Dear Editor.*

Food and nutritional security (FNS) is a vital concept because it is related to life, human rights, and health; however, it leads to a diversity of scopes and understandings<sup>i</sup> because it can be considered an objective such as solving the problem of hunger and nutrition in the world; it can be an end or goal such as the search for safe food, or a paradigm from the political, economic, social, cultural, legal and the sciences and technologies related to food.<sup>i</sup> It has a multi-dimensional character expressed in the distance between the conceptual formulations in national and international public policies, as it also depends on the context and the formulations of academia since it is a concept in continuous change.

The conceptual evolution of FNS began as a matter of public attention at the conference in Hot Springs, Virginia, United States of America, in 1943 “with the conviction that the eradication of hunger and poverty is a condition for peace.”<sup>ii</sup> Later, in 1974, during the “World Food Conference” held by the Food and Agriculture Organization of the United Nations (FAO) in Rome, the concept of food and nutritional security “as sufficiency” was formulated. This conference developed the definition of food security based on food supply: “Availability at all times of sufficient world supplies of basic

staple foods to sustain the steady increase in food consumption and compensate for fluctuations in production and prices.”<sup>iii</sup>

In 1995, the International Food Policy Research Institute (IFPRI) proposed an approach based on this Framework, formulating the concept of nutrition security as “the right thing to do.”<sup>iv</sup> The formulation of food and nutrition security emerged later as a proposal of field practices from the health and nutrition sector; it was globally adopted in 2008 by UNICEF, which states that: “Food and nutrition security is achieved when all people, at all times, have adequate food (in terms of quantity, quality, safety, and sociocultural acceptability), have access to it, and use it satisfactorily to ensure a healthy and active life.”<sup>v</sup>

FAO in 2011 stated that: “food and nutritional security exists when all people at all times have physical, social, and economic access to food in sufficient quantity and quality in terms of variety, diversity, nutrient content, and safety to meet their dietary needs, and food preferences, to enjoy an active and healthy life, have an adequate environment, health, education, and care.”<sup>vi</sup>

Over the years, other influencing factors have been added to the concept of FNS, such as health, the economy, or the environment, and various dimensions such as individual, family, community, national and international. These complexities were

incorporated without delimiting or differentiating their nature, which explains part of the imprecision of the boundaries of the FSN concept.<sup>vi</sup>

The Committee on Economic, Social and Cultural Rights of the United Nations, in the General Comment No. 12 of 1999, mentioned the obligations that Member States must comply with to fulfill the right to adequate food, which is achieved when every man, woman, and child alone or in community with others, has physical and economic access at all times to adequate food or means for its procurement. This right has become a priority for public action after successive crises that led to tensions, both globally and in Central America. In this context, concepts, instruments, and indicators have been discussed to organize public and private actions.<sup>iv</sup>

There have been efforts to develop public policies on food and nutritional security, as well as in terms of concepts, indicators, and institutional articulations; however, there are still unclear elements that prevent the development of instruments and the implementation of adequate, effective, and sustainable policies.<sup>vi</sup>

The international political community has worked on understanding the scope of these concepts, but the academic community does not seem to follow this effort in a concordant manner, as reflected in the divergent definitions of the political community in public instruments and definitions and the academic community in the Descriptors of Health Science.

It is necessary to develop a debate aimed at discerning the nature of the phenomena we designate as food security (related to agriculture, economy), nutritional security (at the biological and life cycle level), food and nutritional security, and the different approaches, dimensions, and measurements.<sup>vi</sup> The purpose of the discussion would be to clarify the elements or characteristics that make up FNS and to evaluate the relevance of establishing a specific institutional framework to strengthen it and a national food and nutrition security system, to provide recommendations for its effective implementation.

To facilitate the discussion, it is proposed to simplify the factors and dimensions and focus on the nutritional status of individuals, rather than considering various determinants and dimensions related to food and nutritional security. It is also advised that the values of a healthy environment be considered constant and positive, and the values of healthy consumption be managed as

variable values during the development of explanatory models. Then, for the models' simplification, it is proposed to focus solely on healthy food consumption.

From this perspective, the nature of food and nutritional security can be defined from an individual perspective, as well as differentiate the indicators in which it is expressed; this also involves identifying the accompanying positive public policy instruments. From this point, it is possible to advance in a finer understanding of the set of factors and dimensions that affect each of these conditions.

The issue of food and nutritional security is a challenge that must be addressed to develop effective, efficient, and sustainable national systems; the different actors involved must be integrated to conceptualize FNS in a clearer and more precise way.

---

## References

- i. Pastorino LF. La seguridad alimentaria-un concepto pretencioso. *Przegląd Prawa Rolnego*. 2020;(2(27)):183-206. Available at: <https://www.semanticscholar.org/reader/2b3b9e9a6a1c056457d43cb656ca062c98cbb4cb>
- ii. Aylwin P. Disertación en honor de Frank L. McDougall. En: Sesión de apertura del 31º período de sesiones de la FAO. Roma: Organización de las Naciones Unidas para la Alimentación y la Agricultura (FAO); 1996. Consulted date: July 15, 2024 Available at: <https://www.fao.org/4/y2255s/y2255s.htm>
- iii. Comité de Seguridad Alimentaria Mundial (CFS). En buenos términos con la terminología: Seguridad alimentaria, Seguridad nutricional, Seguridad alimentaria y nutrición, Seguridad alimentaria y nutricional. CFS 2012/39/4. Comité de seguridad alimentaria mundial. 39.º período de sesiones. September 2012. Available at: <https://www.fao.org/docrep/meeting/026/MD776s.pdf>
- iv. Zúñiga-Escobar M, Grisa C, Coelho-de-Souza G. Gobernanza de estrategias bajo el enfoque sistémico de la seguridad alimentaria y nutricional. *Agroalimentaria Journal-Revista Agroalimentaria*. 2022;27(53):17-32. DOI: 10.22004/ag.econ.320410
- v. Naciones Unidas, Consejo Económico y Social. Observación general N.º 12: El derecho a una alimentación adecuada (artículo 11 del Pacto Internacional de Derechos Económicos, Sociales y Culturales). Ginebra: Naciones Unidas; 1999. Consulted date: July 15, 2024. Available at: <https://www.refworld.org/es/leg/coment/cescr/1999/es/87491>

- vi. Ramírez R, Vargas P, Cárdenas O. La seguridad alimentaria: una revisión sistemática con análisis no convencional. *Revista Espacios*. 2020; 41:319-328. Available at: <https://revistaespacios.com/a20v41n45/a20v41n45p25.pdf>



# Relevance of sanitary law in health legislation

DOI: 10.5377/alerta.v7i2.17583

Javier Isaac Molina Velásquez<sup>1\*</sup>, Susana Patricia Erazo Salas<sup>2</sup>

1. Speciality Clinic, Otorhinolaryngology Service. Salvadoran Social Security Institute (ISSS). San Salvador, El Salvador.

2. Amatepec Hospital. Salvadoran Social Security Institute (ISSS). Soyapango, El Salvador.

2. El Salvador National Hospital(HES). San Salvador, El Salvador.

\*Correspondence

✉ javier\_molina100@hotmail.com

1.  0000-0002-0520-2707

2.  0000-0002-1179-0875

Dear Editor.

An article published in the journal *Alerta* Volumen 4, number 2, about risk factors for COVID-19 in the likelihood of being endemic, which describes the importance of strengthening epidemiological measures within an opportune time, for example, with the implementation of mobile sample collection booths during the COVID-19 pandemic in El Salvador, emphasizes that these measures can be considered as public health protection that is in line with compliance with the Universal Declaration of Human Rights and government policies developed on these bases. It is evident that the right to health is essential to guarantee a health system that protects and promotes the health of the population, ensuring at the same time that health services are accessible, safe, and of high quality as was the case during the COVID-19 emergency, when the Government of El Salvador decreed a health emergency on January 23, 2020 due to the probable arrival of suspected cases, and announced its first case on March 18,<sup>iii</sup> in preparation for the response to the pandemic with this measure.

Consequently, it is relevant that health professionals, decision-makers, and mainly, authorities, as part of their professional ethics and responsibility, know and interpret the international consensus on health law. Health law is the branch of the legal sciences that joins medicine to deal with the health and life of people, regulates the legal relationships that have with individual and collective human health, and the protection of health personnel, which is necessary

for the optimal and efficient management of health resources.<sup>iii</sup>


Health workers must respond and work within the legal framework, making health law a key, essential, and transcendental element for interpreting and applying health legislation effectively. For health managers, it is a vital tool for effective, efficient, and ethical health management. It must be noted that health law complements and extends itself beyond health legislation, and its purpose is to enforce the human right to health.

The role of a health manager represents a great responsibility and is more than managing a hospital, a hospital area, or the management of resources and financing; it implies being an ambassador of health law in the relationship between the health facility, patients, and the State, under the institutional authority of the health area.

The right to health, which as an initial and ultimate principle is linked to protecting life and guaranteeing the wellbeing of the inhabitants of El Salvador, as established in the Constitution, implies that patients receive dignified and respectful treatment and that their rights are safeguarded through the right to information, informed consent, and confidentiality of medical data.

The health manager has the responsibility to do everything in his or her power to ensure the well-being and health of patients and to carry on actions to ensure that health personnel work proactively and in partnership, as well as to enforce the regulation of training and conduct of health professionals.

Likewise, it is important to emphasize the proper knowledge that health managers should have of the different international

 OPEN ACCESS

**La importancia del derecho sanitario en la legislación en salud**

**Suggested citation:**

Molina Velásquez JI, Erazo Salas SP. The importance of knowing and applying health law in health legislation. *Alerta*. 2024;7(2):217-218. DOI: 10.5377/alerta.v7i2.17583

**Editor:**

Nadia Rodríguez.

**Received:**

January 21, 2024.

**Accepted:**

June 21, 2024.

**Published:**

July 24, 2024.

**Author contribution:**

JIMV<sup>1</sup>: study conception, manuscript design, literature search, data collection. SPES<sup>2</sup>: data management or software, writing, revising, and editing.

**Conflicts of interest:**

The authors declared there are not conflicts of interest.



© 2024 by the authors. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

instruments, constitutional foundations, the Health Code, and other related laws and regulations. Similarly, they must interpret and apply the technical legal instruments that complement health right to enforce the human right to health, which is a universal and fundamental human right, so that the commitment to the right to health is also reflected at the international level with compliance with the Universal Declaration of Human Rights.<sup>iv</sup>

The approach to health rights is related to health and connected with the origin and ultimate purpose of the State, which is grounded on the human person who cannot prescind from health for his development, survival, and compliance with the exigencies and functioning that society demands; thus, the development of health legislation. Therefore, it is necessary to establish institutional regulations that integrate laws, policies, and rules that regulate the functioning and performance of those who execute them because it is reasonable that in a framework in which order and organization prevail, it is possible to meet their goals and purposes.

Likewise, the standardization of medical care processes through the classic standards of diagnosis and treatment is relevant.<sup>v</sup> In connection, the country demonstrates its commitment to health legislation through the creation of a series of laws and regulations in the health sector, such as the Health Code, the Law of the Higher Council of Public Health and the Health Professions Oversight Boards, the Law of Duties and Rights of Patients and Health Service Providers. These regulations are responsible for ensuring the population's rights to health and to protect against violations and misconduct of personnel to these rights, regulating the conduct and behavior of health personnel.

It is also essential to search for solutions to modify the contribution of universities and health management programs and thus obtain improved knowledge in legal

matters regarding health legislation, with a vision focused on constant improvement, since it is clear that there are challenges at all levels and in all areas related to the provision of health services, allowing the right to health to be valid for the entire population.

Finally, strategies related to the administration and management of health personnel and the strengthening of their capacities can be built, compatible with methods such as empowerment, motivational techniques, and frequent training so that they develop the capacity to provide a quality public health service that responds to the health needs of the people in their territory and to the fulfillment of the human right to health.

---

## References

- i. Garat MP, Riso Ferrand M, Ramos Cabanellas BV, *et al.* El Derecho frente a la pandemia por COVID-19. *Revista de Derecho* (Universidad Católica Dámaso A. Larrañaga, Facultad de Derecho) 21(2020):1-24. DOI: [10.22235/rd.vi21.2193](https://doi.org/10.22235/rd.vi21.2193)
- ii. López A, Domínguez R. Medidas de contingencia ante el COVID-19 en El Salvador. *Alerta*. 2021;4(1):78-79. DOI: [10.5377/alerta.v4i1.10762](https://doi.org/10.5377/alerta.v4i1.10762)
- iii. Madies CV. *Derecho Sanitario*. Argentina: Ministerio de Salud, Organización Mundial de la Salud; 2017. Available at: <https://www.salud.gob.ar/dels/entradas/derecho-sanitario>.
- iv. The Universal Declaration of Human Rights. New York: United Nations General Assembly; 1948. Available at: <https://www.un.org/es/about-us/universal-declaration-of-human-rights>
- v. Sarrión Esteve J. La competencia de las autoridades sanitarias para restringir derechos en situación de crisis sanitaria. *Gac Sanit*. 2022;36(1):37-40. DOI: [10.1016/j.gaceta.2020.07.009](https://doi.org/10.1016/j.gaceta.2020.07.009)

# Alerta

## Types of articles and preparation

Alerta offers authors the opportunity to publish different types of articles. The types of manuscripts allowed are below. Please read the instructions carefully prior to submitting your article.

### Original article

Research works that have not been published or proposed for revision in other journals and provide information to understand or propose solutions to the main health problems. Case series studies, descriptive and analytical cross-sectional studies, case-control studies, cohort studies, and randomized controlled trials are considered for publication. Results must be original.

The article must have the following structure: abstract, keywords, introduction, methodology, results, discussion, conclusion and references. The text must have a maximum of 4000 words and a minimum of 3000, not including references, abstract and text of figures and tables. The abstract must have a maximum of 250 words and must be structured in introduction, objective, methodology, results and conclusion. Use of acronyms, abbreviations and bibliographic citations in the abstract is not allowed. A maximum of 35 references and a minimum of 25 are allowed. 65 % of references must not be older than five years since their publication date. Only 10 % of grey literature is allowed as part of references. Tables and figures must not be more than five in total.

For observational studies, it is recommended the format according to [STROBE](#) guidelines. For randomized controlled trials, it is recommended the format according to the [CONSORT](#) statement.

### Review article

Review articles that present the result of an analysis of recent information or a thematic update of interest in public health, following any of the accepted methodologies for this purpose. It is required to indicate that it is a narrative or systematic review.

### Systematic review and meta-analysis

Systematic reviews representing a synthesis of evidence, original, quantitative or qualitative studies, that use a rigorous process to minimize biases and that identify, evaluate and synthesize studies to answer a specific clinical question are accepted. The search process for the original studies, the criteria used for the selection of those that were included in the review and the procedures used in the synthesis of the results obtained by the reviewed studies must be described in detail.

The article must have the following sections: abstract, keywords, introduction, methodology, results, discussion, conclusion and references. The text must have a maximum of 4000 words and a minimum of 3000, not including references, abstract and text of figures and tables. The abstract must have a maximum of 250 words and must be structured in introduction, objective, methodology, results and conclusion. Use of acronyms, abbreviations and references in the abstract is not allowed. There is no limit to the number of references. 75 % of them must not be older than five years since their publication date. The use of grey literature as part of references is not permitted. Tables and figures cannot be more than five in total.

Recommended format: [PRISMA](#) guide.

### Narrative or critical review

Narrative or critical review must have descriptive writing and make a comprehensive presentation and discussion of topics of scientific interest in the field of public health. A clear formulation of a scientific object of interest with logical argumentation must be presented.

The article must have the following sections: abstract, keywords, introduction, discussion, conclusion and references. The text must have a maximum of 3500 words and a minimum of 2500, not including references, abstract and text of figures and tables. The abstract must have a maximum of 200 words. Use of acronyms, abbreviations and references in the abstract is not allowed. A maximum of 50 references and a minimum of 30 are allowed. 70 % of them must not be older than five years since their publication date. Only 15 % of grey literature is allowed as part of references. Tables and figures cannot be more than three in total.

### Brief communication

This type of scientific paper is shorter than an original article. They are works that aim to publish data of interest in the health situation on a report of a research in development and innovative techniques or methodologies, among others.

The article must have the following sections: abstract, keywords, introduction, methodology, results, discussion, conclusion and references. The text must have a maximum of 2000 words and a minimum of 1500, not including references, abstract and text of figures and tables. The abstract must have a maximum of 200 words and must be structured in introduction, objective, methodology, results and conclusion. Use of acronyms, abbreviations and bibliographic citations in the abstract is not allowed. A maximum of 20 references and a minimum of 15 are allowed. 65 % of them must not be older than five years since their publication date. Only 5 % of grey literature is allowed as part of references. Tables and figures cannot be more than three in total.

### Case report

This type of text refers to the presentation of clinical cases that meet established criteria and whose diagnostic and treatment aspects make a considerable contribution to scientific knowledge on the subject. It must respect the provisions of the Declaration of [Helsinki](#) and [international ethics guidelines](#) for health-related research involving human beings.

The text must have the following sections: abstract, keywords, introduction, case presentation, treatment, outcome, clinical diagnosis, discussion, ethical aspects and references. The text must have a maximum of 2000 words and a minimum of 1500, not including references, abstract and text of figures and tables. The abstract must have a maximum of 200 words and must be structured in case presentation, treatment and outcome. Use of acronyms, abbreviations and bibliographic citations in the abstract is not allowed. A maximum of 20 references and a minimum of 15 is allowed. 70 % of them must not be older than five years since their publication date. Only 5 % of grey literature is allowed as part of references. Tables and figures cannot be more than five in total.

Recommended format: [CARE](#) guide.

### Letter to the editor

Letter to the editor or the editorial committee clarifying, discussing or commenting on the content presented in previous issues of this journal. Comment letters on specific public health issues may also be accepted. Letters must have the following sections: title and object of correspondence. It can have a maximum of 1000 words and a minimum of 700. Tables and figures are not accepted. A maximum of five references and a minimum of three are accepted.

## Summary of the characteristics of the different articles

General format for the presentation of articles					
Type of manuscript		Word count	References	Abstract	Tables or figures
Original articles		3000 – 4000	25 – 35	250 words (structured)	Up to 5
Review articles	Systematic	3000 – 4000	As appropriate	250 words (structured)	Up to 5
	Narrative	2500 – 3500	30 – 50	200 words	Up to 3
Brief communications		1500 – 2000	15 – 20	200 words (structured)	Up to 3
Case report		1500 – 2000	15 – 20	200 words (structured)	Up to 5
Letter to editor		700 – 1000	3 – 5	No	No

For further information, please refer to the instructions to authors on our website at: [www.alerta.salud.gob.sv](http://www.alerta.salud.gob.sv)

## Peer reviewers 2024

Erick Nelson Campos Campos  
El Salvador  
✉ [nelsonfenc.1991@hotmail.com](mailto:nelsonfenc.1991@hotmail.com)

Audelin Meliton Mira Burgos  
El Salvador  
✉ [audelin.mira@salud.gob.sv](mailto:audelin.mira@salud.gob.sv)

Angela María Castro Arca  
Cuba  
✉ [castroarca60@gmail.com](mailto:castroarca60@gmail.com)

Sigifredo Macossay Santiago  
México  
✉ [sigimacossay@outlook.com](mailto:sigimacossay@outlook.com)

Yuri Medrano Plana  
Ecuador  
✉ [yuri.medrano@uleam.edu.ec](mailto:yuri.medrano@uleam.edu.ec)

Ana Margarita Jerez Castro  
Cuba  
✉ [jerezanamargarita@gmail.com](mailto:jerezanamargarita@gmail.com)

Martha Alicia Ramírez Guerra  
México  
✉ [martha\\_guerra\\_89@hotmail.com](mailto:martha_guerra_89@hotmail.com)

Cintha Carrasco Encalada  
Ecuador  
✉ [cintha\\_elizabeth.07@hotmail.com](mailto:cintha_elizabeth.07@hotmail.com)

María Beatriz López Castellanos  
Guatemala  
✉ [fdx8@cdc.gov](mailto:fdx8@cdc.gov)

Adán Martínez Alvarenga  
El Salvador  
✉ [dradanma@yahoo.com](mailto:dradanma@yahoo.com)

Violeta Nohelí Ricart  
Paraguay  
✉ [violeta.ricart@gmail.com](mailto:violeta.ricart@gmail.com)

Luis Dulcey  
Venezuela  
✉ [luismedintcol@gmail.com](mailto:luismedintcol@gmail.com)

Patricio Suárez Gil  
Spain  
✉ [patricio.suarez@ispasturias.es](mailto:patricio.suarez@ispasturias.es)

Wilmer Guzmán Ventura  
Perú  
✉ [wilmerguzmanventura@hotmail.com](mailto:wilmerguzmanventura@hotmail.com)

Glauco Valdivieso Jiménez  
Perú  
✉ [glauco.valdivieso@unmsm.edu.pe](mailto:glauco.valdivieso@unmsm.edu.pe)

Montserrat Amorós Gómez  
Spain  
✉ [montserrat.amoros@unir.net](mailto:montserrat.amoros@unir.net)

Rafael Gaia Zurrado Saiz  
Spain  
✉ [rafazurrado@gmail.com](mailto:rafazurrado@gmail.com)

Susana Peña  
El Salvador  
✉ [supeamart@yahoo.com](mailto:supeamart@yahoo.com)

Nancy Rita Alarcón Henríquez  
Chile  
[n.alarcon@ulagos.cl](mailto:n.alarcon@ulagos.cl)

Rose Pastsam  
Mexico  
✉ [dra.pastsam@gmail.com](mailto:dra.pastsam@gmail.com)

Alex Medina  
Canada  
✉ [alexmedinaescobar@gmail.com](mailto:alexmedinaescobar@gmail.com)

Ricardo López  
El Salvador  
✉ [jrlopezcontreras@yahoo.com](mailto:jrlopezcontreras@yahoo.com)

Horacio Matías Castro  
Argentina  
✉ [matias.castro@hospitalitaliano.org.ar](mailto:matias.castro@hospitalitaliano.org.ar)

Vicente Artola Arita  
The Netherlands  
✉ [v.a.artolaarita@umcutrecht.nl](mailto:v.a.artolaarita@umcutrecht.nl)

Andrés Felipe Ríos Piedrahita  
Colombia  
✉ [andres.rios@correounivalle.edu.co](mailto:andres.rios@correounivalle.edu.co)

Eva Rossina Duarte Juárez  
Guatemala  
✉ [erduarte@elpilar.gt](mailto:erduarte@elpilar.gt)

José Nemesio Portillo  
El Salvador  
✉ [nemesioportillo@gmail.com](mailto:nemesioportillo@gmail.com)

Edith Verális Moran de Valladares  
El Salvador  
✉ [everalis.moran@salud.gob.sv](mailto:everalis.moran@salud.gob.sv)

Alerta is a journal of the National Institute of Health, Ministry of Health  
El Salvador, Central America

### Alerta

Urb. Lomas de Altamira, Bulevar Altamira y av. República de Ecuador, No.33,  
San Salvador, El Salvador, C.A.  
PBX: 2591-8200  
[www.alerta.salud.gob.sv](http://www.alerta.salud.gob.sv)