Boletín Médico del Hospital Infantil de México

L-ISSN 0539-8115
ISSN 1865-1146

Volumen 82, Número 1
Enero - Febrero 2025

PERMANYER MÉXICO
www.permanyer.com

Boletín Médico del Hospital Infantil de México

L-ISSN: 0539-6115
ISSN: 1665-1146

Volumen 82, Número 1 - Enero - Febrero 2025 - **www.bmhim.com**

Incluida en/Indexed in: PubMed/Medline, Emerging Sources Citation Index (ESCI)™, Scielo, Scopus, Latindex, Embase, EBSCO Directory/EssentialsTM y DOAJ

Hospital Infantil de México Federico Gómez
Instituto Nacional de Salud

PERMANYER MÉXICO
www.permanyer.com

PERMANYER
www.permanyer.com

Permanyer
Mallorca, 310 – Barcelona (Cataluña), España – permanyer@permanyer.com

Permanyer México
Temístocles, 315
Col. Polanco, Del. Miguel Hidalgo – 11560 Ciudad de México
mexico@permanyer.com

www.permanyer.com

ISSN: 0539-6115
Ref.: 10968AMEX251

Boletín Médico del Hospital Infantil de México

Vol. 82 • Núm. 1 • Enero-Febrero 2025 www.bmhim.com Indexada en Scopus y MEDLINE

Contenido

Boletín Médico del Hospital Infantil de México

Vol. 82 • No. 1 • January-February 2025 www.bmhim.com Indexed in Scopus and MEDLINE

Contents

Agradecimiento a revisores 2024

Acknowledgments to reviewers 2024

El Boletín Médico del Hospital Infantil de México agradece a los revisores por brindar su tiempo y esfuerzo para evaluar los trabajos que se someten a esta revista. Gracias por su destacada colaboración y valiosas aportaciones.

Adrián Jair Ortega Vargas, México
Adriana Arnao Noboa, Ecuador
Adriana Geraldinne Zavaleta Carreón, México
Aixa Xiomara Vargas Cárdenas, Colombia
Alberto Daniel Saucedo Campos, México
Alejandra Coronado Zarco, México
Alejandra Sánchez Cruz, México
Alejandro Donoso, Chile
Alejandro Weber Sánchez, México
Alfonso Buendía Hernández, México
Alyssa Comfort, Canadá
Amaranto Suárez Mattos, Colombia
Ana Maria Sánchez Torres, España
Andrea Catalina Nassar Tobón, Colombia
Angélica Castro, México
Angélica Paola Fajardo Escolar, Colombia
Antonio Muñoz, México
Argelia Medeiros, México
Ariadna Ayerza Casas, España
Arianna Omaña Covarrubias, México
Arlette Patricia Doussoulin Sanhueza, Chile
Arturo Vargas Origel, México
Beatriz Aranegui, España
Camila Montoya Bueno, Colombia
Carlos Alejandro Chávez Gutiérrez, México
Carmita Esperanza Villavicencio Aguilar, Ecuador
Carolina Beltrán Dulcey, Colombia
Carolina Tovar Moreno, México
César Nureña, Perú
Cynthia Shanat Cruz Medina, México
Daniel Andrés De la Torre Diamante, Argentina
Daniel Ibarra Ríos, México
Daniel Ortiz Morales, México
Dante Amato Martínez, México
David Calderon Uriostegui, México
David Peláez Mata, España
Diana Aidee Guerrero Resendiz , México
Diana Laura Vázquez Cantú, México
Edgar García, México
Edgar Manuel Vasquez Garibay, México
Eduardo Marín Hernández, México
Elisa Dorantes Acosta, México
Elisa García Morales, México
Elizabeth Estevez Fregoso, México
Emanuele Panza, Italia
Enrique Palomo Atance, España
Enrique Villareal Ríos, México
Eulalia Alfonso Muñoz, Cuba
Federico Martínez Montes, México
Fernando Silva, México
Fernando Vázquez Rueda, España
Fortino Solórzano, México
Francisco Ortega Suárez, México
Francisco Javier Prado Galbarro, México
Gabriela Bustillos, Bolivia
Gina Chapa Koloffon, México
Guadalupe Bestina Tapia Amador, México
Guillermo José Ruiz Arguelles, México
Guillermo Salinas Escudero, México
Héctor Ochoa Díaz López, México

Boletín Médico del
Hospital Infantil de México

PERMANYER

EDITORIAL

Homenaje al Dr. Luis Velásquez Jones

Mara Medeiros

Dirección de Investigación, Hospital Infantil de México Federico Gómez, Ciudad de México, México

El Dr. Luis Fernando Velásquez Jones nació en la ciudad de Trujillo, al norte de Perú, el 22 de agosto de 1942, hijo del Dr. Gonzalo A. Velásquez Pérez y la Sra. Blanca Jones de Velásquez, siendo el cuarto de seis hermanos. Realizó sus estudios de primaria y secundaria en el colegio seminario de San Carlos y San Marcelo de su ciudad natal, donde destacó por su inteligencia y desempeño. Posteriormente, cursó la carrera de Medicina entre 1962 y 1967 en la Universidad Nacional de Trujillo, obteniendo el primer lugar de su generación.

Por sugerencia de su cuñado, el Dr. Javier Medina, viajó a México para realizar la residencia en Pediatría en el Hospital Infantil de México Federico Gómez, donde posteriormente cursó la especialidad en Nefrología Pediátrica de 1972 a 1974. Al finalizar su entrenamiento, trabajó como adscrito al Departamento de Nefrología

Correspondencia:
Mara Medeiros
E-mail: medeiromara@gmail.com

Fecha de recepción: 10-12-2024
Fecha de aceptación: 15-12-2024
DOI: 10.24875/BMHIM.M24000040

Disponible en internet: 28-02-2025
Bol Med Hosp Infant Mex. 2025;82(1):3-4
www.bmhim.com

junto al Dr. Gustavo Gordillo Paniagua. Fue coordinador del programa de Nefrología de la UNAM y contribuyó a la redacción del libro Nefrología Pediátrica, editado por la Asociación de Médicos del Hospital Infantil de México, que fue un referente en la nefrología pediátrica latinoamericana durante décadas[1].

Regresó a Perú en 1976 como pediatra de base y profesor en la Universidad Peruana Cayetano Heredia, donde permaneció hasta 1978. Durante este periodo, realizó la primera diálisis pediátrica en Perú y reportó la lesión renal aguda inducida por el piquete de la araña violinista[2].

En 1979 decidió regresar a México con su familia y trabajó como jefe del Departamento de Asistencia Médica en la Dirección General de Servicios Médicos de la UNAM hasta 1984. Posteriormente, fue invitado por el Dr. Felipe Mota Hernández a integrarse como adscrito del nuevo Departamento de Hidratación Oral del *Hospital Infantil de México Federico Gómez*, donde tuvo una participación activa en la generación de conocimiento en esta área. En 1986 realizó una estancia en la India dentro de un programa de investigación en salud auspiciado por la OMS y el *British Medical Journal*, entrenándose en metodología de la investigación y bioestadística. Fue admitido en la Academia Mexicana de Medicina en junio de 1989, con la propuesta de una nueva solución para hidratación oral en lactantes con diarrea[3].

En 1988 se integró al Departamento de Medicina del *Hospital Infantil de México Federico Gómez*, trabajando junto al Dr. José Domingo Gamboa Marrufo y el Dr. Antonio Zamora Chávez. En 1991 fue invitado como médico adscrito e investigador al Departamento de Nefrología Pediátrica, participando en el proyecto del Dr. Ricardo Muñoz Arizpe. Posteriormente, fue jefe del departamento entre 2012 y 2015, y continuó como médico especialista hasta su jubilación en 2018.

El Dr. Velásquez Jones tuvo una prolífica carrera científica, publicando 267 artículos en revistas indizadas, 108 capítulos de libro, 25 libros como autor y editando o coeditando cuatro libros. Entre sus obras más influyentes destacan *Alteraciones hidroelectrolíticas en pediatría*[4] y *Redacción del escrito médico*[5].

Entre sus contribuciones destacan el uso de nitroprusiato intravenoso para tratar hipertensión arterial grave[6], la descripción de los primeros casos de cistinosis nefropática en México[7], y el estudio sobre el bloqueo mineralocorticoide en la nefropatía crónica del injerto renal, registrado como ensayo clínico y financiado por CONACYT[8].

El Hospital Infantil de México Federico Gómez rindió homenaje al Dr. Velásquez Jones el 8 de octubre de 2024, reconocimiento que puede verse en la página de Facebook institucional[9].

El Dr. Velásquez Jones también se desempeñó en el Departamento de Ediciones Médicas del hospital desde 1981, primero como editor asociado y, posteriormente, como jefe del departamento entre 1984 y 2005, así como editor en jefe del *Boletín Médico del Hospital Infantil de México*.

Referencias

1. Gordillo PG, Mota HF, Velásquez JL. Nefrologfa pediatrica. Mexico: Ediciones Médicas del Hospital Infantil de Mexico; 1976.
2. Salazar LE, Velásquez JL, Caravedo RL, Schoemaker E, Zegana RO, Benavente L. Insuficiencia renal aguda por loxoscelismo. Pediatría (Santiago). 1978; 21: 337-346.
3. Velásquez JL, Mota F: Efecto de una nueva solución para hidratación oral de lactantes con diarrea aguda. Gac Med Mex 1990; 47: 315-322
4. Velásquez JL. Alteraciones hidroelectroliticas en Pediatría. Tercera edición. Mexico: Editorial Prado; 2017. ISBN: 978-607-9476-01-4
5. Velásquez JL. Redacción del escrito médico. Quinta ed. México: Editorial Prado; 2012. ISBN: 978-607-7566-45-8.
6. Gordillo PG, Velasquez JL, Maiiini R, Valdez BE. Sodium nitroppruSside treatment of severe a1ierial hypertension in children. J Pediatr. 1975; 87: 799-802.
7. Velásquez JL, Rego FEA, Ajuria de Vargas LM, Mota HF, Gordillo PG. Cistinosis tipo infantil: consideraciones sobre diagn6stico y evoluci6n. Bol Med Hosp Infant Mex. 1976; 33: 777-791
8. Medeiros M, Velasquez-Jones L, Hernandez AM, Ramon-Garcia G, Valverde S, Fuentes Y, Vargas A, Patifio M, Perez-Villalba R, O1iega-Trejo JA, Barrera-Chimal J, Bobadilla NA. Randomized controlled trial of mineralocorticoid receptor blockade in children with chronic kidney allograft nephropathy. Clin J Am Soc Nephrol, 2017.
9. https://www.facebook.com/watch/live/?mibextid=WC7FNe&ref=watch_permalink&v=1305834327247223&rdid=j1AKWJh91OrFtYBk

Boletín Médico del
Hospital Infantil de México

PERMANYER

EDITORIAL

Tribute to Dr. Luis Velásquez Jones

Mara Medeiros

Directorate of Research, Hospital Infantil de México Federico Gómez, Mexico City, Mexico

Dr. Luis Fernando Velásquez Jones was born on 22 August 1942 in the city of Trujillo in northern Peru. He was the fourth of six children born to Dr. Gonzalo A. Velásquez Pérez and Mrs. Blanca Jones de Velásquez. He completed his primary and secondary education at the San Carlos and San Marcelo Seminary School in his hometown, where he stood out for his intelligence and academic achievement. He studied medicine at the *Universidad Nacional de Trujillo* from 1962 to 1967, graduating at the top of his class.

At the suggestion of his brother-in-law, Dr. Javier Medina, he traveled to Mexico to complete his pediatric residency at the *Hospital Infantil de México Federico Gómez*, where he later specialized in pediatric nephrology from 1972 to 1974. After completing his training, he worked as a staff physician in the Nephrology

Correspondence:
Mara Medeiros
E-mail: medeiromara@gmail.com

Date of reception: 10-12-2024
Date of acceptance: 15-12-2024
DOI: 10.24875/BMHIME.M24000072

Available online: 28-02-2025
Bol Med Hosp Infant Mex. 2025;82(1):5-6
www.bmhim.com

Department under Dr Gustavo Gordillo Paniagua. He was the coordinator of the nephrology program at UNAM and co-authored the textbook on pediatric nephrology published by the Association of Physicians of the *Hospital Infantil de México*, which remained a reference in Latin American pediatric nephrology for decades[1].

He returned to Peru in 1976 to accept a coveted position as staff pediatrician and professor at the University of Cayetano Heredia, where he remained until 1978. During this time, he performed the first pediatric dialysis in Peru and reported on acute kidney injury caused by brown recluse spider bites[2].

In 1979, he decided to return to Mexico with his family and worked as Head of the Medical Assistance Department at the General Directorate of Medical Services of the UNAM until 1984, when Dr. Felipe Mota Hernández invited him to join the staff of the new Oral Hydration Department at the *Hospital Infantil de México Federico Gómez*. There he actively contributed to the knowledge generated in this field. In 1986, he completed a one-month fellowship in India as part of a health research program sponsored by the World Health Organization and the *British Medical Journal*, where he received training in research methodology and biostatistics. In June 1989, he was inducted into the Mexican Academy of Medicine for his proposal of a new oral rehydration solution for infants with diarrhea[3].

In 1988, he joined the Department of Medicine at the Hospital Infantil de México Federico Gómez, along with Dr. José Domingo Gamboa Marrufo and Dr. Antonio Zamora Chávez, a unit where difficult cases were admitted. Under these three giants of Mexican pediatrics, accurate diagnosis and treatment were always achieved.

In 1991, he was invited to join the Department of Pediatric Nephrology as a staff physician and researcher as part of the project of the new head of the department, Dr. Ricardo Muñoz Arizpe. He later served as head of this department from 2012 to 2015 and remained as a specialist until his retirement in 2018.

During his extensive career at the hospital, in addition to contributing to the training of pediatricians, pediatric internists, and nephrologists, he developed numerous research projects, published 267 articles in indexed journals, authored 108 book chapters, wrote 25 books, and served as editor or co-editor of four books.

Among his influential books that have played an important role in the training of pediatricians are *Alteraciones hidroelectrolíticas en pediatría* (Electrolyte Disorders in Pediatrics), which has had three editions, the most recent in 2017[4], and *Redacción del Escrito Médico* (Writing Medical Documents), which has had five editions[5].

Among his countless contributions to pediatric nephrology, the use of intravenous nitroprusside for the treatment of severe hypertension[6], the description of the first cases of nephropathic cystinosis in Mexico[7], and the use of mineralocorticoid blockade to prevent the progression of chronic nephropathy in kidney transplantation, a study registered as a clinical trial and funded by CONACYT[8], are noteworthy.

The *Hospital Infantil de México Federico Gómez* held a well-deserved tribute on October 8, 2024, to this distinguished and illustrious pediatric nephrologist who, as Dr. Jesús Kumate said, chose to stay in our country, being “Mexico’s gain and Peru’s loss”. The tribute can be viewed on the institution’s Facebook page[9].

Dr. Velásquez Jones was actively involved in the medical publications department of the *Hospital Infantil de México Federico Gómez* since 1981, first as associate editor and later as head of the *Departamento de Ediciones Médicas* (Medical Publishing Department) from 1984 to 2005 and as editor-in-chief of the *Boletín Médico del Hospital Infantil de México*.

References

1. Gordillo PG, Mota HF, Velásquez JL. Nefrologfa pediatrica. Mexico: Ediciones Médicas del Hospital Infantil de Mexico; 1976.
2. Salazar LE, Velásquez JL, Caravedo RL, Schoemaker E, Zegana RO, Benavente L. Insuficiencia renal aguda por loxoscelismo. Pediatría (Santiago). 1978; 21: 337-346.
3. Velásquez JL, Mota F: Efecto de una nueva solución para hidratación oral de lactantes con diarrea aguda. Gac Med Mex 1990; 47: 315-322
4. Velásquez JL. Alteraciones hidroelectroliticas en Pediatría. Tercera edición. Mexico: Editorial Prado; 2017. ISBN: 978-607-9476-01-4
5. Velásquez JL. Redacción del escrito médico. Quinta ed. México: Editorial Prado; 2012. ISBN: 978-607-7566-45-8.
6. Gordillo PG, Velasquez JL, Maiiini R, Valdez BE. Sodium nitroprusside treatment of severe a1ierial hypertension in children. J Pediatr. 1975; 87: 799-802.
7. Velásquez JL, Rego FEA, Ajuria de Vargas LM, Mota HF, Gordillo PG. Cistinosis tipo infantil: consideraciones sobre diagn6stico y evoluci6n. Bol Med Hosp Infant Mex. 1976; 33: 777-791
8. Medeiros M, Velasquez-Jones L, Hernandez AM, Ramon-Garcia G, Valverde S, Fuentes Y, Vargas A, Patifio M, Perez-Villalba R, O1iega-Trejo JA, Barrera-Chimal J, Bobadilla NA. Randomized controlled trial of mineralocorticoid receptor blockade in children with chronic kidney allograft nephropathy. Clin J Am Soc Nephrol, 2017.
9. https://www.facebook.com/watch/live/?mibextid=WC7FNe&ref=watch_permalink&v=1305834327247223&rdid=j1AKWJh91OrFtYBk

Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

REVIEW ARTICLE

Mitochondria-based medicine

*Salvador Vázquez-Vega[1], José D. Martínez-Ezquerro[2,3], Sergio Sánchez-García[2], Edwin R. Marka-Castro[4], and Fernando Minauro-Sanmiguel[5]**

[1]Unit of Epidemiological and Health Services Research, Instituto Mexicano del Seguro Social (IMSS), Centro Médico Nacional Siglo XXI; [2]Unit of Epidemiological and Health Services Research, Aging Area, IMSS, Centro Médico Nacional Siglo XXI; [3]Center for Complexity Sciences (C3), Universidad Nacional Autónoma de México; [4]Centro Médico Nacional Siglo XXI Hospital de Especialidades "Bernardo Sepúlveda Gutiérrez", IMSS; [5]Unit of Medical Research in Human Genetics, IMSS, Centro Médico Nacional Siglo XXI. Mexico City, Mexico

Abstract

At the balance between human health and disease (from the very first moments to the end of life), the mitochondrion is central players because of its metabolic role in adenosine triphosphate synthesis, cell signaling, immune response, and other processes of clinical interest. On the other hand, impairments at the optimal mitochondria function have important consequences in complex diseases, such as heart disease, diabetes, and cancer, among others. These mitochondrial impairments can occur at any age damaging multiple body systems, which have prompted the mitochondrial medicine development. Since mitochondrial diseases have great variability in their clinical manifestations, early studies were centered on mitochondriopathies, however nowadays, this focus has broadened to understand and encompass the mitochondrial role of in diseases development of both pediatric and adult age. The mitochondria potential to improve diagnostic, prognostic, and treatment response strategies has been revealed by experimental approaches using proteomics, genomics, and metabolomics to identify clinical biomarkers showing disease development. Thus, the perspective of mitochondria-based medicine recognizes the importance of generating scientific evidence related to mitochondria and their role in pathological conditions from a comprehensive approach.

Keywords: *Mitochondria. Mitochondrial diseases. Chronic non-communicable diseases. Metabolic diseases.*

Medicina basada en mitocondrias

Resumen

En el equilibrio entre la salud y la enfermedad de un individuo (desde los primeros instantes de su vida y durante el resto de ella), la mitocondria tiene un papel central en el correcto funcionamiento del metabolismo. Además, su papel es primordial en la síntesis de ATP, en la señalización celular, la respuesta inmune, entre otros procesos de interés clínico. Por otro lado, las afecciones al funcionamiento óptimo de la mitocondria tienen consecuencias importantes en las enfermedades complejas, tal es el caso de las enfermedades cardíacas, la diabetes y el cáncer, entre otras. Estas afecciones en la función mitocondrial pueden ocurrir a cualquier edad y dañar a múltiples sistemas del cuerpo lo que ha impulsado el desarrollo de la medicina mitocondrial, pues las enfermedades mitocondriales pueden presentar una gran variabilidad en sus manifestaciones clínicas. Inicialmente, el estudio se enfocó en las mitocondriopatías, actualmente su enfoque se ha ampliado para

***Correspondencia:**
Fernando Minauro-Sanmiguel
E-mail: misaf73@gmail.com

Date of reception: 18-04-2024
Date of acceptance: 04-10-2024
DOI: 10.24875/BMHIM.24000058

Available online: 28-02-2025
Bol Med Hosp Infant Mex. 2025;82(1):7-14
www.bmhim.com

comprender y abarcar el papel de la mitocondria en el desarrollo de enfermedades, tanto de la edad pediátrica como de la edad adulta. El potencial de la mitocondria para mejorar las estrategias de diagnóstico, pronóstico y respuesta al tratamiento ha sido revelado por abordajes experimentales que emplean a la proteómica, la genómica y la metabolómica, para identificar biomarcadores con utilidad clínica que muestran el desarrollo de enfermedades. Por lo que la perspectiva de la medicina basada en mitocondrias reconoce la importancia de la generación de la evidencia científica relacionada con las mitocondrias y su papel en condiciones patológicas desde un enfoque integral.

Palabras clave: *Mitocondria. Enfermedades mitocondriales. Enfermedades crónicas no transmisibles. Enfermedades metabólicas.*

Introduction

The mitochondrion is the cellular organelle that regulates metabolism, cell signaling, and immune response; therefore, it requires coordination with other organelles and cellular niches to maintain cellular homeostasis. Disease disrupts this homeostasis or balance, and mitochondria register these changes, defining useful elements in recognizing and managing different diseases[1,2]. This relationship directly impacts medicine, as understanding the mitochondria-health-disease axis could improve decision-making and generate solutions in the context of mitochondria-based medicine.

Mitochondria possesses their own genome (mitochondrial DNA [mtDNA]); in humans, it contains 37 genes, 13 of which encode proteins related to oxidative phosphorylation (OXPHOS, the adenosine triphosphate [ATP] synthesis process)[3]; however, it contains a significant diversity of proteins (approximately 2000), such that the majority are encoded and imported from the nucleus[4]. mtDNA can also vary: a cell contains between 100 and 10,000 copies[3], which can have subtle differences and form populations (heteroplasmy) that could influence the health/disease phenotype. Furthermore, mitochondria communicate with virtually all cellular structures both intrinsically and extrinsically, as they make use of various extracellular structures (nanotubes, vesicles, and bloodstream) that allow them to establish long-distance communication; thus, they have also become attractive tools for the design of novel therapies[5,6].

Mitochondrial medicine

Initially, mitochondrial medicine focused on mitochondriopathies (inherited metabolic disorders that affect ATP synthesis)[7]. These diseases primarily present in childhood, although they can also appear in adults; they lack well-defined diagnostic criteria and treatment protocols, their symptoms are nonspecific, and the molecular defect is difficult to pinpoint, thus requiring different methodological strategies to resolve these ambiguities[8].

Mitochondriopathies are frequently confused with other pathologies (neuropathies, movement disorders, or heart diseases)[9,10], which can delay their diagnosis. For example, in cardiac diseases (one of the most frequent pediatric problems), mitochondrial alterations can go unnoticed and be treated inappropriately; hypertrophic cardiomyopathy[11] and tachycardias[12] associated with mitochondrial disease represent 20-40% of cases and present significantly higher mortality (71%) compared to patients without mitochondrial alterations (26%)[11]. This reveals that mitochondrial alterations are of utmost importance because, although they appear rare, their consequences can be substantial.

One of the most effective traditional approaches for determining mitochondriopathies is through catalytic activity assays that allow the identification of functional defects. However, these require various resources and involve invasive procedures (biopsies). At present, some strategies improve the diagnosis of mitochondriopathies; the proteins FGF21 and GDF15 (two mitokines found circulating in the blood) reflect mitochondrial damage and identify disease carriers[13]. Meanwhile, omic platforms define molecules that could guide a more accurate diagnosis and provide better monitoring of these diseases[14,15]. The diagnosis of a mitochondriopathy requires understanding the defect at the genetic level; conventional molecular biology strategies such as Sanger sequencing and polymerase chain reaction have relative success (≈6%) in determining genetic defects, in contrast to massive genome/exome sequencing strategies that achieve close to 45-60%, positioning themselves as the best diagnostic strategy[15,16].

On the other hand, proteomic analysis of primary human skin fibroblast cultures from patients with mitochondriopathy allows the detailing of the molecular mechanisms at the protein level[17]. Through metabolomics,

easily accessible biomarkers (metabolites) have been proposed with potential clinical utility in the development and treatment response of these diseases. Implementing these approaches improves the diagnosis of mitochondriopathies; however, their widespread use still requires corresponding clinical validation.

Mitochondrial alterations beyond mitochondriopathies

Non-communicable chronic diseases (NCDs) are long-term conditions and are the leading cause of death worldwide (80%)[18]. In these conditions, mitochondrial alterations can be found from their onset[19] and impact different processes that can be used to identify, monitor, or treat these diseases (Table 1), as well as extend diagnostic options and develop better mitochondria-targeted treatments (Table 2)[19,20].

This includes pediatric patients, as their main health conditions (obesity, diabetes, infections, among others) are related to mitochondria; therefore, the mitochondrial approach is very important in developing diagnostic tests and effective treatments. Mitochondria-related biomolecules (nucleic acids, proteins, and metabolites) can define useful elements in the stratification and pathophysiology of these diseases[21,22]. For example, in intractable childhood epilepsy, there are various mitochondrial aspects[23], such as variations between copy number and mtDNA damage[24,25] that are involved.

The outer mitochondrial membrane contains transporter complexes that activate the immune system: the translocase of the outer membrane, the sorting and assembly machinery and import machinery, as well as proteins sensitive to Damage Associated Molecular Patterns[26], whose alteration could indicate preferential signaling pathways associated with NCDs. Proteomic analysis of brain tumors in children and adults shows relevant participation of mitochondrial proteins; in fact, for glioblastomas, there are proposals for molecular classification that include mitochondrial categories[21,22]. Furthermore, in breast cancer, mitochondrial cristae are altered[27], and their evaluation could improve diagnosis and clinical monitoring, as their integrity and size are associated with the degree or advancement of malignancy[28]; in contrast, in gastric cancer, some mitochondrial proteins involved in energy metabolism (OXPHOS, TCA), mitochondrial dynamics (fusion/fission), and mitophagy[29] could function as early markers of the disease.

In cancer, energy metabolism (ATP synthesis) shifts in favor of anerobic glycolysis (Warburg effect) outside the mitochondria[30,31], such that mitochondria redirect their functions (Fig. 1)[30,32]. Based on this change, a bioenergetic signature was established to categorize prognosis in various types of cancer[33]. Furthermore, analysis of the mitochondrial proteome can distinguish different stages of cancer, with specific molecular events additional to this change in energy metabolism[34].

The distribution of mitochondria in the cell fluctuates and is found in different configurations, from bacteria-like units to tubular conglomerates extending and forming contact with other organelles[35]. Mitochondrial dynamics (fusion/fission processes) change notably in different pathologies, making their monitoring relevant in distinguishing health/disease. The mitochondrial arrangement reflects the metabolic-functional state and cellular health. A mitochondrial network increases oxidative capacity and is related to good health, while fragmentation into small units could indicate stress or the repair/degradation of damaged elements[35].

Mitochondrial dynamics is a quality control mechanism that requires specific proteins; some, like dynamin-like protein and dynamin-related protein, are related to processes involved in multiple pathologies[36]. Mitochondria continuously fluctuate in number, function, and form in response to inter- and intracellular stimuli, whether due to changes in location or metabolic rate (Fig. 1), grouping them according to energy demands[35].

Many pathologies involve mitochondrial dynamics; obesity, for example, has a particular interest in medical care as it is one of the main health problems in the pediatric population, and it implies and predicts other health problems such as infertility, hypertension, high cholesterol, and fatty liver, among others. Childhood obesity can lead to adult obesity with other health risks such as cardiovascular conditions and increased mortality rates[37]. It is interesting to note that these changes are described from the neonatal period and involve intrauterine processes since mothers with obesity during pregnancy have children who retain these changes after birth[38,39]. In this context, mitochondrial defects are usually found in energy metabolism, mtDNA mutations, increased oxidative stress, and, as mentioned, changes in mitochondrial dynamics. As a result, various therapeutic strategies targeting mitochondria have been proposed, such as the induction of thermogenesis or the use of natural molecules targeting mitochondria[40], like MOTS-c, which, in addition to decreasing body fat, regulates insulin sensitivity and metabolic homeostasis[41,42].

In this context, genomic variants and mitochondrial populations should be investigated considering their

Table 1. ECNTs with mitochondrial defects in their pathogenesis

Disease	Mitochondrial alteration	Cellular alterations
Obesity	Fragmentation, overproduction of mtROS, reduction of ETC components, decreased ATP synthesis, impaired membrane potential	Increased proliferation and differentiation, metabolic shift, and cell death.
Insulin resistance	Fragmentation, Ca+2 handling, mtROS production, MAM deregulation	Defective insulin-related signaling, decreased glucose uptake, GLUT4 translocation, defective insulin signaling, insulin resistance.
Type 2 diabetes mellitus	Respiratory uncoupling, decreased ATP synthesis, mitophagy, exacerbated fission/fusion	Decreased insulin secretion.
Cancer	Reduction of PGC-1α, increased mitophagy and glycolysis, moderate mtDNA mutations, metabolic hyperactivity	Metabolic shift, exacerbated biosynthesis, proliferation, tumorigenesis, aggressiveness, cell migration, and invasion.
Cardiovascular diseases	mtDNA damage, fragmentation, MAM deregulation, mtROS overproduction, Ca+2 handling defects, decreased oxygen consumption	Proliferation, hypertrophy, Ca+2 overload, energy crisis, impaired contractility, cell death.

mtROS: mitochondrial reactive oxygen species; ETC: electron transport chain; ATP: adenosine triphosphate; MAM: mitochondria-associated membranes; mtDNA: mitochondrial DNA (modified from 19).

Table 2. Treatment of NCDs through mitochondria-targeted molecules (*modified from 20*)

Type	Effect	Disease
Antioxidants	ROS neutralizers, SIRT activators based on CoQ	Neurodevelopment (Rett, Duchenne), Parkinson's, chronic kidney disease, among others.
Metabolism modulators	Niacin derivatives, metabolic (creatine, metformin), AMP kinase activators	Obesity, type 1 diabetes mellitus, myocardial infarction, liver disease (non-alcoholic).
PtPm inhibitors	Translocators, cyclophilin D	Acute kidney injury, Alzheimer's disease.

NCDs: non-communicable diseases; ROS: reactive oxygen species; SIRT: sirtuin; CoQ: Coenzyme Q; PtPm: permeability transition pore.

surroundings, as specific contacts with other organelles are established in the mitochondrial microenvironment. A mitochondrion can contact the endoplasmic reticulum (ER) and nucleus, with each interface involving different proteins[43]. The interaction with the ER is better understood where contacts occur through mitochondria-associated membranes (MAMs)[44]; the proteins located there are required for common activities (mitochondrial dynamics, calcium homeostasis, transport, among others) and become highly responsive metabolic platforms[44]. Regarding nucleus-mitochondria interaction, it has been observed that it regulates OXPHOS performance and determines somatic heteroplasmy dynamics[45].

MAMs participate in signaling and maintenance of cellular homeostasis44,46, contain regulatory proteins and tumor suppressors[47], and activate the immune system, as they harbor inflammasomes (Nlrp3: NOD-[nucleotide-binding oligomerization domain), LRR-Leucine rich repeats domain and pyrin domain-containing protein 3) which are activated during microbial infections or by interleukin secretion in the inflammatory response[48,49]. In common pediatric infections, such as *Mycobacterium tuberculosis*, *Proteus mirabilis*, *Escherichia coli*, *Salmonella enterica*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and Plasmodium *falciparum*, there is generally an increase in reactive oxygen species, metabolic changes, and apoptosis, which occur through mitochondrial mediation; furthermore, it should be considered that various antibiotic treatments can damage mitochondrial function. Microbial pathogenicity is closely linked to mitochondrial damage, as many products derived from bacterial infections, such as nitric oxide, are respiratory complex inhibitors; the molecular and structural alterations of mitochondria caused by pathogens and treatments show great adaptability and therefore, their potential as therapeutic targets[50].

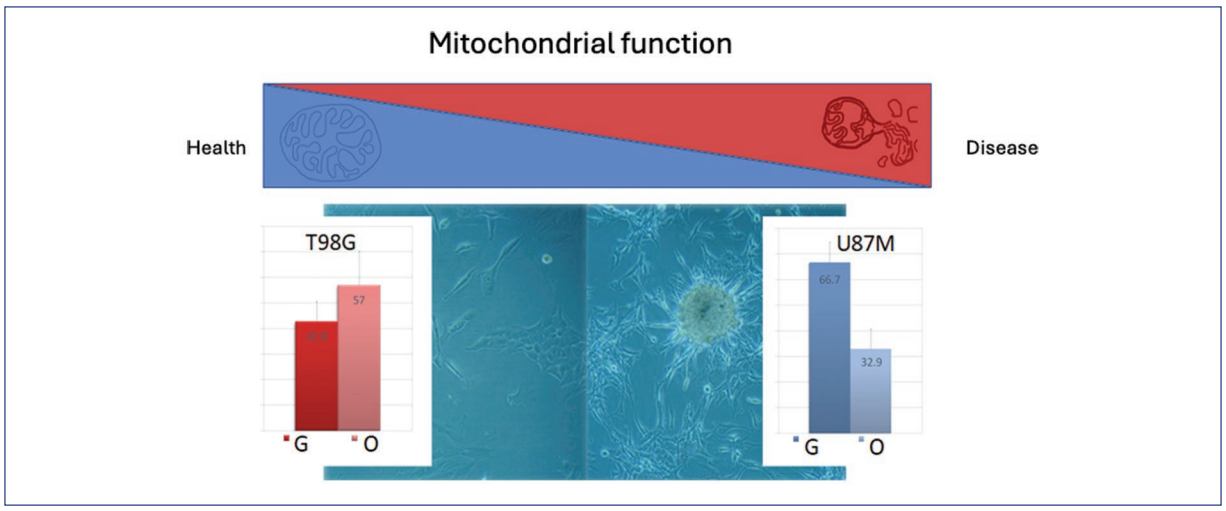


Figure 1. The transition to disease as a result of mitochondrial deterioration and resulting homeostatic loss. In cancer, mitochondria can follow the course of the disease and accompany disease progression (red triangle); the same occurs with non-communicable diseases, enabling the search for early markers of various diseases. In health, mitochondria are functional and structurally intact (blue triangle). In a glioblastoma cell model, less aggressive cancer (T98G cells) follows a more oxidative metabolism (O), as occurs in healthy cells, while advanced glioblastoma (U87 cells), where cells tend to form tumors, the metabolism becomes glycolytic (G), and mitochondrial structure is fragmented. This transition is associated with the dominance of certain metabolic pathways and structural changes in the mitochondria.

Other proteins in MAMs are involved in neurodegenerative diseases: Presenilin 1 and 2 (PSEN1 and PSEN2) in Alzheimer's; DJ1, Parkin (Park) 1 and 2, and Pink in Parkinson's; while AKT, mTORC2, GSK3b, and PTEN are involved in diabetes, and Sig1 in breast, liver, and colon cancer, among others[44].

MAMs also contain chaperones generated during the unfolded protein response (UPR), which is involved in stress response and the biogenesis of various pathologies where nucleus-mitochondria communication is established[51,52] and induces a response according to the stimulus. For example, when faced with a stressor, a transcriptional response can be activated, producing proteins safeguarded by chaperones while they achieve their functional structure. The UPR is distributed in MAMs[53,54] and regulates synthesis/alarm (apoptosis) cycles (Figs. 1 and 2), which is exacerbated in various diseases and infections[55]. Therefore, the UPR proteins involved could serve as biomarkers or therapeutic targets.

Therapeutic possibilities

There are several areas of interest for mitochondrial therapeutics, primarily focused on disease diagnosis, prognosis, and treatments. One of these approaches is through extracellular vesicles (EVs)[56], which function in biomolecule transport and communication between cells and tissues[57,58]. Their content varies according to biological conditions[5], and one advantage of EVs is that they are found in easily accessible fluids such as blood, saliva, and urine. The content of EVs can reach different tissues and influence the function, signaling, and regulation of various biological processes; they can also contain complete mitochondria or fragments, and there are even mitochondria-derived vesicles whose content has demonstrated diagnostic and therapeutic utility[59-61]. In experimental models, EVs correct the energy imbalance produced by ischemic, dilated, and hypertrophic heart diseases[62]. In disease, the number and diversity of EVs are exacerbated and affect different metabolic pathways[34,58,59,63], so identifying their content could benefit the clinical approach to various diseases[5,63,64].

Therapeutic targets for mitochondria-based medicine

Mitochondria-based medicine is founded on metabolic changes caused by disease[32,65,66], thus functioning as a sensor for different clinical phases and stages, which could help define various biomarkers to facilitate treatment selection. Regarding treatment, there is a wide variety of antioxidant reagents, both natural and designed, that can target mitochondria to prevent, modulate, or treat NCDs[67]. For example, mitocans prevent cancer

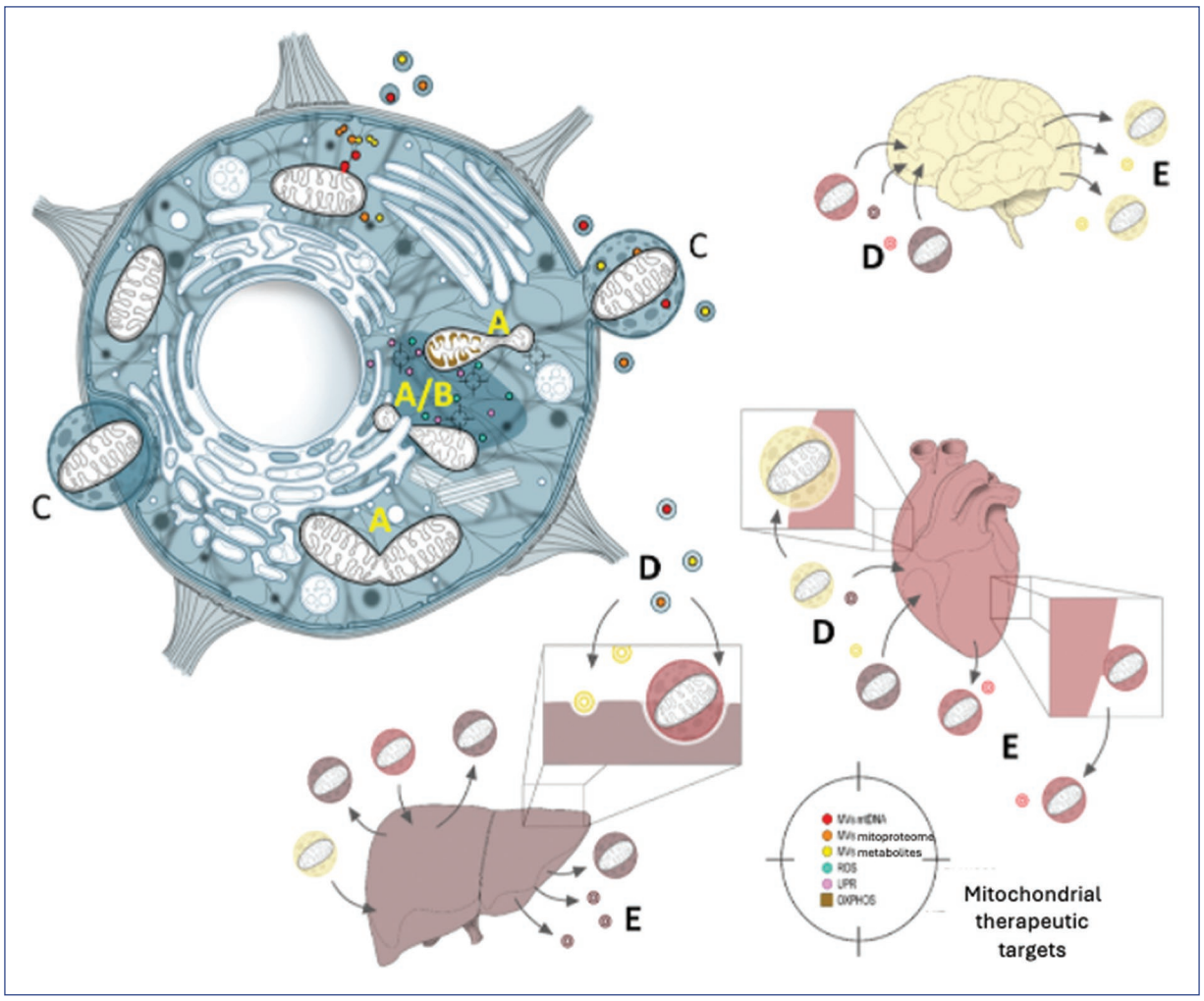


Figure 2. Mitochondria have great communication capacity at intra- and intercellular levels with various capabilities that can be used as therapeutic targets: At the intracellular level, fusion/fission (A/B) can signal different events in non-communicable disease pathogenesis as the damage caused leads to mitochondrial dysfunction. Likewise, mitochondria obtain information from the environment (unfolded protein response response, mitochondria-associated membranes), communicate with other cell organelles, and carry diverse information in extracellular vesicles (C, MVs) where they can even be contained completely and, in turn, can be directed to other targets or tissues such as brain, heart, or liver among others, through the bloodstream (D). The mitochondrial content they carry could activate (incoming arrows) a response to disease or release warning messages (E, outgoing arrows), a useful process in designing therapeutic strategies.

progression or drug resistance, and several of these can be easily manipulated[68,69]. Mitochondria have great inter- and intracellular communication capacity, making them novel therapeutic options, such as mitochondrial transplantation, which was conceived to restore or recover optimal functional and structural states of cells comprising the organ[70,71]. Mitochondrial transplantation emerges as a treatment strategy due to mitochondria's ability to transfer from one cell to another, particularly when mitochondrial damage exists. It could thus function as a treatment for diseases where typical therapies have not been effective. The process involves obtaining mitochondria (from adipose tissue, liver, or muscle) from a donor and transplanting them intranasally or by injection (systemic delivery) and has been tested primarily in murine models. Transfer can be facilitated using peptides that aid membrane absorption. At present, the technique's application focuses mainly on assisted reproduction to prevent transmission of mitochondrial diseases from mother to child; however, it has not been applied as a treatment for children who already have diseases[72]. Research is currently being conducted to evaluate its viability and safety as therapy for pediatric mitochondrial diseases[73,74] such as Leigh syndrome, Mitochondrial

Encephalopathy with Lactic Acidosis and Stroke-like episodes, Kearns-Sayre syndrome, Leber's Hereditary Optic Neuropathy, or mtDNA depletion syndrome.

There are still several challenges regarding mitochondrial transplantation for treating existing diseases, as ethical and biosafety considerations must be addressed. However, it is important to note that although the therapeutic potential is promising, widespread clinical application requires more research[75]. While the clinical potential of mitochondria is evident, there are limitations to their implementation. Much of our current information comes from biological models[76] or has only been determined in small population samples and may vary. In addition, proteins with multiple functions require further studies about their role. Such is the case of ATP synthase and its intrinsic inhibitor (IF1)[77] or sigma 1 receptor (a MAM chaperone)[78], which perform multiple functions according to their location or interactions. Therefore, the identification and validation of mitochondria-related biomarkers, as well as the development of targeted therapies, offer new perspectives in disease diagnosis and treatment, making mitochondria-based medicine a field of research and clinical application of growing relevance. Thus, information about mitochondrial function and its byproducts becomes central aspects in the health/disease balance that can be approached as potential therapeutic targets (Fig. 2).

Conclusions

Mitochondria-based medicine emerges as a promising field of research and clinical application for treating diseases acquired in childhood or NCDs. This approach focuses on understanding how mitochondrial alterations can trigger and contribute to developing these diseases. Mitochondria-based medicine contributes to developing options targeting these organelles, offering new perspectives on disease understanding and treatment, including personalized approaches.

In a context where complex and multifactorial diseases represent a significant challenge for contemporary medicine, mitochondria-based medicine opens new opportunities to advance patient care and quality of life.

Acknowledgments

The authors thank Carlos Saldaña for his help with the design and visualization of figure 2.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Tian C, Liu Y, Li Z, Zhu P, Zhao M. Mitochondria related cell death modalities and disease. Front Cell Dev Biol. 2022;10:832356.
2. Yapa NM, Lisnyak V, Reljic B, Ryan MT. Mitochondrial dynamics in health and disease. FEBS Lett. 2021;595:1184-204.
3. Chinnery PF, Hudson G. Mitochondrial genetics. Br Med Bull. 2013;106:135-59.
4. Maity S, Chakrabarti O. Mitochondrial protein import as a quality control sensor. Biol Cell. 2021;113:375-400.
5. Shanmughapriya S, Langford D, Natarajaseenivasan K. Inter and intracellular mitochondrial trafficking in health and disease. Ageing Res Rev. 2020;62:101128.
6. Al Amir Dache Z, Thierry AR. Mitochondria-derived cell-to-cell communication. Cell Rep. 2023;42:112728.
7. DiMauro S. A brief history of mitochondrial pathologies. Int J Mol Sci. 2019;20:5643.
8. Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, McFarland R, et al. Mitochondrial diseases. Nat Rev Dis Primers. 2016;2:16080.
9. Flønes IH, Tzoulis C. Movement disorders in mitochondrial disease: a clinicopathological correlation. Curr Opin Neurol. 2018;31:472-83.
10. Meyers DE, Basha HI, Koenig MK. Mitochondrial cardiomyopathy: pathophysiology, diagnosis, and management. Tex Heart Inst J. 2013;40:385-94.
11. Brunel-Guitton C, Levtova A, Sasarman F. Mitochondrial diseases and cardiomyopathies. Can J Cardiol. 2015;31:1360-76.
12. Heinzmann D, Klingel K, Müller K, Kumbrink J, Kirchner T, Schreieck J, et al. Mitochondrial dynamics in tachycardiomyopathy. Cell Physiol Biochem. 2019;52:435-8.
13. Li Y, Li S, Qiu Y, Zhou M, Chen M, Hu Y, et al. Circulating FGF21 and GDF15 as biomarkers for screening, diagnosis, and severity assessment of primary mitochondrial disorders in children. Front Pediatr. 2022;10:851534.
14. Rahman J, Rahman S. Mitochondrial medicine in the omics era. Lancet. 2018;391:2560-74.
15. Legati A, Reyes A, Nasca A, Invernizzi F, Lamantea E, Tiranti V, et al. New genes and pathomechanisms in mitochondrial disorders unraveled by NGS technologies. Biochim Biophys Acta. 2016;1857:1326-35.
16. Schon KR, Ratnaike T, van den Ameele J, Horvath R, Chinnery PF. Mitochondrial diseases: a diagnostic revolution. Trends Genet. 2020;36:702-17.
17. Salvador-Severo K, Gómez-Caudillo L, Quezada H, García-Trejo JJ, Cárdenas-Conejo A, Vázquez-Memije ME, et al. Mitochondrial proteomic profile of complex IV deficiency fibroblasts: rearrangement of oxidative phosphorylation complex/supercomplex and other metabolic pathways. Bol Med Hosp Infant Mex. 2017;74:175-80.
18. Gong JB, Yu XW, Yi XR, Wang CH, Tuo XP. Epidemiology of chronic noncommunicable diseases and evaluation of life quality in elderly. Aging Med (Milton). 2018;1:64-6.
19. Diaz-Vegas A, Sanchez-Aguilera P, Krycer JR, Morales PE, Monsalves-Alvarez M, Cifuentes M, et al. Is mitochondrial dysfunction a common root of noncommunicable chronic diseases? Endocr Rev. 2020;41:bnaa005.

20. Wang W, Karamanlidis G, Tian R. Novel targets for mitochondrial medicine. Sci Transl Med. 2016;8:326rv3.
21. Garofano L, Migliozzi S, Oh YT, D'Angelo F, Najac RD, Ko A, et al. Pathway-based classification of glioblastoma uncovers a mitochondrial subtype with therapeutic vulnerabilities. Nat Cancer. 2021;2:141-56.
22. Lasorella A, Iavarone A. The making of the glioblastoma classification. Br J Cancer. 2021;125:4-6.
23. Moos WH, Faller DV, Glavas IP, Kanara I, Kodukula K, Pernokas J, et al. Epilepsy: mitochondrial connections to the "sacred" disease. Mitochondrion. 2023;72:84-101.
24. Luna B, Bhatia S, Yoo C, Felty Q, Sandberg DI, Duchowny M, et al. Proteomic and mitochondrial genomic analyses of pediatric brain tumors. Mol Neurobiol. 2015;52:1341-63.
25. Luna B, Bhatia S, Yoo C, Felty Q, Sandberg DI, Duchowny M, et al. Bayesian network and mechanistic hierarchical structure modeling of increased likelihood of developing intractable childhood epilepsy from the combined effect of mtDNA variants, oxidative damage, and copy number. J Mol Neurosci. 2014;54:752-66.
26. Banoth B, Cassel SL. Mitochondria in innate immune signaling. Transl Res. 2018;202:52-68.
27. Vincent AE, Ng YS, White K, Davey T, Mannella C, Falkous G, et al. The spectrum of mitochondrial ultrastructural defects in mitochondrial myopathy. Sci Rep. 2016;6:30610.
28. Putignani L, Raffa S, Pescosolido R, Rizza T, Del Chierico F, Leone L, et al. Preliminary evidences on mitochondrial injury and impaired oxidative metabolism in breast cancer. Mitochondrion. 2012;12:363-9.
29. Yang H, Li Y, Hu B. Potential role of mitochondria in gastric cancer detection: fission and glycolysis. Oncol Lett. 2021;21:439.
30. Potter M, Newport E, Morten KJ. The Warburg effect: 80 years on. Biochem Soc Trans. 2016;44:1499-505.
31. Warburg O. On respiratory impairment in cancer cells. Science. 1956;124:269-70.
32. Obre E, Rossignol R. Emerging concepts in bioenergetics and cancer research: metabolic flexibility, coupling, symbiosis, switch, oxidative tumors, metabolic remodeling, signaling and bioenergetic therapy. Int J Biochem Cell Biol. 2015;59:167-81.
33. Isidoro A, Martínez M, Fernández PL, Ortega AD, Santamaría G, Chamorro M, et al. Alteration of the bioenergetic phenotype of mitochondria is a hallmark of breast, gastric, lung and oesophageal cancer. Biochem J. 2004;378:17-20.
34. Gómez-Caudillo L, Ortega-Lozano AJ, Martínez-Batallar ÁG, Rosas-Vargas H, Minauro-Sanmiguel F, Encarnación-Guevara S. Principal component analysis on LCMS/MS and 2DEMALDITOF in glioblastoma cell lines reveals that mitochondria act as organelle sensors of the metabolic state in glioblastoma. Oncol Rep. 2020;44:661-73.
35. Rambold AS, Pearce EL. Mitochondrial dynamics at the interface of immune cell metabolism and function. Trends Immunol. 2018;39:6-18.
36. Chan DC. Mitochondrial dynamics and its involvement in disease. Annu Rev Pathol. 2020;15:235-59.
37. Wang J, Lin X, Zhao N, Dong G, Wu W, Huang K, et al. Effects of mitochondrial dynamics in the pathophysiology of obesity. Front Biosci. 2022;27:107.
38. Abraham M, Collins CA, Flewelling S, Camazine M, Cahill A, Cade WT, et al. Mitochondrial inefficiency in infants born to overweight African-American mothers. Int J Obes. 2018;42:1306-16.
39. Silveira MA, Marcondes JP, Lara JR, Scarano WR, Calderón IM, Rudge MV, et al. Mitochondrial-related gene associated to obesity can be modulated by in utero hyperglycemic environment. Reprod Toxicol. 2019;85:59-64.
40. Zheng Y, Yang N, Pang Y, Gong Y, Yang H, Ding W, et al. Mitochondria-associated regulation in adipose tissues and potential reagents for obesity intervention. Front Endocrinol. 2023;14:1132342.
41. Reynolds JC, Lai RW, Woodhead JS, Joly JH, Mitchell CJ, Cameron-Smith D, et al. MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis. Nat Commun. 2021;12:470.
42. Zheng Y, Wei Z, Wang T. MOTS-c: a promising mitochondrial-derived peptide for therapeutic exploitation. Front Endocrinol. 2023;14:1120533.
43. Kwak C, Shin S, Park JS, Jung M, Nhung TTM, Kang MG, et al. Contact-ID, a tool for profiling organelle contact sites, reveals regulatory proteins of mitochondrial-associated membrane formation. Proc Natl Acad Sci U S A. 2020;117:12109-20.
44. Perrone M, Caroccia N, Genovese I, Missiroli S, Modesti L, Pedriali G, et al. The role of mitochondria-associated membranes in cellular homeostasis and diseases. Int Rev Cell Mol Biol. 2020;350:119-96.
45. Lechuga-Vieco AV, Latorre-Pellicer A, Johnston IG, Prota G, Gileadi U, Justo-Méndez R, et al. Cell identity and nucleo-mitochondrial genetic context modulate OXPHOS performance and determine somatic heteroplasmy dynamics. Sci Adv. 2020;6:eaba5345.
46. Patergnani S, Bouhamida E, Leo S, Pinton P, Rimessi A. Mitochondrial oxidative stress and "mito-inflammation": actors in the diseases. Biomedicines. 2021;9:216.
47. Marchi S, Giorgi C, Oparka M, Duszynski J, Wieckowski MR, Pinton P. Oncogenic and oncosuppressive signal transduction at mitochondria-associated endoplasmic reticulum membranes. Mol Cell Oncol. 2014;1:e956469.
48. Elliott EI, Miller AN, Banoth B, Iyer SS, Stotland A, Weiss JP, et al. Cutting edge: mitochondrial assembly of the NLRP3 inflammasome complex is initiated at priming. J Immunol. 2018;200:3047-52.
49. Mills EL, Kelly B, O'Neill LA. Mitochondria are the powerhouses of immunity. Nat Immunol. 2017;18:488-98.
50. Romero-Cordero S, Kirwan R, Noguera-Julian A, Cardellach F, Fortuny C, Morén C. A mitocentric view of the main bacterial and parasitic infectious diseases in the pediatric population. Int J Mol Sci. 2021;22:3272.
51. Wang S, Gao K, Liu Y. UPR coordinates immunity to maintain mitochondrial homeostasis and animal fitness. Mitochondrion. 2018;41:9-13.
52. Anderson NS, Haynes CM. Folding the mitochondrial UPR into the integrated stress response. Trends Cell Biol. 2020;30:428-39.
53. Jovaisaite V, Auwerx J. The mitochondrial unfolded protein response-synchronizing genomes. Curr Opin Cell Biol. 2015;33:74-81.
54. Saito A, Imaizumi K. Unfolded protein response-dependent communication and contact among endoplasmic reticulum, mitochondria, and plasma membrane. Int J Mol Sci. 2018;19:3215.
55. Zhu L, Zhou Q, He L, Chen L. Mitochondrial unfolded protein response: an emerging pathway in human diseases. Free Radic Biol Med. 2021;163:125-34.
56. Zhang S, Mulder C, Riddle S, Song R, Yue D. Mesenchymal stromal/stem cells and bronchopulmonary dysplasia. Front Cell Dev Biol. 2023;11:1247339.
57. Yuana Y, Sturk A, Nieuwland R. Extracellular vesicles in physiological and pathological conditions. Blood Rev. 2013;27:31-9.
58. Liu D, Dong Z, Wang J, Tao Y, Sun X, Yao X. The existence and function of mitochondrial component in extracellular vesicles. Mitochondrion. 2020;54:122-7.
59. Todkar K, Chikhi L, Desjardins V, El-Mortada F, Pépin G, Germain M. Selective packaging of mitochondrial proteins into extracellular vesicles prevents the release of mitochondrial DAMPs. Nat Commun. 2021;12:1971.
60. Puhm F, Afonyushkin T, Resch U, Obermayer G, Rohde M, Penz T, et al. Mitochondria are a subset of extracellular vesicles released by activated monocytes and induce type I IFN and TNF responses in endothelial cells. Circ Res. 2019;125:43-52.
61. Martínez-Ezquerro JD. El Epigenoma Circulante; 2020. Available from: https://osf.io/87wbu
62. Ikeda G, Santoso MR, Tada Y, Li AM, Vaskova E, Jung JH, et al. Mitochondria-rich extracellular vesicles from autologous stem cell-derived cardiomyocytes restore energetics of ischemic myocardium. J Am Coll Cardiol. 2021;77:1073-88.
63. Berridge MV, Neuzil J. The mobility of mitochondria: intercellular trafficking in health and disease. Clin Exp Pharmacol Physiol. 2017;44 Suppl 1:15-20.
64. Picca A, Guerra F, Calvani R, Coelho-Junior HJ, Bossola M, Landi F, et al. Generation and release of mitochondrial-derived vesicles in health, aging and disease. J Clin Med Res. 2020;9:1440.
65. Burns JS, Manda G. Metabolic pathways of the warburg effect in health and disease: perspectives of choice, chain or chance. Int J Mol Sci. 2017;18:2755.
66. Dard L, Blanchard W, Hubert C, Lacombe D, Rossignol R. Mitochondrial functions and rare diseases. Mol Aspects Med. 2020;71:100842.
67. Mani S, Swargiary G, Singh KK. Natural agents targeting mitochondria in cancer. Int J Mol Sci. 2020;21:6992.
68. Oliver D, Reddy PH. Dynamics of dynamin-related protein 1 in Alzheimer's disease and other neurodegenerative diseases. Cells. 2019;8:961.
69. Marzetti E, Calvani R, Cesari M, Buford TW, Lorenzi M, Behnke BJ, et al. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. Int J Biochem Cell Biol. 2013;45:2288-301.
70. McCully JD, Cowan DB, Emani SM, Del Nido PJ. Mitochondrial transplantation: from animal models to clinical use in humans. Mitochondrion. 2017;34:127-34.
71. Liu Z, Sun Y, Qi Z, Cao L, Ding S. Mitochondrial transfer/transplantation: an emerging therapeutic approach for multiple diseases. Cell Biosci. 2022;12:66.
72. Zou W, Slone J, Cao Y, Huang T. Mitochondria and their role in human reproduction. DNA Cell Biol. 2020;39:1370-8.
73. Zhou M, Yu Y, Luo Y, Luo X, Zhang Y, Zhou X, et al. Mitochondrial transplantation: a unique treatment strategy. J Cardiovasc Pharmacol. 2022;79:759-68.
74. Koene S, Hendriks JC, Dirks I, de Boer L, de Vries MC, Janssen MC, et al. International paediatric mitochondrial disease scale. J Inherit Metab Dis. 2016;39:705-12.
75. Kubat GB. Mitochondrial transplantation and transfer: the promising method for diseases. Turk J Biol. 2023;47:301-12.
76. Malty RH, Jessulat M, Jin K, Musso G, Vlasblom J, Phanse S, et al. Mitochondrial targets for pharmacological intervention in human disease. J Proteome Res. 2015;14:5-21.
77. Gatto C, Grandi M, Solaini G, Baracca A, Giorgio V. The F1Fo-ATPase inhibitor protein IF1 in pathophysiology. Front Physiol. 2022;13:917203.
78. Hayashi T. Sigma-1 receptor: the novel intracellular target of neuropsychotherapeutic drugs. J Pharmacol Sci. 2015;127:2-5.

Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

REVIEW ARTICLE

Antibiotic therapy in dysentery of infectious etiology in early childhood: a systematic scoping review

Juan F. Guevara-Ramírez[1], Andrés F. Rodríguez-Gutiérrez[1], Ingrid S. Sánchez-Escobar[1], Samuel D. Bolaños-Rodríguez[1], Valentina Adames-Restrepo[1], Simón A. Ruiz-Galvis[1], Valentina Sánchez-Sánchez[1], Néstor A. De La Cruz-Torres[1], Erwin H. Hernández-Rincón[2], and Samuel D. Barbosa[3,4,5]*

[1]Faculty of Medicine, Universidad de La Sabana, Chía, Cundinamarca, Colombia; [2]Department of Family Medicine and Public Health, School of Medicine, Faculty of Medicine, Universidad de La Sabana, Chía, Cundinamarca, Colombia; [3]Colegio Médico Colombiano, Bogotá, Colombia; [4]Universitat Oberta de Catalunya, Barcelona, Cataluña, España; [5]Sociedad Colombiana de Pediatría, Bogotá, Colombia

Abstract

Acute diarrhea (AD) is one of the leading causes of child mortality, particularly in children under 5 years old. Dysentery, a severe form of AD characterized by blood and mucus in the stool, raises controversies regarding the appropriate use of antibiotics. The objective of this manuscript is to synthesize the available information on the indications, risks, and benefits of antibiotics used in infectious dysentery during early childhood. A scoping systematic review was conducted using international reference documents and the databases PubMed, Scopus, and Google Scholar, following the PRISMA-ScR guidelines. Studies from 2014 onwards that addressed antibiotic management in children under 5 years old with bacterial or parasitic dysentery were included. Among the 39 selected studies, the evidence shows limited benefits and significant risks associated with antibiotic use, with recommendations varying based on specific etiology and the patient's clinical conditions, where it is evident that the rational use of antibiotics in pediatric dysentery is crucial to avoid bacterial resistance and adverse effects. There is a need for future research to establish guidelines based on robust clinical trials, to optimize targeted treatment and improve clinical outcomes in this population.

Keywords: *Dysentery. Antibiotics. Children. Diarrhea. Infantile. Drug Resistance. Microbial.*

Antibioticoterapia en la disentería de etiología infecciosa en la primera infancia: una revisión sistemática panorámica

Resumen

La enfermedad diarreica aguda (EDA) es una de las principales causas de mortalidad infantil, especialmente en menores de 5 años. La disentería, una forma severa de EDA con sangre y moco en las heces, genera controversias sobre el uso adecuado de antibióticos. El objetivo de este manuscrito es sintetizar la información disponible sobre las indicaciones, riesgos y beneficios de los antibióticos en la disentería infecciosa en la primera infancia. Se realizó una revisión sistemática panorámica utilizando documentos de referencia internacional y las bases de datos PubMed, Scopus y Google Scholar, siguiendo los lineamientos PRISMA-ScR. Se incluyeron estudios desde 2014 que abordaran el manejo antibiótico en menores de 5 años con disentería

***Correspondence:**
Juan F. Guevara-Ramírez
E-mail: juanguera@unisabana.edu.co

Date of reception: 19-06-2024
Date of acceptance: 09-09-2024
DOI: 10.24875/BMHIM.24000085

Available online: 28-02-2025
Bol Med Hosp Infant Mex. 2025;82(1):15-27
www.bmhim.com

de origen bacteriano o parasitario. De 39 documentos seleccionados, la evidencia muestra beneficios limitados y riesgos significativos en el uso de antibióticos, con recomendaciones que varían según la etiología específica y las condiciones clínicas del paciente, donde se evidencia que el uso racional de antibióticos en disentería infantil es crucial para evitar la resistencia bacteriana y efectos adversos. Se destaca la necesidad de investigaciones futuras para establecer guías basadas en ensayos clínicos robustos, que optimicen el tratamiento dirigido y mejoren los resultados clínicos en esta población.

Palabras clave: *Disentería. Antibióticos. Niños. Diarrea Infantil. Farmacorresistencia. Microbiana.*

Introduction

Acute diarrheal disease (ADD) accounts for 8.6% of infant mortality. It is one of the main reasons for medical consultation worldwide, primarily in children under 5 years of age (early childhood). It is the fourth leading cause of such outcomes in 499 thousand patients affected by this condition[1]. Most of these cases are due to complications such as dehydration from the number of stools, oral intolerance, and septic shock related to acute gastroenteritis, defined as any gastrointestinal infection lasting < 2 weeks[2], clinically identified by at least three episodes of liquid or watery stools within 24 h, usually associated with fever and emetic episodes[3].

One of its clinical manifestations is dysentery, characterized by the presence of blood and mucus in stools, which can occur due to different infectious agents and their biological toxins (Table 1), causing an intestinal inflammatory process with polymorphonuclear infiltrates leading to mucosal ulcers, hemorrhage, production of peptide cytokines that generate changes in metabolism, appetite, and loss of nutrients and body fluids, clinically referred to as a "dysenteric syndrome," which also includes certain associated symptoms such as fever, colic, tenesmus, and straining[2,3].

This phenomenon represents a major challenge in reaching consensus and institutional proposals, including those from international organizations such as the World Health Organization (WHO)[4], Pan American Health Organization (PAHO)[5], and the Infectious Diseases Society of America (IDSA)[6]. These bodies have not managed to align on universal proposals that would establish definitive and clear recommendations for standardized empirical management.

The lack of clear protocols for managing dysentery in early childhood has been a significant issue since the original 2005 WHO guidelines on ADD management, which remain current. This originates from their recommendation to empirically administer antibiotic therapy for dysentery in early childhood without demonstrating which studies at that time supported such a decision, along with the scarcity of specific studies in children under 5 years of age across indexed databases and grey literature. All of this has resulted in a lack of international consensus on adjunctive management beyond the rehydration inherent to conventional ADD treatment, which aims to reduce symptom intensity and duration regardless of etiology[7]. One of the key issues in this context is whether or not to administer antibiotic therapy to the affected patients.

Table 1. Relevant micro-organisms in early childhood dysentery

Bacteria	Parasites
*Escherichia coli**	*Entamoeba histolytica*
Salmonella	*Cystoisospora*
Shigella	*Cyclospora cayetanensis*
Campylobacter	
Clostridioides difficile	
Yersinia enterocolitica	

Source: Authors' own elaboration based on information extracted from Kliegman et al.[1], Levy[27].
*Includes Shiga toxin-producing bacteria (STEC).

This article aims to synthesize the available evidence from the last 10 years addressing the following question: in early childhood children with dysentery of infectious etiology, what are the indications, risks, and benefits of antibiotic therapy compared to non-administration? Given the limited available information, conducting a panoramic systematic review was deemed appropriate to gather information from various sources, obtaining an overview of the topic with emphasis on available information and identifiable knowledge gaps for each possible bacterial and parasitic micro-organism.

This has been viewed as an opportunity for rational antibiotic use in the everyday clinical setting of pediatricians and primary care physicians, calling attention to a critical and updated perspective due to its clinical impact in a world striving to reduce bacterial resistance through clear indications and correct dosing. In addition, it aims to avoid unfavorable outcomes when antibiotics are not indicated, which affect not only the individual and their family but also the community at large[1].

Method

Study design

A scoping review of medical literature was conducted to evaluate the available evidence on the indications, risks, and benefits of antibiotic therapy in infectious dysentery during early childhood. This review followed international guidelines established by the Enhancing the Quality and Transparency of Health Research network, using their PRISMA Extension for Scoping Reviews (PRISMA-ScR)[8] guidance.

Search strategy

The search was conducted in PubMed, Scopus, UpToDate, and Google Scholar databases, as well as in gray literature, using the following search terms in English and their Spanish equivalents: ("Antibiotics" OR "Antibiotic therapy") AND "Dysentery" AND ("Bacteria" OR "Parasite" NOT "Virus") AND ("Infant" OR "Children" NOT "Adults"). The search strategy was designed to capture the largest possible number of relevant studies, ensuring a comprehensive and transparent evaluation of the studies found and available for review.

Study selection

Studies were selected based on the following predefined criteria:

- Inclusion criteria: Publication from 2014 onwards, complete document with available access, studies including children under 5 years with dysentery of bacterial or parasitic origin, written in Spanish or English. Study types had to be meta-analyses, review articles, analytical and experimental studies, guideline documents, or management references
- Exclusion criteria: Publications before 2014, studies on prophylactic antibiotic management, or non-scientific sources.

Selection process

Search results were managed bibliographically using Mendeley reference software after duplicate studies were removed. Titles and abstracts of identified manuscripts were evaluated to determine their eligibility for full-text review and subsequent extraction of their analyses and conclusions for synthesis and comparison with other sources found in the text, according to each infectious etiology. This allowed for identifying common patterns and discrepancies among recommendations regarding antibiotic use in our target population.

Data extraction and analysis

Relevant data regarding recommendations, population characteristics, isolates, and association measures were extracted from the selected studies, identifying possible indications, risks, and benefits of antibiotic use in infectious dysentery in children under 5 years of age.

Study characteristics, design, sample size, main outcomes, and recommendations were considered in writing this article as a practical aid for primary care physicians and general pediatricians who face this clinical challenge. This information is presented through synthesis tables and sections in the subsequent discussion of the article. In addition, secondary references from the main articles contributing to the development were included.

Results

Following the described processes, 39 documents were selected for complete review. These included 18 reference articles and consensus statements and 15 additional studies discussed in detail (Fig. 1).

The analysis proceeded from an initial general approach toward identifying specific etiologies and particular situations of infectious dysentery in early childhood. From the selected documents, the following types of studies were identified:

- Two narrative reviews
- Two cross-sectional studies
- Two cohort studies
- One case–control study
- Three systematic reviews
- One meta-analysis
- One clinical trial.

Table 2 synthesizes the main findings from these studies, providing a comprehensive overview of the different perspectives and available data.

Antibiotic therapy regimens

The respective dosing schedules found for each indication are summarized in table 3. This table provides a detailed summary of the different antibiotic regimens currently recommended by international expert societies in this field of study, along with those used in intervention articles identified after the search process,

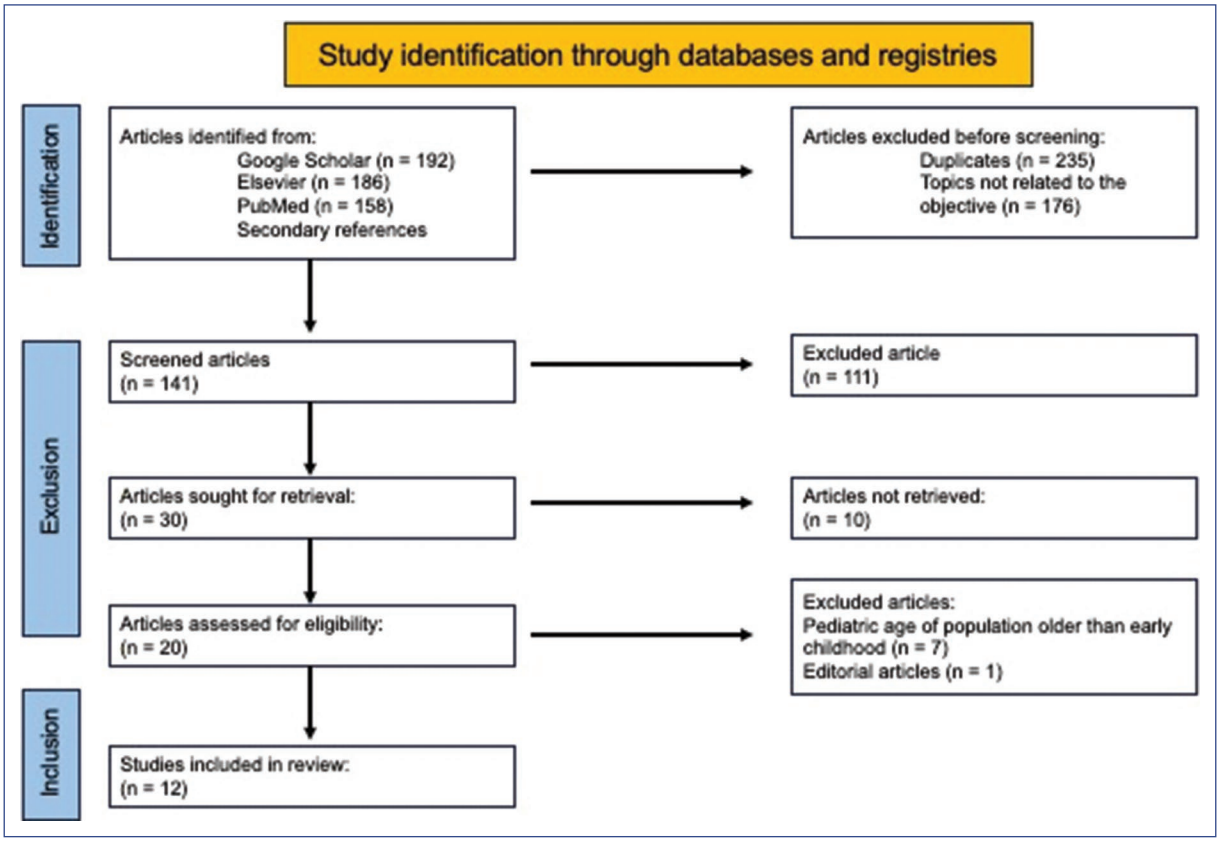


Figure 1. PRISMA flow chart for study selection.

based on specific etiology and the patient's clinical conditions as appropriate.

Discussion

Isolates and empirical management

Implementing new technologies for diagnosing and isolating specific pathogens in dysentery has undergone multiple changes, facilitating the identification of causative micro-organisms. Despite this, at the international level, no consensus indicates how to direct antimicrobial therapy in the pediatric population with infectious dysentery[7].

The only current international guideline on empirical management of dysentery in early childhood is WHO's fourth edition recommendations from 2005, which suggests 3 days of ciprofloxacin or 5 days of another antimicrobial effective against local *Shigella* strains[4]. Although this controversial point was mentioned without supporting clinical trials or studies, the use of nalidixic acid is discouraged, apparently due to increased antibiotic resistance against this antimicrobial[4]. In contrast, the Procedures Manual for the Integrated Management of Childhood Illness written by PAHO does recommend it as the first-line treatment based on expert consensus due to the risk of complications from dysenteric syndrome, given the difficulty in patient follow-up and limited resources in the areas where it is applied[5]. However, considering the recent changes in international antibiotic resistance patterns, it coincides with the WHO reference document in not citing studies supporting this decision.

In 2017, IDSA initiated an approach not previously mentioned by these two prior organizations, which was to give precedence to microbiological diagnosis before deciding on antibiotic treatment in cases of clinical significance, especially for identifying infections caused by *Salmonella enterica*, *Shigella*, *Campylobacter*, *Yersinia*, Shiga toxin-producing bacteria (STEC), and other local parasites[6].

Thus, they acknowledge the importance of microbiological technology use in clinical decision-making, prioritizing the clinical scenarios outlined in table 4, where they consider the need for immediate antimicrobial treatment with azithromycin or third-generation cephalosporins[6]. However, the results of the studies

Table 2. Evidence from studies included in the text

Study data	Study type	Objectives and/or type of intervention	Results and Conclusions
Authors: Bruzzese et al., 2018[7] Country: Italy	Narrative review	Based on 57 published articles without a specific population, this study aims to describe the indications and antibiotic regimens used internationally for the treatment of acute gastroenteritis, including in South America, Europe, Asia, and Africa, based on the microbiological isolates reported in these studies.	The authors conclude that the administration of antibiotic therapy in the context of acute gastroenteritis may be justified under the following factors: Clinical conditions: dysenteric diarrhea, fever, increased inflammatory markers, prolonged diarrhea, small intestinal bacterial overgrowth, antibiotic-associated diarrhea, and toxic state. Host-related risk factors: age under<3 or 6 months, severity of clinical presentation, malnutrition, underlying chronic disease, and immunodeficiency. Environmental factors: daycare centers, hospitals, institutions, and traveler's diarrhea.
Authors: Kotloff et al., 2018[23] Country: United States	Narrative review	A total of 139 articles and clinical trials were reviewed to establish a standardized definition, pathogenesis, and epidemiology of *Shigella* dysentery, considering its clinical manifestations, diagnostic tests, treatment, and environmental prevention.	First- and second-line treatments for managing shigellosis in both adults and children have been established. However, the presence of Shiga toxin does not always guarantee pharmacological success in patients. Consequently, preventive measures, such as hygiene, proper nutrition, and environmental contamination prevention, have been suggested and progressively implemented.
Authors: O'Ryan et al., 2014[21] Country: United States	Narrative review	A review was conducted analyzing the rationale and potential pathogen-specific benefits of antimicrobials and empirical management based on 75 articles.	Underlying malnutrition and diseases such as AIDS increase the severity and risk of unfavorable outcomes. Evidence showed that early hospitalization in severely malnourished children reduces mortality. In addition, the review emphasizes the importance of limiting antibiotic use exclusively to patients at high risk of complications, rather than employing it as a routine practice.
Authors: Morán et al., 2023[34] Country: Mexico	Narrative review	Current concepts in the pathogenesis, diagnosis, treatment, and interactions with the microbiota during *Entamoeba* infection were reviewed across 115 articles, comparing amebicide management in international guidelines.	The study suggests the importance of reliable diagnostic tools, such as molecular tests, to guide treatment. A proposed approach includes luminal treatments (paromomycin, diloxanide furoate, iodoquinol, and nitazoxanide) and extraluminal amebicides (chloroquine, tinidazole, and metronidazole) to reduce morbidity and mortality and ensure appropriate management. However, these tests are high-cost and may be challenging to implement in certain contexts.
Authors: Somji et al., 2024[15] Country: Bangladesh, India, Kenya, Malawi, Mali, Pakistan, and Tanzania	Cross-sectional analysis	A total of 6,692 children under 2 years of age with moderate-to-severe diarrhea and available qPCR isolates were analyzed to identify clinical characteristics associated with a likely bacterial etiology. The findings revealed correlations with more than six stools in the previous 24 h (OR 1.20, 95% CI 1.05–1.36), moderate acute malnutrition (OR 1.56, 95% CI 1.18–2.08, $p = 0.002$), dehydration (OR 1.66, 95% CI 1.25–2.22, $p < 0.001$), and the combination of these two conditions (OR 2.21, 95% CI 1.61–3.06, $p < 0.001$). No clinical correlation was found with reports of fever or prolonged diarrhea duration.	It was concluded that the presence of moderate acute malnutrition, dehydration, or high stool frequency can help identify children with moderate-to-severe diarrhea who may benefit from antibiotic treatment.
Authors: Zachariah et al., 2021[29] Country: Kenya	Cross-sectional study	The study aimed to determine the prevalence of antibiotic resistance and sensitivity profiles of *Shigella* and *Campylobacter* in fecal samples from 139 children with diarrhea at a hospital in Kenya.	High resistance to common antibiotics was found in *Shigella spp.* and *Campylobacter jejuni*, with 33.1% of samples testing positive for enteric pathogens. *Shigella spp.* exhibited resistance to erythromycin (91.7%), doxycycline (83.3%), ampicillin (82.1%), cotrimoxazole (73.1%), minocycline (66.7%), and cefuroxime (54.2%). *Campylobacter jejuni* also showed resistance to erythromycin (87.5%), doxycycline (75%), ampicillin (73.7%), cotrimoxazole (73.3%), and minocycline (68.8%). These findings underscore the importance of appropriate antibiotic use.

(*Continues*)

Table 2. Evidence from studies included in the text *(continued)*

Study data	Study type	Objectives and/or type of intervention	Results and Conclusions
Authors: Yehonatan et al., 2023[11] Country: Israel	Retrospective cohort study	The study included 281 patients aged 0-18 years with a clinical diagnosis of dysentery, of whom 247 (88%) were under 7 years old, and only 234 (83%) received antibiotic treatment. Cultures were positive in 162 cases (58%), showing that among children receiving empirical treatment, only 134 (57%) had a positive culture, whereas 28 children (60%) were not empirically treated despite having a positive culture.	No correlation was found between microbiological isolation and initiation of antibiotic therapy (p = 0.77) or patient age (under 5 years, p = 0.314). However, there was an association between the initiation of antibiotic therapy and the presence of fever (p = 0.004), leukocytosis (> 15×10≥/uL, p = 0.026), and neutrophilia (> 15×10≥/uL, p = 0.002). Finally, 34 children (16.7%) with positive isolates for *Shigella spp.*, *Salmonella spp.*, or *Campylobacter spp.* did not receive antibiotics and did not require emergency readmission.
Authors: Wong et al., 2012[13] Country: United States	Prospective cohort study	From 1997 to 2006, a population of 259 children under 10 years old and older than 7 days, infected with *E. coli* O157:H7 and presenting with diarrhea, was included in a clinical and paraclinical follow-up to monitor their hematological and renal function until diarrhea resolved or hemolytic uremic syndrome (HUS) developed. HUS was defined as a hematocrit < 30% with evidence of hemolysis in a peripheral blood smear, platelet count < 150,000/µL, and serum creatinine above the age-specific normal limit with oligoanuria. Of the total population, 36 children (14%) developed HUS, showing that children who received antibiotics during the diarrheal episode were more likely to develop HUS compared to those who did not (13%, p = 0.001). This increased risk was observed across all classes of antibiotics used (TMP/SMX, beta-lactams, metronidazole, azithromycin). A multivariate analysis demonstrated that elevated leukocyte count (OR 1.10, 95% CI 1.03–1.19), emesis (OR 3.05, 95% CI 1.23–7.56), and antibiotic exposure (OR 3.62, 95% CI 1.23–10.6) during the 1st week of illness were independently associated with the development of HUS.	In children with diarrhea caused by *E. coli* O157:H7, emesis, elevated leukocyte counts, and antibiotic use during the 1st week of illness independently increased the risk of developing HUS.
Authors: Zamanlou et al., 2022[26] Country: Iran	Case–control study	A total of 89 fecal samples were collected from children under 12 years old with diarrhea or dysentery, comprising 56 samples of *Shigella flexneri* and 33 of *Shigella sonnei*. These samples underwent disk diffusion testing, agar dilution methods, and detection of class 1 or 2 extended-spectrum beta-lactamase (ESBL) integrons through PCR.	Antimicrobial resistance mechanisms were detected, complicating the selection of appropriate antimicrobial agents for children with shigellosis. These mechanisms included the presence of ESBL genes in 60 samples (67.4%) and azithromycin resistance in 16 isolates. In addition, 71.24% of the strains harbored class 1 integrons, whereas 95.82% carried class 2 integrons.

(Continues)

Table 2. Evidence from studies included in the text *(continued)*

Study data	Study type	Objectives and/or type of intervention	Results and Conclusions
Authors: Gonzales et al., 20193[5] Country: Philippines	Systematic review	The effectiveness of tinidazole and metronidazole for amebic colitis was compared across 41 trials involving a total of 4,999 participants. Only one trial met the criteria for random allocation, blinding, and analysis of all participants.	Tinidazole may be more effective than metronidazole in reducing clinical failure (RR 0.28; 95% CI 0.15–0.51, low-certainty evidence) and is probably associated with fewer adverse events (RR 0.65; 95% CI 0.46–0.92, moderate-certainty evidence). Compared to metronidazole, combination therapy may result in fewer parasitological failures (RR 0.36; 95% CI 0.15–0.86, low-certainty evidence). However, no conclusive findings suggested that combination therapy is superior to other treatments. Nevertheless, the evidence is based on small and outdated studies, highlighting the need for updated and robust research.
Authors: Khademi et al., 2019[25] Country: Iran	Meta-analysis	Data from 25 published articles on antibiotic resistance in *Shigella* among individuals under 18 years old were collected from various databases. All included studies utilized the disk diffusion test as the sole susceptibility testing method.	Across the included studies, ciprofloxacin can still be used as a first-line treatment, whereas antimicrobials like ceftriaxone and azithromycin are not recommended for treatment. Resistance was found as follows: Ciprofloxacin: *S. dysenteriae* 7%, *S. flexneri* 3.8%, S. boydii 6.9%, and *S. sonnei* 2.6%. Ceftriaxone: *S. dysenteriae* 27.9%, *S. flexneri* 19.3%, S. boydii 15.7%, and *S. sonnei* 9.5%. Azithromycin: *S. dysenteriae* 91.7%, *S. flexneri* 20.7%, S. boydii 46.7%, and *S. sonnei* 32.3%.
Authors: Ahmed et al.[12] Year: 2021 Country: Bangladesh, India, Kenya, Malawi, Mali, Pakistán y Tanzania.	Randomized Clinical Trial	The study aimed to determine whether adding azithromycin to standard treatment for acute non-bloody watery diarrhea in 8,598 dehydrated or malnourished children aged 2-23 months could reduce mortality and improve linear growth. Participants were randomly assigned to receive either oral azithromycin 10 mg/kg or placebo once daily for 3 days in cases of acute watery diarrhea. The study included children with mild and/or severe dehydration, or moderate malnutrition, and/or severe growth retardation. Primary outcomes were all-cause mortality within 180 days of enrollment and change in linear growth measured as change in length-for-age z-score at 90 days. The antibiotic was administered to 4,463 children (54.0%), with a mean age of 11.6 months. In this group, 0.5% (20) died, compared to 0.7% (28) of 4,135 children in the placebo group (RR 0.72; 95% CI, 0.40-1.27; p = 0.25). The azithromycin group had 170 hospitalizations by day 90 compared to 211 in the placebo group (4.1% vs. 5.1%; RR 0.81; 95% CI, 0.66-0.98). The change in standard deviations in length-for-age z-scores at 90 days was –0.16 (0.59) in the azithromycin group and –0.19 (0.60) in the placebo group (risk difference, 0.03; 95% CI, 0.01-0.06; p = 0.007).	The study found no survival benefit from adding azithromycin to WHO standard treatment for acute watery diarrhea cases in low-resource settings. There was a small reduction in linear growth retardation, though it was not considered clinically significant. The trial was ultimately stopped for futility at the pre-specified interim analysis, concluding that expanding antibiotic use in low-resource settings is not justified.

qPCR: quantitative polymerase chain reaction; RR: relative risk; CI: confidence interval; *S. dysenteriae: Shigella dysenteriae; S. flexneri: Shigella flexneri; S. boydii: Shigella boydii; S. sonnei: Shigella sonnei.*

Table 3. Summary of antibiotic dosing for infectious dysentery in early childhood according to etiology

Note: Isolation of any of these micro-organisms is not an absolute indication for antibiotic therapy. Review indications and susceptibility for each case before prescription.	
Micro-organism	**Dosage and duration**
Salmonella	Typhoid: Ceftriaxone 75-80 mg/kg (maximum 2 g/dose) or 1 g/day (HIV) IV as single dose for 5-14 days, or cefotaxime 150-200 mg/kg/day IV divided every 6-8 h for 10-14 days, or azithromycin 10-20 mg/kg PO as single dose (maximum 1 g/day) for 5-7 days, or *ciprofloxacin 30 mg/kg/day (maximum 1 g/day) PO divided every 12 h for 7-10 days, or *ciprofloxacin 20 mg/kg/day (maximum 800 mg/day) IV divided every 12 h for 7-10 days, or *cefixime 20 mg/kg/day (maximum 400 mg/day) PO divided every 12 h for 10-14 days, or *meropenem 20 mg/kg/dose IV (maximum 1 g/dose) every 8 h. Non-typhoid: Azithromycin 10 mg/kg PO as single dose on day one, followed by 5 mg/kg PO as single dose to complete 5-10 days of treatment, or ceftriaxone 50 or 75-100 mg/kg IV as single dose for 5-14 days, or *ciprofloxacin 15 or 20-30 mg/kg/dose (maximum 500 mg/dose) PO divided every 12 h for 3-7 days, or *TMP/SMX at 8-10 mg/kg/day of TMP PO divided every 12 h for 3-7 days. Salmonellosis in immunocompromised cases should be treated for at least 14 days, whereas meningitis cases should extend treatment to 4 weeks, or 4-6 weeks in cases of osteomyelitis or other metastatic focal lesions.
Shigella	Ceftriaxone 50 mg/kg/day (maximum 1.5 g/day) IV or IM as a single dose for 2-5 (usually 3) days, or ciprofloxacin 15 mg/kg/dose (maximum 400 mg/dose) PO divided every 12 h for 3-5 days, or azithromycin 12 mg/kg (maximum 500 mg/dose) PO as a single dose on day one. Complete regimen with 3-4 more days at 5-6 mg/kg (maximum 250 mg/dose) PO as single dose, or azithromycin 10 mg/kg (maximum 500 mg/dose) PO as single dose for 3 days, or *cefixime 8 mg/kg PO as a single dose for 3 days, or *TMP/SMX at 4 or 8-10 mg/kg/day of TMP PO divided every 12 h for 3-5 days.
Campylobacter	Azithromycin 10 mg/kg PO as a single dose for 3 days (5 days in HIV cases), or erythromycin 40 mg/kg/day PO divided every 8 h for 5 days, or *azithromycin 30 mg/kg PO as a single dose. *ciprofloxacin 10-15 mg/kg/dose (maximum 750 mg/dose) PO every 12 h for 3-5 days. HIV cases may require 7-10 days.
Clostridioides difficile	Mild-or-moderate disease: Metronidazole 30 mg/kg/day PO divided every 6 h (maximum 500 mg/dose) for 10 days, or *vancomycin 40 mg/kg/day PO divided every 6 h (maximum 125 mg/dose) for 10 days. Severe disease: Consider in cases of leukocytosis, leukopenia, or clinical deterioration. Vancomycin 40 mg/kg/day PO divided every 6 h for 10 days, or the same vancomycin dose PR in a ratio of 500 mg/100 ml NS as enema. Either option +/- metronidazole 30 mg/kg/day IV divided every 8 h for 10 days. Severe and complicated disease: Intensive care admission, hypotension, shock, endoscopy with pseudomembranous colitis, ileus, or toxic megacolon. Vancomycin 40 mg/kg/day PO divided every 6 h for 10 days, with metronidazole 30 mg/kg/day IV divided every 6 h for 10 days. In cases of distention, ileus, or toxic megacolon, add vancomycin enema until improvement (see above). Second or additional episodes: Vancomycin 10 mg/kg/dose (maximum 125 mg/dose) PO every 6 h for 7 days, then every 8 h for 7 days, then every 12 h for 7 days, then every 24 h for 7 days, then every 48 h for 7 days, then every 72 h for 7 days, or vancomycin 10 mg/kg/dose (maximum 125 mg/dose) PO every 6 h for 14 days, then every 12 h for 7-14 days, then every 24 h for 7-14 days, then every 24-72 h for 2-8 weeks, or vancomycin 10 mg/kg/dose (maximum 125 mg/dose) PO every 6 h for 14 days, followed by rifaximin 400 mg PO as single dose every 8 h for 14 days, or fidaxomicin with weight-based dosing** PO every 12 h for 10 days.
Yersinia enterocolitica	TMP/SMX at 8-10 mg/kg/day of TMP PO divided every 12 h for 7 days, or cefotaxime 150-200 mg/kg/day IV divided every 6-8 h. No defined duration period.
Entamoeba histolytica	Cyst carrier: Iodoquinol 30-40 mg/kg/day PO divided every 6-8 h (maximum 650 mg/dose) for 20 days, or paromomycin 25-35 mg/kg/day PO divided every 8 h for 7-10 days, or diloxanide furoate 20 mg/kg/day PO divided every 8 h (maximum 500 mg/dose) for 10 days. Invasive disease: Metronidazole 30-40 or 50 mg/kg/day PO divided every 8 h for 7-10 days, or tinidazole 50 mg/kg PO as a single dose (maximum 2 g/day) for 3 days. Consider 5 or even 10 days in severe cases. Either option should be followed by one of the treatments used for cyst carriers at those doses.
Cystoisospora	TMP/SMX at 8-10 mg/kg/day of TMP or 15-20 mg/kg/day (HIV) (maximum 160 mg/dose) PO or IV divided every 12 h for 7-10 days or up to 3-4 weeks in HIV cases.
Cyclospora cayetanensis	TMP/SMX at 8-10 mg/kg/day of TMP PO divided every 12 h for 7-10 days.

IM: intramuscular; IV: intravenous; NS: normal saline; PO: oral route; PR: intrarectal route; *alternative second-line regimens; **4 kg to < 7 kg, 80 mg; 7 kg to < 9 kg, 120 mg; 9 kg to < 12.5 kg, 160 mg; ≥ 12.5 kg, 200 mg.

Source: Authors' own elaboration based on extracted information from Kliegman[1], World Health Organization[4], Shane et al.[6], American Academy of Pediatrics[18], Hohmann[19], Andrews et al.[20], American Academy of Pediatrics[22], Crews and Nicholson[30], McDonald et al.[31], Kotloff[37], American Academy of Pediatrics[38-45].

supporting such a suggestion show that the benefits are modest, reducing symptomatic duration by only 1 day. Furthermore, they declare inconsistencies in the clinical trials they found without specifying particulars of study design or population characteristics.

A middle ground among these three important international entities could be found in an interesting recommendation from a Colombian expert panel in 2015. They recommend empirical antibiotic administration in infectious dysentery during early childhood in cases of symptomatic persistence, clinical deterioration (partially following IDSA's approach), or if *Shigella* is found in the patient's stool culture, aligning with WHO's emphasis on its presence and the potential deterioration that occurs when antibiotic therapy is not provided[9].

This was also found in a cohort study conducted in Botswana, where the presence of *Shigella*, *Campylobacter*, or enterotoxigenic *Escherichia coli* was documented and associated with higher mortality in patients with severe acute malnutrition or human immunodeficiency virus (HIV) infection when empirical antibiotic therapy was not administered[10]. However, they related this as a possible confounding factor due to the patients' critical underlying condition, beyond the use of antibiotics, due to limitations in the logistic regression analysis of their results.

However, this contrasts with an Israeli retrospective study of 281 participants with a mean age of 2 years, in which clinical criteria for initiating empirical antibiotic therapy (fever, leukocytosis, and neutrophilia) were applied, but this did not correlate with positive stool cultures, hospitalization requirements, or clinical worsening[11]. They noted that 17.7% of children who presented with dysentery positive for *Shigella* or *Campylobacter* did not receive antibiotics and did not require hospital readmission, questioning the need for empirical treatment. However, it is important to understand the cultural and social differences compared to low-income countries, from which most available information comes regarding early childhood morbidity and mortality from this disease.

On the other hand, a clinical trial published in the *Journal of the American Medical Association*, which included 8,266 participants aged between 2 and 23 months with watery diarrhea, found no significant differences in mortality and weight-for-height growth delay between patients empirically treated with azithromycin and those treated with placebo[12]. Although this study did not specifically address dysentery, it did document positive isolates for *E. coli* among its participants.

Table 4. IDSA recommendations for immediate antimicrobial treatment initiation in patients with dysentery

Sepsis and septic shock.
Children under 3 months with suspected bacterial infection.
Fever in cases of immunocompromise or recent international travel.
Acute abdomen.
Suspected *Shigella* infection.

Source: Authors' own elaboration based on information extracted from Shane et al.[6].
IDSA: Infectious Diseases Society of America.

Escherichia coli

The presence of STEC, whether O157:H7 or regardless of its toxin genotype[6], is a known reason to avoid antibiotic use due to the release of intracellular Shiga toxin at the tissue level and its impact on the development of hemolytic-uremic syndrome (HUS)[13]. This complication is especially relevant in regions such as Latin America, where microbiological panels are limited, and the enteroinvasive strain can be clinically similar, with no clear benefits from antibiotic administration. At present, no studies demonstrate the benefits of antibiotic therapy in cases of dysentery, except in cases of persistent traveler's watery diarrhea, treated with ciprofloxacin, azithromycin, and rifaximin[1].

A study performed by the Washington Department of Health analyzing 405 cases of O157:H7, including adults and children, among whom 211 were under 18 years and received antibiotic treatment with nitroimidazoles, fluoroquinolones, or beta-lactams, found that the presence of *E. coli* in children under 5 years is more frequent than in adults. Furthermore, it found that antibiotic use in this population may be harmful and slightly increase the risk of STEC-associated HUS[14]. However, given the wide confidence intervals, they did not propose a specific conclusion, limiting clinically or statistically significant indications, in addition to the heterogeneity of HUS definitions used in the article. Thus, the patient's context and clinical manifestations determine the appropriateness of antibiotic therapy administration.

A cross-sectional study conducted across seven countries in Asia and Africa with 6,692 children found that in scenarios of moderate or severe diarrhea with factors such as moderate acute malnutrition, dehydration, and high fecal output are associated with bacterial agents and could benefit from antibiotics[15]. However, in reviewing this manuscript, no suggestions of protective effects were found for any strains.

Salmonella

In its latest 2024 report, WHO identified typhoid and non-typhoid *Salmonella* species as a high-risk public health concern due to their antibiotic multi-resistance, especially to fluoroquinolones[16]. This is another reason to reconsider the widespread use of antibiotics in ADD and dysentery, where their inappropriate use may increase the possibility of becoming a chronic carrier[1].

This problem has been seen with an increasing frequency, so much so that the Cochrane Collaboration, since 2011, has insisted on the importance of regulation according to local patterns despite their utility[17]. In contrast, there are no specific studies of this etiology in children, and there is an urgent need for such studies due to the health emergency it represents. The only international reference entity specifically addressing the topic through expert committees is the American Academy of Pediatrics (AAP), which dedicates a section to the disease in this population group.

Initially, recommendations for typhoid fever in this population group mention the use of fluoroquinolones due to the high risk of complications, as the historically mentioned osteoarticular adverse effects which have not been substantiated in subsequent studies. However, azithromycin and third-generation cephalosporins should be considered alternatives to quinolones given the indiscriminate use of the latter in adults, which has produced resistance as documented in different regions of the world such as Pakistan or Iraq[1].

Regarding non-typhoid fever, some experts recommend the use of ciprofloxacin or, according to the AAP, a single dose of ceftriaxone followed by an azithromycin regimen[18], including alternatives such as cefixime or trimethoprim/sulfamethoxazole (TMP/SMX). However, based on adult studies and expert opinions in the field of pediatrics, it should be reserved for cases of disseminated and high-risk disease, with special emphasis on HIV/acquired immunodeficiency syndrome (AIDS), and other immunosuppressive states, hemoglobinopathies, high-output diarrhea, infants under 3 months, chronic gastrointestinal disease, or significant heart and joint diseases[1,19,20]. Relapse rates have been shown to be lower with ciprofloxacin or oral azithromycin compared to oral TMP/SMX, amoxicillin, or parenteral ceftriaxone[18].

Shigella

This is a controversial agent due to WHO's 2005 recommendation to use antibiotic therapy in all cases of dysentery, considering that most cases are caused by this bacterium, which, along with *E. coli*, are the main responsible agents for this clinical presentation[6], as well as considering dysentery as a criterion for initiating antibiotic therapy in *Shigella* infection[1].

However, recommendations have changed again according to the AAP's 2024 guidelines, now recommending antibiotic therapy for immunocompromised patients, those with severe disease, those requiring hospitalization, attending daycare or living in institutions, or those involved in food handling, as it reduces transmission and leads to faster pathogen eradication, shortening diarrhea duration, preventing clinical deterioration, and the development of chronic symptoms and malnutrition[21-23]. This recommendation aligns with findings from a review published by Kotloff et al. in *The Lancet*[23] in 2017, and the findings from the previously mentioned Botswana cohort study, where 671 participants had a mean age of 8.3 months. The study documented that *Shigella* had a strong association with bloody diarrhea, although a high proportion (37%) did not present with dysentery despite positive pathogen cultures, and there was a high diarrhea-related mortality rate (3.7%)[11]. Similarly, in cases where *Shigella dysenteriae* type 1 is isolated, there is a higher risk of invasive infection and intestinal complications when associated with malnutrition, and an increased mortality risk when there is a higher number of bowel movements before hospital admission, hyponatremia, altered consciousness, and seizures[23].

Treatment guidelines are similar to those for *Salmonella*, with differences in treatment duration[23]. The previously mentioned clinical considerations should be considered given the increasing resistance to azithromycin, fluoroquinolones, ampicillin, TMP/SMX[21], and even the possibility of HUS. A systematic review from Pediatrics and International Child Health found that ciprofloxacin, pivmecillinam, and ceftriaxone reduce the clinical failure rate by 82% in cases of shigellosis. Ciprofloxacin resistance increased in Asia and Africa while remaining low in Europe and America, with higher rates in children than adults globally[24]. Regarding alternatives, macrolides, cephalosporins, and aminoglycosides showed higher resistance in children, limiting their usefulness. Gatifloxacin showed poorer clinical outcomes compared to ciprofloxacin[24].

Cephalosporins, especially cefixime, demonstrated high effectiveness as an alternative when fluoroquinolone resistance is present; however, studies have been conducted in hospital settings, limiting extrapolation to outpatient contexts where future research may be

needed[24]. This contrasts with findings from an Iranian meta-analysis, which showed low *Shigella* resistance to ciprofloxacin (*S. dysenteriae* 7%, *Shigella flexneri* 3.8%, *Shigella boydii* 6.9%, and *Shigella sonnei* 2.6%) and high resistance to ceftriaxone and azithromycin, recommending reevaluation of these antibiotics' use based on the population and local resistance patterns[25,26].

Campylobacter

Considered one of the main causes of food poisoning, it still shows 95% sensitivity to macrolides, fluoroquinolones, and aminoglycosides[27]. In the few studies on treatment efficacy in this population, azithromycin has been the drug of choice, reducing symptom duration by 1.3 days according to a 2007 meta-analysis[28], suggesting its use in all cases of dysentery, as this is considered a marker of disease severity.

There are no subsequent articles reassessing this result, and this therapeutic concept has persisted until today, with a lengthy period without evidence regarding this etiology, except for the AAP expert panel in 2024[18], which recommends limiting antibiotic use to invasive cases, such as bacteremia or in patients at risk of severe disease, preferring azithromycin and erythromycin[18]. While their efficacy has been preserved over time, there is an increasing incidence of antimicrobial resistance of *Campylobacter jejuni* to ampicillin, cotrimoxazole, and erythromycin[29], compromising therapeutic options in areas with limited access to ciprofloxacin and norfloxacin, presenting a serious threat to global public health.

Clostridioides difficile

It can be rarely defined as a pathogen causing dysentery. IDSA indicates that it is not expected to cause dysentery[6], although it can be found in up to 15% of cases[30]. When isolated, basic treatment should follow the same approach as a conventional case of pseudomembranous colitis, requiring discontinuation of all non-essential antibiotics, and administration of oral metronidazole in mild-to-moderate cases.

In patients with risk factors such as oncological conditions, immunosuppression, transplants, or cystic fibrosis, severe complications may occur more frequently, including pseudomembranous colitis, intestinal pneumatosis, toxic megacolon, perforation, peritonitis, and shock with multisystem failure, as well as in recurrent infection, requiring combined use of oral vancomycin[31] with intravenous metronidazole[32].

Unlike adults, children require clinical analysis of each scenario to define disease severity and specific therapy in fulminant cases. In these cases, intrarectal vancomycin administration and ileostomies have been attempted in surgical emergencies, with mortality rates reaching 2-4%[32]. In 2020, the Food and Drug Administration approved the use of the macrolide fidaxomicin in children from 6 months of age based on retrospective studies, and according to the AAP in 2024, its utility has been considered in recurrent cases with concomitant hematological-oncological diseases[32,33].

Yersinia enterocolitica

There have been no recent trials on antibiotic therapy, apparently because most cases are self-limited. However, the AAP[18], through its 2024 expert panel, recommends antibiotic use in neonates due to their higher risk of sepsis[1], immunocompromised patients, and cases of enterocolitis, pseudoappendicitis syndrome, or mesenteric adenitis. Suggested treatments include third-generation cephalosporins, TMP/SMX, aminoglycosides, fluoroquinolones, chloramphenicol, tetracyclines, or doxycycline[18].

Entamoeba histolytica

There are various complex aspects of amebiasis at the medical care level and even of a cultural nature. One of the most relevant medical errors is failing to recognize the trophozoite as its infective form, and considering that cysts, its stationary form, require urgent antibiotic management and cause dysentery when found in an isolated coproparasitological sample; this is why, when requesting a coproparasitological test, antimicrobial decisions in emergency services can become confused and should be reserved only for persistent cases or therapeutic failures[9].

It is common to find inappropriate antimicrobial administration for this condition, making it necessary to clarify its indications, which have been defined by guideline documents and secondary references. These indications are hepatic abscesses or invasive disease characterized by a rapidly progressive dysenteric phenomenon in infants. In such cases, metronidazole or tinidazole is suggested, followed by a luminal agent such as iodoquinol or paromomycin for the eradication of intestinal cysts and prevention of recurrence[1], with these last two being indicated when treating an asymptomatic cyst carrier[34,35].

Cystoisospora and Cyclospora cayetanensis

Although dysentery is rare, most evidence comes from cases with HIV/AIDS. Some suggest universal management with TMP/SMX in all symptomatic children[1,36]. In contrast, others posit that it should only be given in immunocompromised situations to reduce the possibility of chronification in these cases[18], which reconsiders its true benefit in immunocompetent patients as it is self-limited. Results show lower effectiveness with ciprofloxacin or nitazoxanide, which could be useful in cases of sulfa intolerance in cystoisosporiasis[1,18].

Conclusions

At present, infectious dysentery in early childhood presents a clinical decision challenge with an unresolved issue that represents its most relevant adjunct management: antimicrobial therapy. This controversy arises from the lack of standardized management protocols, limitations in building clinical evidence due to ethical dilemmas in clinical trial development, and the coexistence of the pathogen to be treated in the microbiome rather than its true eradication, which in some scenarios becomes a chronic carrier state.

According to the literature review, indications for antibiotic therapy vary depending on clinical compromise, relevant individual susceptibility factors, and the possibility of specific microbiological isolation, potentially being more useful in scenarios of infections produced by *Shigella*, *Campylobacter*, *C. difficile*, and *E. histolytica*, while being limited to specific scenarios with *Y. enterocolitica*, and avoided when isolating Shiga toxin-producing *E. coli* O157:H7.

With the technological advancement of medicine, it was found that a problem arises from the lack of precise microbiological diagnosis before the physician's decision, particularly in regions with limited resources. The absence of advanced diagnostic tools limits therapeutic management, promoting indiscriminate use of antibiotics and contributing to growing bacterial resistance. Moreover, the fact that much of the information found is extrapolated from adults or comes from expert panels further reflects the critical gap in knowledge and management of infectious dysentery in children under 5 years of age. This area has been insufficiently addressed in the existing literature.

The advancement toward greater coverage in the use of molecular diagnostics offers a promising path to improve precision in pathogen identification, supporting clinical practice, and guiding specific treatment, which could transform antibiotic therapy. While it is clear that the widespread implementation of these technologies still faces barriers, their potential for precision medicine is evident.

In addition, it is necessary to implement and develop continuing education programs for pediatricians, primary care physicians, and the general community, focusing on rational antibiotic management, prevention of bacterial resistance, primary prevention measures, and local epidemiological knowledge to promote informed therapeutic decision-making following the best scientific evidence to significantly improve the clinical management of infectious dysentery in early childhood and contribute to the global fight against microbial resistance.

Finally, although the management of infectious dysentery in early childhood remains an area of controversy and challenge, with microbiological identification and susceptibility along with patient comorbidity assessment being today's key to antibiotic decision-making, the integration of advanced diagnostics and implementation of robust research strategies are the true gateway of understanding the real indications and risks of administering antibiotic therapy in the near future.

Declaration

The authors declare their complete authorship of the article as part of project MED-342-2023 from Universidad de La Sabana.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Kliegman R, Blum N, Shah S, St Geme J, Tasker R, Wilson K, et al. Nelson: Tratado de Pediatría. 21st ed. Barcelona: Elsevier Inc.; 2020.
2. CaJacob NJ, Cohen MB. Update on diarrhea. Pediatr Rev. 2016;37:313-22.
3. Ministerio de Salud y Protección Social - Colciencias - Universidad de Antioquia. Guía de Práctica Clínica Para Prevención, Diagnóstico y Tratamiento de la Enfermedad Diarreica Aguda en Niños Menores de 5 Años SGSS - 2013 Guía No. 8 GPC-EDA. Bogota: Ministerio de Salud y Protección Social - Colciencias; 2013.
4. World Health Organization. The Treatment of Diarrhoea. A Manual for Physicians and Other Senior Health Workers. Geneva, Switzerland: World Health Organization; 2005.
5. Organización Panamericana de la Salud. AIEPI - Cuadro de Procedimientos. 3rd ed. United States: Organización Panamericana de la Salud; 2023.
6. Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, et al. Infectious diseases society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis. 2017;65:e45-80.
7. Bruzzese E, Giannattasio A, Guarino A. Antibiotic treatment of acute gastroenteritis in children. F1000Res. 2018;7:193.
8. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169:467-73.
9. Flórez ID, Contreras JO, Sierra JM, Granados CM, Lozano JM, Lugo LH, et al. Guía de práctica clínica de la enfermedad diarreica aguda en niños menores de 5 años. Diagnóstico y tratamiento. Pediatria. 2015;48:29-46.
10. Pernica JM, Steenhoff AP, Welch H, Mokomane M, Quaye I, Arscott-Mills T, et al. Correlation of clinical outcomes with multiplex molecular testing of stool from children admitted to hospital with gastroenteritis in Botswana. J Pediatric Infect Dis Soc. 2016;5:312-8.
11. Azulai Y, Schwartz S, Heiman E, Berliner E, Weiser G. Antibiotics for clinical dysentery in the pediatric emergency department. Isr Med Assoc J. 2023;25:5-7.
12. Ahmed T, Chisti MJ, Rahman MW, Alam T, Ahmed D, Parvin I, et al. Effect of 3 days of oral azithromycin on young children with acute diarrhea in low-resource setting: a randomized clinical trial. JAMA Netw Open. 2021;4:e2136726.
13. Wong CS, Mooney JC, Brandt JR, Staples AO, Jelacic S, Boster DR, et al. Risk factors for the hemolytic uremic syndrome in children infected with *Escherichia coli* O157:H7: a multivariable analysis. Clin Infect Dis. 2012;55:33-41.
14. Tarr GA, Oltean HN, Phipps AI, Rabinowitz P, Tarr PI. Strength of the association between antibiotic use and hemolytic uremic syndrome following *Escherichia coli* O157:H7 infection varies with case definition. Int J Med Microbiol. 2018;308:921-6.
15. Somji S, Ashorn P, Manji K, Ahmed T, Chisti M, Dhingra U, et al. Clinical and nutritional correlates of bacterial diarrhoea aetiology in young children: a secondary cross-sectional analysis of the ABCD trial. BMJ Paediatr Open. 2024;8:e002448.
16. World Health Organization. WHO Bacterial Priority Pathogens List, 2024: Bacterial Pathogens of Public Health Importance to Guide Research, Development and Strategies to Prevent and Control Antimicrobial Resistance. Geneva, Switzerland: World Health Organization; 2024.
17. Effa EE, Lassi ZS, Critchley JA, Garner P, Sinclair D, Olliaro PL, et al. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Cochrane Database Syst Rev. 2011;2011:CD004530.
18. American Academy of Pediatrics. Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024.
19. Hohmann E. Nontyphoidal *Salmonella*: Gastrointestinal Infection and Asymptomatic Carriage. United States: UpToDate; 2024.
20. Andrews J, John J, Charles R. Enteric (Typhoid and Paratyphoid) Fever: Treatment and Prevention. United States: UpToDate; 2024.
21. O'Ryan GM, Ashkenazi-Hoffnung L, O'Ryan-Soriano MA, Ashkenazi S. Management of acute infectious diarrhea for children living in resource-limited settings. Expert Rev Anti Infect Ther. 2014;12:621-32.
22. American Academy of Pediatrics. *Shigella* infections. In: Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024. p. 756-60.
23. Kotloff KL, Riddle MS, Platts-Mills JA, Pavlinac P, Zaidi AK. Shigellosis. Lancet 2018;391:801-12.
24. Williams PC, Berkley JA. Guidelines for the treatment of dysentery (shigellosis): a systematic review of the evidence. Paediatr Int Child Health. 2018;38:S50-65.
25. Khademi F, Sahebkar A. Fluoroquinolones-resistant *Shigella* species in Iranian children: a meta-analysis. World J Pediatr. 2019;15:441-53.
26. Zamanlou S, Omidnia P, Babaie F, Mehraban A, Koochaki P, Azizian K, et al. Emergence of azithromycin and third-generation cephalosporins resistant *Shigella* isolated from Iranian children. Gene Rep. 2022;26:101485.
27. Levy J. Diagnostic Approach to Diarrhea in Children in Resource-abundant Settings. UpToDate; 2024. Available from: https://www-uptodate-com.ez.unisabana.edu.co/contents/diagnostic-approach-to-diarrhea-in-children-in-resource-abundant-settings [Last accessed on 2024 May 08].
28. Harris J, Pietroni M, Jobayer M. Approach to the Child with Acute Diarrhea in Resource-limited Settings. UpToDate; 2024. Available from: https://www-uptodate-com.ez.unisabana.edu.co/contents/approach-to-the-child-with-acute-diarrhea-in-resource-limited-settings [Last accessed on 2024 May 08].
29. Zachariah OH, Lizzy MA, Rose K, Angela MM. Multiple drug resistance of *Campylobacter jejuni* and *Shigella* isolated from diarrhoeic children at Kapsabet County referral hospital, Kenya. BMC Infect Dis. 2021;21:109.
30. Crews J, Nicholson MR. *Clostridioides difficile* Infection in Children: Clinical Features and Diagnosis. United States: UpToDate; 2024.
31. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:e1-48.
32. Shirley DA, Tornel W, Warren CA, Moonah S. *Clostridioides difficile* infection in children: recent updates on epidemiology, diagnosis, therapy. Pediatrics. 2023;152:e2023062307.
33. Diorio C, Robinson PD, Ammann RA, Castagnola E, Erickson K, Esbenshade A, et al. Guideline for the management of *Clostridium difficile* infection in children and adolescents with cancer and pediatric hematopoietic stem-cell transplantation recipients. J Clin Oncol. 2018;36:3162-71.
34. Morán P, Serrano-Vázquez A, Rojas-Velázquez L, González E, Pérez-Juárez H, Hernández EG, et al. Amoebiasis: advances in diagnosis, treatment, immunology features and the interaction with the intestinal ecosystem. Int J Mol Sci. 2023;24:11755.
35. Gonzales ML, Dans LF, Sio-Aguilar J. Antiamoebic drugs for treating amoebic colitis. Cochrane Database Syst Rev. 2019;1:CD006085.
36. Bartelt LA, Dillingham RA. *Cystoisospora belli* (syn. *Isospora belli*). In: Hunter's Tropical Medicine and Emerging Infectious Diseases. Amsterdam, Netherlands: Elsevier; 2020. p. 722-4.
37. Kotloff KL. Gastroenteritis aguda en niños. In: Kliegman RM, editor. Nelson: Tratado de Pediatría. 21st ed. Amsterdam, Netherlands: Elsevier; 2020. p. 2012-33.
38. American Academy of Pediatrics. Cryptosporidiosis. In: Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024. p. 338-40.
39. American Academy of Pediatrics. Cyclosporiasis. In: Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024. p. 342-3.
40. American Academy of Pediatrics. Cystoisosporiasis (formerly isosporiasis). In: Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024. p. 343-4.
41. American Academy of Pediatrics. Amebiasis. In: Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024. p. 225-8.
42. American Academy of Pediatrics. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* infections (enteritis and other illnesses). In: Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024. p. 960-3.
43. American Academy of Pediatrics. *Clostridioides difficile* (Formerly *Clostridium difficile*). In: Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024. p. 313-9.
44. American Academy of Pediatrics. Campylobacter infections. In: Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024. p. 283-6.
45. American Academy of Pediatrics. *Salmonella* infections. In: Red Book: 2024-2027 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics; 2024. p. 742-50.

Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

RESEARCH ARTICLE

Septic shock upon admission to pediatric intensive care units: prognostic analysis of mortality in a retrospective cohort

Ricardo Rodriguez-Portilla[1,2], Isabel Pinedo-Torres[3], Claudia C. Guerra-Ríos[4], Angela Parra del Riego-Freundt-Thurne[5], and Nilton Yhuri-Carreazo[6,7]*

[1]Pediatric Intensive Care Unit,Hospital Nacional Edgardo Rebagliati Martins; [2]Pediatric Intensive Care Unit, Clínica Delgado – Auna; [3]Neurosciences, Metabolism, Clinical and Health Effectiveness - NEMECS, Universidad Cientifica del Sur; [4]Pediatric Intensive Care Unit, Hospital Guillermo Almenara Irigoyen. Lima, Peru; [5]Division of Medical Education, Nicklaus Children's Hospital, Miami, FL, EEUU; [6]School of Medicine, Universidad Peruana de Ciencias Aplicadas; [7]Pediatric Intensive Care Unit, Hospital de Emergencias Pediátricas. Lima, Peru

Abstract

Background: *Septic shock is a common cause of admission to pediatric intensive care units (PICU) and is associated with significant mortality. Our objective was to analyze the association between septic shock diagnosis at PICU admission and mortality during hospitalization.* **Method:** *This retrospective cohort study was conducted in the PICU of Hospital Nacional Edgardo Rebagliati Martins (HNERM) in Lima, Peru, from January 2018 to December 2021.The sample size was determined based on annual mortality rates, and randomization was used to create two groups: patients with and without septic shock. To evaluate mortality risk, we performed a Poisson regression with robust variances and 95% confidence intervals (CI) using both crude and adjusted models.* **Results:** *Of 1,341 patients admitted to the PICU during the study period, 358 were included in the analysis. The study population was 51.9% female, with a median age of 3.7 years. The largest age group was children under 1 year, comprising 29.6% of participants. The septic shock group showed higher rates of mechanical ventilation requirement, longer hospital stays, and increased mortality. The risk of mortality was 2.73 times higher in patients admitted with septic shock compared to those admitted with other diagnoses (relative risks: 2.73; 95% CI: 1.36–5.46).* **Conclusion:** *Patients admitted to the PICU with septic shock demonstrated a 2.73 times higher risk of death compared to those admitted for other reasons.*

Keywords: *Septic shock. Pediatric intensive care units. Mortality. Cohort studies. Peru.*

Choque séptico al ingreso a una unidad de cuidados intensivos pediátricos: análisis pronóstico de mortalidad en una cohorte retrospectiva

Resumen

Introducción: *El shock séptico es motivo de ingreso a Unidades de Cuidados Intensivos Pediátricos (UCIP) y conlleva una importante mortalidad. Nuestro objetivo fue analizar la asociación entre el diagnóstico de shock séptico al ingreso de una UCIP y la mortalidad durante su estancia.* **Método:** *Estudio de cohortes retrospectivo desarrollado en la UCIP del Hospital Nacional Edgardo Rebagliati Martins (HNERM) de Lima-Perú de enero del 2018 a diciembre del 2021. Se determinó el*

***Correspondence:**
Ricardo Rodríguez-Portilla
E-mail: ricardo.rodriguez@upch.pe

Date of reception: 26-04-2024
Date of acceptance: 25-11-2024
DOI: 10.24875/BMHIM.24000056

Available online: 28-02-2025
Bol Med Hosp Infant Mex. 2025;82(1):28-34
www.bmhim.com

tamaño de muestra con base en tasas de mortalidad anuales y se realizó una aleatorización para conformar dos grupos: uno con shock séptico y otro sin él. Para evaluar el riesgo de muerte se realizó una regresión de Poisson con varianzas robustas y un intervalo de confianza (IC) al 95% con modelos crudos y ajustados. **Resultados:** *De los 1341 pacientes ingresados a la UCIP durante el periodo de estudio se incluyeron 358 pacientes. De ellos, el 51.9 % eran mujeres, la mediana de edad fue de 3.7 años y la mayor cantidad de participantes estuvo en el grupo de menores de 1 año 29.6%. La necesidad de ventilación mecánica, la duración de la estancia hospitalaria y la mortalidad fueron más altas en el grupo de shock séptico. El riesgo de mortalidad fue 1.73 veces más en el grupo que ingresó con shock séptico en comparación al grupo que ingresó con otros diagnósticos (RR: 2.73; IC 95% 1.36 – 5.46).* **Conclusión:** *Los pacientes ingresados a la UCIP por shock séptico presentaron mayor riesgo de morir en comparación con aquellos que ingresaron por otras causas.*

Palabras clave: *Choque séptico. Unidades de cuidado intensivo pediátrico. Mortalidad. Estudios de Cohortes. Perú.*

Introduction

Septic shock is a significant cause of admission to pediatric intensive care units (PICUs) and is associated with substantial mortality[1-7]. In developing countries, septic shock accounts for up to 20% of ICU admissions, with mortality rates exceeding 30%[2-4]. In contrast, developed countries report approximately 10% of admissions due to septic shock, with mortality rates below 20%[6,8-11]. Despite the disproportionate impact of septic shock on pediatric populations in developing countries, most available research comes from developed nations.

Other common causes of PICU admission have been well documented. Respiratory infections comprise 12% of admissions with approximately 20% mortality, whereas infections at other sites account for an additional 12% with an average mortality of 19%[5]. Trauma cases represent 6% of admissions with 10% mortality[5,8], and post-operative patients constitute up to 40% of admissions with 1% mortality[8]. Overall, PICU mortality rates range from 3% to 25%, with developing countries consistently reporting higher rates than developed nations[1,5,8,12-15].

While it is well established that patients admitted to PICUs with septic shock experience higher mortality rates than those admitted for other conditions, the magnitude of this increased risk remains unclear. Therefore, our primary objective was to quantify the relative mortality risk for patients admitted to PICU with septic shock compared to those admitted with other diagnoses.

Method

This study was approved by the hospital's Ethics Committee (registration code 1434-GRPR-ESSALUD -2022) and was conducted following the Declaration of Helsinki and Peru's General Health Law regarding health research.

Study design, population, and sample

We conducted a retrospective cohort study using data from patients admitted to the PICU of the National Hospital Edgardo Rebagliati Martins (NHERM) from January 1, 2018, to December 31, 2021. NHERM, located in Lima, Peru's capital, is a national reference center serving approximately 2 million people with over 1,600 beds[16]. The pediatric service comprises approximately 100 hospital beds, whereas the PICU maintained nine beds during the first 3 years of the study period, expanding to 13 beds in the final year.

Following our institution's pediatric classification criteria, the study population included patients aged between 1 month and 13 years, 11 months, and 29 days. We included all PICU admission records regardless of diagnosis and followed patients from PICU admission until hospital discharge. We excluded patients with multiple PICU admissions during the study period, regardless of admission diagnosis.

The sample size was calculated using Epidat version 4.2. For the unexposed group (without septic shock), we assumed a mortality risk of 12.7%, based on the HNERM PICU's annual mortality rate[12]. For the exposed group (with septic shock), we used a mortality risk of 24.8%, derived from a systematic review and meta-analysis of global case fatality rates in severe sepsis and pediatric septic shock[6]. Using an exposed/unexposed ratio of 1:1, 80% power, and 95% confidence level with Yates correction, we calculated a required sample size of 179 patients per group. We created a sampling frame from the digital PICU admission records, which were updated daily. After applying selection criteria, patients were stratified into two groups based on exposure status. Simple random sampling was then performed to achieve the required number of patients in each group.

Variables

The independent variable (exposure) was septic shock diagnosis, defined by suspected or confirmed infection plus a combination of fever or hypothermia, altered capillary refill, reticulated skin, decreased mental status, oliguria, and hypotension, based on international criteria[17]. The primary outcome was all-cause mortality during the PICU stay. Additional variables included sex, age categories, comorbidity presence, prematurity history, and mechanical ventilation use. We also collected numerical data on age, PICU length of stay, and pediatric risk of mortality (PRISM) III scores. The PRISM III score predicts PICU mortality risk by evaluating 17 physiological variables during the first 24 h after admission[18]. When analyzing mortality by comorbidity type, we included only patients with underlying pathologies to avoid bias.

Statistical analysis

Data were collected in Microsoft Excel, with two authors independently verifying each value twice. Statistical analyses were performed using Stata 14.0 (StataCorp, TX, US). We conducted descriptive analyses using frequency measures for qualitative variables and summary measures for quantitative variables. For inferential statistics, we compared quantitative variables between groups using the Mann–Whitney U test, as assumptions of normality and homogeneity of variances were not met. For proportion comparisons, we used χ^2 or Fisher's exact tests depending on expected values.

To evaluate the risk of death during hospitalization in relation to admission cause, we performed a Poisson regression with logarithmic link function and robust variances. We calculated both crude and adjusted models. We included variables that were both accessible and relevant from the authors' perspective, selected from those controlling backdoor pathways identified in the directed acyclic diagram[19]. We estimated relative risks (RR) with corresponding 95% confidence intervals (CI).

Results

Descriptive analysis of the sample

From 1,341 PICU admissions during the study period, we preselected 236 patients admitted with septic shock and 749 with other diagnoses after applying the selection criteria. Following randomization, 179 patients were included in each group (Fig. 1). The total sample comprised 51.96% (n = 186) females, with a median age of 3.7 years. The largest age group was children under 1 year, representing 29.61% (n = 106) of participants. The most prevalent comorbidities were respiratory, cardiological, neuromuscular, oncological, and digestive conditions (Fig. 2). In addition, 15% of patients had a history of prematurity, and 60% (n = 215) presented with at least one comorbidity (Table 1).

Patient characteristics upon PICU admission

The septic shock group showed a significantly higher proportion of children under 1 year compared to those admitted for other reasons (41.33% vs. 17.88%; $p < 0.001$). This group also demonstrated a slightly higher frequency of at least one comorbidity (60.33% vs. 59.78%; $p = 0.021$). Patients with septic shock were significantly younger (median age 1.67 vs. 4.67 years; $p < 0.001$) and had significantly higher PRISM scores (median 13.25 vs. 1.26 points; $p < 0.001$) (Table 1).

Clinical course of patients in the PICU

Mechanical ventilation requirement was significantly higher in the septic shock group compared to other admissions (100% vs. 86.59%; $p < 0.001$). These patients also had longer hospital stays (median 7 vs. 3.99 days; $p < 0.001$). The overall mortality rate was 21.23% (n = 76), with septic shock patients showing a significantly higher mortality rate of 32.96% (n = 59; $p < 0.001$) compared to other admissions (Table 2).

Association between PICU admission due to septic shock and mortality

Patients admitted with septic shock demonstrated a 2.73 times higher risk of death compared to those admitted for other causes. This association persisted after adjusting for age, prematurity history, number of comorbidities, PRISM score, mechanical ventilation requirement, and length of hospital stay (RR: 2.73; 95% CI 1.36–5.46; $p = 0.005$) (Table 3).

Discussion

In this study of pediatric patients admitted to a Peruvian national reference hospital's PICU, we found a statistically significant association between septic

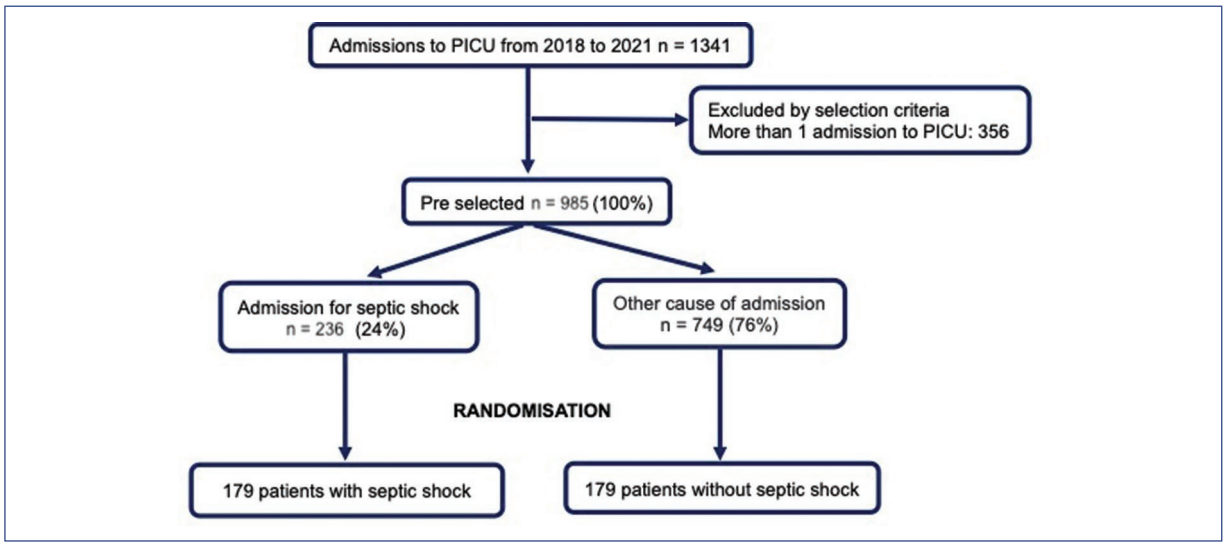
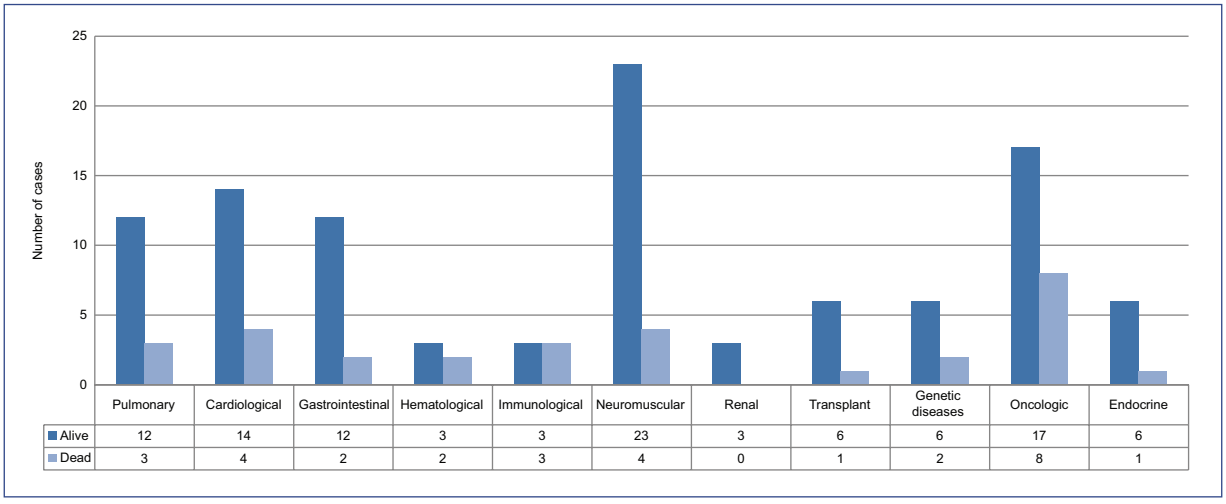


Figure 1. Participant selection flow diagram.



	Pulmonary	Cardiological	Gastrointestinal	Hematological	Immunological	Neuromuscular	Renal	Transplant	Genetic diseases	Oncologic	Endocrine
Alive	12	14	12	3	3	23	3	6	6	17	6
Dead	3	4	2	2	3	4	0	1	2	8	1

Figure 2. Distribution of prior medical conditions and mortality*.
*Patients who had a single comorbidity were considered, and the mortality evaluated was general.

shock admission and mortality during PICU stay. This association persisted after adjusting for other variables. Our findings contrast with those of Ahmed et al., who found no statistical association between sepsis and mortality in Ethiopian neonates[20]. This discrepancy may be attributed to differences in study populations, clinical practices, health-care conditions, or statistical power. Our results are particularly relevant as our literature review revealed no previous studies comparing mortality rates between patients admitted to PICU with septic shock versus other diagnoses.

Among patients admitted with septic shock, 60% presented with one or more comorbidities, slightly higher than the 43%[3] and 50%[2,4] reported in other studies. This difference might be explained by our study's exclusive focus on septic shock patients, whereas other studies included sepsis and severe sepsis cases. Current understanding suggests that patients with comorbidities have an increased likelihood of progressing from sepsis to shock, organ dysfunction, and mortality[21]. We concur with De Souza et al.'s findings of an association between multiple comorbidities and

Table 1. General characteristics of the patients at the time of admission to the PICU

Variable	Total, n (%)	With septic shock, n (%) (n = 179)	Without septic shock, n (%) (n = 179)	p
Sex				
Female	186 (51.96)	94 (52.51)	92 (51.40)	0.832[a]
Male	172 (48.04)	85 (47.49)	87 (48.60)	
Age				
p50 [IQR]	3.70 [9.42-0.75]	1.67 (7.75-0.42)	4.76 (10.5-1.58)	< 0.001[b]
Age group (years)				
< 1	106 (29.61)	74 (41.34)	32 (17.88)	< 0.001[a]
1-< 5	98 (27.37)	39 (21.79)	59 (32.96)	
5-< 10	75 (20.95)	38 (21.23)	37 (20.67)	
10 to more	79 (22.07)	28 (15.64)	51 (28.49)	
History of prematurity (wks. of gestation)				
No	304 (84.92)	155 (86.59)	149 (83.24)	0.306[c]
PTNB < 28	8 (2.23)	2 (1.12)	6 (3.35)	
PTNB 28-< 32	25 (6.98)	14 (7.82)	11 (6.15)	
PTNB 32-< 37	21 (5.87)	8 (4.47)	13 (7.26)	
Number of comorbidities				
None	143 (39.94)	71 (39.66)	72 (40.22)	0.021[a]
1	135 (37.71)	58 (32.40)	77 (43.02)	
2 or more	80 (22.35)	50 (27.93)	30 (16.76)	
PRISM, score				
p50 [IQR]	3.89 (21.3-0.95)	13.25 (46.6-3.8)	1.26 (3.94-0.52)	< 0.001[b]

PICU: pediatric intensive care unit, n: sample, %: percent, p50: median, IQR: interquartile range, wks: weeks, PTNB: preterm newborns, PRISM: pediatric risk of mortality score
a. p value obtained with χ^2 test
b. p value obtained with Mann–Whitney U-Test
p value obtained with Fisher's exact test

Table 2. Clinical course of patients in PICU

Variable	Total	With septic shock, n (%) (n = 179)	Without septic shock, n (%) (n = 179)	p
Mechanical ventilation				
No	24 (6.70)	0 (0.0)	24 (13.41)	< 0.001[a]
Yes	334 (93.30)	179 (100.00)	155 (86.59)	
Length of hospital stay (days)				
p50 [IQR]	5.37	7 (15-4)	3.99 (7.37-1.94)	< 0.001[b]
Discharge condition				
Alive	282 (78.77)	120 (67.04)	162 (90.50)	< 0.001[a]
Dead	76 (21.23)	59 (32.96)	17 (9.50)	

PICU: pediatric intensive care unit, n: sample, %: percent, p50: median, IQR: interquartile range
[a]p value obtained with χ^2 test
[b]p value obtained with Mann–Whitney U-Test

mortality in children with sepsis[3]. However, this analysis was exploratory, as our sample size calculation was not specifically designed to evaluate this relationship.

Children under 1 year of age constituted the largest group with septic shock (41%). Similarly, Schlapbach et al., analyzing data from Australia and New Zealand, found that children under 1 year represented 30% of cases[9]. Jaramillo-Bustamante et al. from Colombia reported that 56% of patients with sepsis, severe sepsis, or septic shock were under 2 years old[4]. These findings consistently indicate that young children, particularly those under 1 year, are most vulnerable to septic shock. However, in our study, age group was not associated with mortality risk in either crude or adjusted analyses.

Table 3. Association between septic shock admission to the PICU and mortality: Crude and adjusted model

Variable	Crude Model			Adjusted Model[a]		
	RR	95% CI	p	RR	95% CI	p value
Diagnosis						
Not Septic shock	Ref.			Ref.		
Septic shock	3.47	2.11-5.72	< 0.001	2.73	1.36-5.46	0.005
Age						
Years	1.00	0.96-1.05	0.830	1.04	0.99-1.09	0.119
History of prematurity weeks						
No	Ref.			Ref.		
PTNB < 28	0.58	0.09-3.71	0.569	1.37	0.29-6.54	0.694
PTNB 28-< 32	1.50	0.81-2.76	0.196	0.86	0.45-1.64	0.653
PTNB 32-< 37	0.45	0.12-1.70	0.236	0.41	0.11-1.55	0.191
Number of comorbidities						
None	Ref.			Ref.		
1	1.14	0.71-1.82	0.590	1.42	0.88-2.27	0.148
2 or more	1.32	0.80-2.21	0.281	1.83	1.08-3.09	0.024
PRISM						
Score	1.02	1.02-1.03	< 0.001	1.02	1.01-1.03	< 0.01
Requirement of mechanical ventilation						
No	Ref.			Ref.		
Yes	1.75	0.59-5.14	0.310	1.23	0.17-9.06	0.840
Length of hospital stay						
Days	0.96	0.92-0.99	0.046	0.97	0.94-0.99	0.041

PICU: pediatric intensive care unit, RR: relative risk, CI: confidence interval, Ref.: reference value
preterm newborns (PTNB), PRISM: pediatric risk of mortality score
[a]Model adjusted by age, prematurity, number of comorbidities, PRISM score, requirement of mechanical ventilation, and length of hospital stay.

The mortality risk in the PICU was significantly higher for patients admitted with septic shock compared to those admitted with other diagnoses, as evidenced by the higher mortality rates in the septic shock group. Multiple publications have reported similar findings regarding calculated mortality percentages and observed mortality rates favoring the septic shock group[3,6,22]. In addition, patients with septic shock demonstrated longer PICU stays compared to those admitted for other diagnoses, consistent with findings from several other studies[2,3,6]. These observations suggest that PICU patients admitted with septic shock present with greater severity and have a higher risk of prolonged unit stays compared to patients admitted with other diagnoses.

In the context of Sustainable Development Goals (SDGs)[23], our findings align directly with SDG 3 (Health and Wellbeing), providing vital information that could inform strategies to improve pediatric health outcomes and reduce mortality. In addition, by conducting this study in a South American population and considering population-specific characteristics and health-care access limitations, our research addresses SDG 10 (Reduce Inequalities) by quantifying clinical outcomes in pediatric PICU patients. From a clinical perspective, our study makes a valuable contribution to the scientific literature. The incorporation of our findings into future systematic reviews[24] will enable a more comprehensive evaluation of the incidence and magnitude of death risk associated with pediatric septic shock. This information will support health managers, political representatives, and stakeholders in better managing and planning for this disease burden[25].

We acknowledge several limitations in our study that may affect the interpretation of our results. The single-hospital sample source represents a selection bias that limits generalizability to other populations. However, as our institution is a national reference hospital adhering to national standards, some extrapolation may be possible within similar contexts. We also acknowledge an information bias due to omitting potentially influential factors on mortality, such as nutritional status and time to medical care, which were not evaluated or included in the adjusted analysis. Nevertheless, our adjustment

for confounding variables helps mitigate this bias and supports the study's internal validity.

Our study has notable strengths. The randomization of patients between groups enhances sample representation, while the 4-year study period allows for the observation of long-term trends. These strengths, combined with our rigorous methodology, reinforce the reliability of our findings.

Conclusion

Patients admitted to PICU with septic shock demonstrated a significantly higher mortality risk compared to those admitted for other causes. This association persisted after adjusting for age, prematurity history, number of comorbidities, PRISM score, mechanical ventilation requirement, and length of hospital stay. We recommend conducting multicenter studies to investigate the generalizability of these findings across different populations.

Acknowledgments

The authors would like to thank Dr. Juan Ortiz Chicchon, Chief of the PICU of HNERM, for facilitating the research permits.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Daher AH, Al-Ammouri I, Ghanem N, Abu Zahra M, Al-Zayadneh E, Al-Iede M. All-cause mortality in a pediatric intensive care unit at a teaching hospital in Amman, Jordan. Pediatr Int. 2022;64:e14940.
2. Jabornisky R, Sáenz SS, Capocasa P, Jaen R, Moreno RP, Landry L, et al. Epidemiological study of pediatric severe sepsis in Argentina. Arch Argent Pediatr. 2019;117:S135-56.
3. de Souza DC, Shieh HH, Barreira ER, Ventura AM, Bousso A, Troster EJ, et al. Epidemiology of sepsis in children admitted to PICUs in South America. Pediatr Crit Care Med. 2016;17:727-34.
4. Jaramillo-Bustamante JC, Marín-Agudelo A, Fernández-Laverde M, Bareño-Silva J. Epidemiology of sepsis in pediatric intensive care units: first Colombian Multicenter Study. Pediatr Crit Care Med. 2012;13:501-8.
5. Punchak M, Hall K, Seni A, Buck WC, DeUgarte DA, Hartford E, et al. Epidemiology of disease and mortality from a PICU in Mozambique. Pediatr Crit Care Med. 2018;19:e603-10.
6. Tan B, Wong JJ, Sultana R, Koh JC, Jit M, Mok YH, et al. Global case-fatality rates in pediatric severe sepsis and septic shock: a systematic review and meta-analysis. JAMA Pediatr. 2019;173:352-62.
7. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med. 2015;191:1147-57.
8. Moynihan KM, Alexander PM, Schlapbach LJ, Millar J, Jacobe S, Ravindranathan H, et al. Epidemiology of childhood death in Australian and New Zealand intensive care units. Intensive Care Med. 2019;45:1262-71.
9. Schlapbach LJ, MacLaren G, Festa M, Alexander J, Erickson S, Beca J, et al. Prediction of pediatric sepsis mortality within 1 h of intensive care admission. Intensive Care Med. 2017;43:1085-96.
10. Schlapbach LJ, Straney L, Bellomo R, MacLaren G, Pilcher D. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. Intensive Care Med. 2018;44:179-88.
11. Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis. Pediatr Crit Care Med. 2013;14:686-93.
12. Rodriguez-Portilla R. Epidemiological differences in SARS-CoV-2 admissions in a Peruvian pediatric intensive care unit during one year of pandemic. Bol Méd Hosp Infant México. 2021;78:6753.
13. Campos-Miño S, Sasbón JS, von Dessauer B. Los cuidados intensivos pediátricos en Latinoamérica. Med Intensiva. 2012;36:3-10.
14. Vásquez A, Herrera-Perez E, Tantaleán J, Escalante-Kanashiro R. PRISM como predictor de mortalidad en la unidad de cuidados intensivos pediátricos del Instituto Nacional de Salud del Niño, Perú 2012. Acta Med Peru. 2016;33:9.
15. Hannegård Hamrin T, Eksborg S. Risks for death after admission to pediatric intensive care (PICU)-A comparison with the general population. PLoS One. 2022;17:e0265792.
16. EsSalud W. Hospital Rebagliati de EsSalud Alcanza Máxima Categoría Por Su Alta Especialidad y Capacidad Resolutiva EsSalud. Available from: https://www.essalud.gob.pe/hospital-rebagliati-de-essalud-alcanza-maxima-categoria-por-su-alta-especialidad-y-capacidad-resolutiva [Last accessed on 2022 Dec 29].
17. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, et al. American College of critical care medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. Crit Care Med. 2017;45:1061-93.
18. Pollack M, Patel K, Ruttimann U. PRISM III: an updated pediatric risk of mortality score. Crit Care Med. 1996;24:743-52.
19. Hernán M, Robins J. Causal Inference: What if. Boca Raton: Chapman & Hall/CRC; 2020.
20. Ahmed AT, Farah AE, Ali HN, Ibrahim MO. Determinants of early neonatal mortality (hospital based retrospective cohort study in Somali region of Ethiopia). Sci Rep. 2023;13:1114.
21. Esper AM, Martin GS. Extending international sepsis epidemiology: the impact of organ dysfunction. Crit Care. 2009;13:120.
22. Breuling T, Tschiedel E, Große-Lordemann A, Hünseler C, Schmidt C, Niemann F, et al. Septic shock in children in an Urban Area in Western Germany-outcome, risk factors for mortality and infection epidemiology. Klin Pädiatr. 2015;227:61-5.
23. Gamez MJ. Objetivos y Metas de Desarrollo Sostenible. Desarrollo Sostenible. Available from: https://www.un.org/sustainabledevelopment/es/objetivos-de-desarrollo-sostenible [Last accessed on 2023 Dec 18].
24. Borges Migliavaca C, Stein C, Colpani V, Barker TH, Munn Z, Falavigna M, et al. How are systematic reviews of prevalence conducted? A methodological study. BMC Med Res Methodol. 2020;20:96.
25. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. Int J Health Policy Manag. 2014;3:123-8.

Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

RESEARCH ARTICLE

Waiting time for pediatric patients to be admitted for elective surgery at a National Pediatric Health Institute in Mexico City

Edmundo Vázquez-Cornejo[1], Elizabeth Cruz-Cruz[2], Heriberto Gómez-Gaytán[3], Daniela de la Rosa-Zamboni[4], Miriam G. Herrera-Segura[5], Araceli Saldívar-Flores[6], Olga Morales-Ríos[7], and Juan Garduño-Espinosa[2]

[1]Department of Drug Evaluation and Pharmacovigilance; [2]Evidence-Based Research Unit; [3]Quality Service; [4]Department of Comprehensive Patient Care; [5]Department of Planning; [6]Department of Nursing; [7]Institutional Center for Pharmacovigilance. Hospital Infantil de México Federico Gómez, Mexico City, Mexico

Abstract

Background: *Waiting times for elective surgery can be a physically and psychologically distressing experience for patients, affecting their satisfaction and perceptions of service quality. This study aimed to estimate the waiting time for pediatric patients admitted for elective surgery, identify events causing delays, and compare variations in the admission process.* **Method:** *Three cohorts of pediatric patients scheduled for elective surgery were prospectively followed: (A) weekday general surgery admissions, (B) weekday admissions to other surgical specialties, and (C) weekend surgical admissions. The admission process was mapped, timescales of each stage were recorded, and delay incidents were identified through direct non-participant observation after obtaining informed consent or assent.* **Results:** *The mean waiting time was 6.9 h (95% confidence interval [CI]: 6.6-7.2 h) for all scheduled surgical admissions. Patients in cohort B experienced the longest waiting time at 8.1 h (95% CI: 7.7-8.5 h, p < 0.0001). Primary causes of delay included lengthy transfers to the admission area, bed management issues, and limited staff availability during shift changes. Avoidable delays resulted in a mean additional waiting time of 1.4 h.* **Conclusions:** *The findings suggest that hospital waiting times could be reduced through organizational interventions targeting the main causes of delay and simplifying administrative processes.*

Keywords: *Waiting times. Process assessment. Patient flow. Public hospital. Process improvement. Pediatric hospital.*

Tiempo de espera para el ingreso hospitalario de pacientes pediátricos a cirugías electivas en un Instituto Nacional de Salud Pediátrico en la Ciudad de México

Resumen

Introducción: *Los tiempos de espera para cirugías electivas pueden ser una experiencia física y psicológicamente angustiante para los pacientes, afectando su satisfacción y percepciones sobre la calidad del servicio. Este estudio tuvo como objetivo estimar el tiempo de espera para pacientes pediátricos admitidos para cirugía electiva, identificar eventos que causan retrasos y comparar variaciones en el proceso de admisión.* **Método:** *Se siguieron prospectivamente tres cohortes de pacientes pediátricos programados para cirugía electiva: (A) admisiones de cirugía general entre semana, (B) admisiones*

***Correspondence:**
Edmundo Vázquez-Cornejo
E-mail: edmundoepiclin.qfb@outlook.com

Date of reception: 27-03-2024
Date of acceptance: 16-08-2024
DOI: 10.24875/BMHIM.24000046

Available online: 28-02-2025
Bol Med Hosp Infant Mex. 2025;82(1):35-43
www.bmhim.com

entre semana para otras especialidades quirúrgicas, y (C) admisiones quirúrgicas en fin de semana. Se mapeó el proceso de admisión, se registraron los plazos de cada etapa y se identificaron los incidentes de retraso mediante observación directa no participante después de obtener consentimiento informado o asentimiento. **Resultados:** *El tiempo medio de espera fue de 6.9 horas (IC 95%: 6.6-7.2 horas) para todas las admisiones quirúrgicas programadas. Los pacientes en la cohorte B experimentaron el tiempo de espera más largo con 8.1 horas (IC 95%: 7.7-8.5 horas, p < 0.0001). Las causas principales de retraso incluyeron transferencias prolongadas al área de admisión, problemas en la gestión de camas y disponibilidad limitada de personal durante los cambios de turno. Los retrasos evitables resultaron en un tiempo adicional medio de espera de 1.4 horas.* **Conclusiones:** *Los hallazgos sugieren que los tiempos de espera hospitalarios podrían reducirse mediante intervenciones organizativas dirigidas a las principales causas de retraso y simplificando los procesos administrativos.*

Palabras clave: *Tiempos de espera. Evaluación de procesos. Flujo de pacientes. Hospital público. Mejora de procesos. Hospital pediátrico.*

Introduction

Assessing waiting times for access to hospital services is relevant for public health systems seeking to expand their coverage[1-4]. Lengthy waiting times influence the perception of quality of care, user satisfaction[5,6], and health service planning, often perceived as inadequate[7]. Consequently, waiting times serve as indicators of service delivery efficiency[2].

Theory suggests that waiting times increase when demand exceeds service capacity[2,8,9]. However, organizational factors can affect waiting times independently of demand. In hospital bed management, up to 97% of incidents that increase waiting times involve clinical or administrative causes[10-14]. These delays lead to the loss of useful hospitalization days and create long queues for scheduled admissions[14-16].

Hospital structures focused on specialized work may impede the coordination of patient flow through multiple internal processes[5,10,17]. Health services commonly experience deficiencies in administrative processes, including unnecessary steps, avoidable delays, bottlenecks, and poor utilization of human and physical resources. These issues contribute to extended patient waiting times, even when care capacity is sufficient[18]. In addition, waiting times can induce anxiety in patients and their companions[19].

Various strategies have been implemented to improve hospital management processes[9]. Evidence supports enhancing existing service capacity or modifying local organizational behavior at the local level[7]. In this context, process re-engineering may facilitate improvements in both productivity and quality of care[20,21].

While waiting lists for elective surgery have been extensively studied, the hospital admission process itself is often excluded from common definitions and monitoring points[1-3,8,9]. Studies typically describe time to initial consultation, time to diagnosis, and time to procedure scheduling[9,20,22]. However, waiting times for hospital admission have not been as thoroughly investigated as those for emergency admissions[1].

This study aimed to estimate and compare waiting times and delay-causing events during the hospitalization of pediatric patients undergoing elective surgery in three different modalities over a week. The investigation spans from the patient and caregiver's arrival at the hospital until the patient occupies the assigned hospital bed.

Method

Study setting

The *Hospital Infantil de México Federico Gómez* is a tertiary care National Health Institute located in Mexico City that provides medical services to a very low-income population. The hospital also conducts research and teaching activities. It has 220 beds and nine operating theaters. Before the severe acute respiratory syndrome coronavirus 2 pandemic, the number of surgical interventions was 3,697, and the occupancy rate for surgical assistance was 64.8%, corresponding to 41.3% of hospital discharges. The Department of Surgery is divided into 11 specialties. General Surgery performs the most operations (39.2%), receiving patients from several services without surgical consultation (Endocrinology, Diabetes Clinic, Infectious Diseases, and anorectal oncological surgery). The remaining operations correspond to specialties with their own surgical consultation: Orthopedics, Oncology, Ophthalmology, Otolaryngology, Urology, Plastic Surgery, Cardiovascular Surgery, Thoracic Surgery, Stomatology, and Neurosurgery. In these specialties, 90.7% of elective surgical procedures involve a hospital stay of more than 24 h[23].

Admission for elective surgery

The scheduling of elective procedures is the responsibility of the attending physicians of each surgical specialty, who are assigned to each specialty during working days and morning shifts. Hospital admission involves three general stages: medical and surgical assessment, hospital admission procedures, and transfer to the inpatient service.

Study design

A prolective comparative cohort study was designed, comprising three cohorts: (A) weekday admissions, primarily general surgery, and oncology, (B) weekday admissions of specialties with their own surgical consultation, and (C) surgical specialties with weekend admissions.

Ethical approval

This study was reviewed and approved by the Hospital Research, Biosafety, and Research Ethics Committees under protocol number HIM-2022-073. Informed consent was obtained from accompanying parents, and assent was obtained before direct non-participant observation for children older than 7 years. Patient and caregiver privacy was protected by avoiding the dissemination of sensitive and identifiable information.

Participants

The study included patients scheduled for elective surgical procedures in any surgical specialty service of the hospital during 4 months of 2022 who were ≤ 18 years of age and had provided signed informed consent and assent. Patients whose scheduled surgeries were converted to emergency procedures due to changes in their health status were not included. Exclusion criteria were voluntary withdrawal under the terms of the informed consent/assent or rescheduling of the surgical admission.

Sample design

To estimate the waiting time for admission, a sample of 14 follow-ups per cohort was calculated based on a finite population of 3,697 annual surgeries[23], a variance of 0.92 h^2 from an initial pilot study, and an absolute precision of 0.5 h with 95% confidence. In addition, the sample size required for a hypothesis test of mean difference among three groups was calculated as 22 follow-ups per cohort, assuming a minimum difference of 1 h between groups, with 80% power and 95% confidence.

Non-probabilistic quota sampling was employed for each specialty, as the dynamics of the scheduling lists precluded the probabilistic selection of scheduled admissions.

Variables studied

Waiting time was defined as the time between the patient's arrival at the surgical admission consultation and their placement in the assigned hospital bed.

A delay incident was defined as any circumstance that, directly or indirectly, negatively affects the sequence of the planned admission process and results in increased hospital waiting time. This variable included both the frequency and duration (hours or minutes) of observed delay incidents within the admission process.

Additional demographic variables collected were age, sex, diagnosis, comorbidities, admitting surgical specialty service, need for mobility assistance (wheelchair, stretcher, other assistive devices), communication barriers (related to health problems), and history of surgery in the hospital.

Method of observation and monitoring

A multidisciplinary group of observers (eight members) was formed, with one researcher serving as lead trainer in the non-participant direct observation method. This method involves placing the observer in contact with the hospital admission process while collecting information externally, without intervention in the social group or process under study[24,25]. A three-week pilot study was conducted to standardize the recording method, identify appropriate spaces for follow-up, and delineate the segments of the admission process in each surgical specialty. Three distinct groups were identified in the admission process.

Data collection

Three forms were developed to record timing during the admission process, considering the operational characteristics of surgical specialties and any observed delays. Mobile phones with synchronized clocks were used for the measurements.

Patient contact and follow-up

The list of scheduled surgical patients was obtained at least 24 h before their admission appointment. Parents were contacted by telephone to confirm their hospital appointment attendance, explain the general nature of the study, and arrange a meeting time and location with the investigators before their admission appointment. At the hospital, the study's nature was explained in detail to the patient and caregiver, and the required informed consent or assent was obtained. Follow-up began when the patient and family member reported their arrival at the outpatient consultation area. The start and end times (in hours and minutes) of each hospital admission process stage were recorded. Monitoring concluded when the nurse in charge of the service instructed the patient and caregiver to occupy the designated bed.

Process mapping

Process mapping methodology was used to represent the existing admission process, following basic principles: process identification, data collection, map generation, process analysis, and action planning. A flowchart was used as the modeling tool for mapping the programmed admission process, developed through presentation and discussion of various sketches among the researchers[26,27].

Statistical analysis

Qualitative variables (gender, age group, comorbidity, mobility assistance, communication barriers, and previous surgery) were summarized as relative frequencies and percentages (%). The age group was determined by categorizing the patient's age, which was calculated using the patient's date of birth and admission follow-up date. The categories were: newborn (< 29 days), infant (29 days-23 months), pre-school (24 months-71 months), school (72 months-143 months), and adolescent (≥ 144 months). The percentage of admissions per hour was also determined for each cohort.

Continuous quantitative variables (age [years], waiting time [h], cumulative delay time [h], and delay-free waiting time [h]) were summarized using estimates of central tendency and dispersion appropriate to the type of distribution.

The point estimate and 95% confidence interval (95% CI) were calculated for waiting time in the whole sample, in the cohorts, and for each surgical specialty service. Using the estimated waiting times, we calculated the percentage of follow-ups that adhered to the World Health Organization (WHO) recommendations of ≤ 4 h for hospital admission[28].

The delay-free waiting time was calculated for each follow-up by subtracting the time spent on delay incidents from the total waiting time. This calculation was performed for each stage of the admission process: medical and surgical assessment, admission procedure, and transfer to the inpatient ward.

The distribution of variables (sex, age group, comorbidity, mobility aid, communication barrier, and previous surgery) was compared among cohorts A, B, and C. χ^2 test was used, or Fisher's exact test when sample sizes were small.

When distribution and homoscedasticity criteria between groups were met, waiting times between cohorts and their segments were compared using Kruskal–Wallis tests or one-way analysis of variance with Tukey's *post hoc* test. For independent pairs with normal distribution, Student's t-test was used; for non-normally distributed independent pairs, the Mann–Whitney U test was applied.

The paired t-test was used to compare the delay-free waiting time with the original waiting time for the entire group. Comparisons between each cohort's waiting time and its adjusted counterpart were performed according to the parametric distribution type of the pairs: Wilcoxon test for cohort A and paired t-test for cohorts B and C. All statistical analyses were performed using SPSS software version 25, with statistical significance set at 95% ($\alpha = 0.05$).

Results

The study included sixty-seven follow-ups across 11 surgical specialties. Sampling quotas were balanced, except for neurosurgery and otolaryngology. General surgery represented the highest scheduling volume (35.8%), followed by orthopedics (10.4%) (Table 1).

The baseline patient characteristics are presented in table 2. Cohort B showed a higher proportion of patients requiring in-hospital mobility assistance, including wheelchairs, stretchers, oxygen tanks, and strollers, among others.

Mapping the hospital admission process

The admission process was illustrated using a general flow chart (Fig. 1). Three main differences were identified between cohort A and cohort B.

Table 1. Composition of the sample by surgical specialty

Surgical specialty	Follow-ups carried out, n (%)	Expected sample, n (%)	Admission group*
General surgery	24 (35.8)	21 (32.5)	A, C
Oncology	5 (7.7)	5 (7.2)	A
Orthopedics	7 (10.4)	5 (7.7)	B
Ophthalmology	6 (9.0)	4 (5.5)	B
Otorhinolaryngology	6 (9.0)	3 (4.9)	B
Urology	5 (7.5)	5 (8.1)	B, C
Plastic surgery	5 (7.5)	4 (6.7)	B, C
Cardiovascular surgery	3 (4.5)	4 (6.5)	B, C
Thoracic surgery	3 (4.5)	2 (2.8)	B, C
Stomatology	2 (3.0)	5 (7.2)	B
Neurosurgery	1 (1.5)	7 (10.9)	B, C
Total	67	66	

*Admission group: **A:** general surgery admission on weekdays. **B:** other specialties admission on weekdays. **C:** weekend specialties admission.

Table 2. Patient characteristics included in the study

Characteristics	Total (n = 67)	Cohort A (n = 27)	Cohort B (n = 22)	Cohort C (n = 18)
Sex, n (%)				
Male	33 (49.3)	20 (74.1)	11 (50.0)	3 (16.7)
Female	34 (50.7)	7 (25.9)	11 (50.0)	15 (83.3)
Age group, n (%)				
Neonates	1 (1.5)	1 (3.7)	0	0
Infants	10 (14.9)	3 (11.1)	3 (13.6)	4 (22.2)
Children	38 (56.7)	16 (59.3)	16 (72.7)	6 (33.3)
Adolescents	18 (26.9)	7 (25.9)	3 (13.6)	8 (44.4)
Comorbidities, n (%)				
Yes	22 (32.8)	10 (37.0)	8 (36.4)	4 (22.2)
No	45 (67.2)	17 (63.0)	14 (63.6)	14 (77.8)
Mobility assistance, n (%)				
Yes	13 (19.4)	2 (7.4)	9 (40.9)	2 (11.1)
No	54 (80.6)	25 (92.6)	13 (59.1)	16 (88.9)
Communication barriers, n (%)				
Yes	14 (20.9)	4 (14.8)	8 (36.4)	2 (11.1)
No	53 (79.1)	23 (85.2)	14 (63.6)	16 (88.9)
Prior surgeries, n (%)				
Yes	37 (55.2)	16 (59.3)	15 (68.2)	6 (33.3)
No	30 (44.8)	11 (40.7)	7 (31.8)	12 (66.7)

Admission cohort. **A:** general surgery admission on weekdays. **B:** other specialties admission on weekdays. C: weekend specialties admission.

Time and order of consultation

In cohort A, 89% of consultations were scheduled between 11:00 and 12:00, followed by medical assessment between 12:00 and 15:00. In cohort B, 78% of consultations were scheduled between 09:00 and 11:00, with care provided on a first-come, first-served basis between 09:00 and 15:00.

Consultation dynamics

In cohort A, a pediatrician and surgeon performed the assessment simultaneously. In cohort B, the pediatrician and surgeon conducted assessments at different times, resulting in an additional 0.5-h wait.

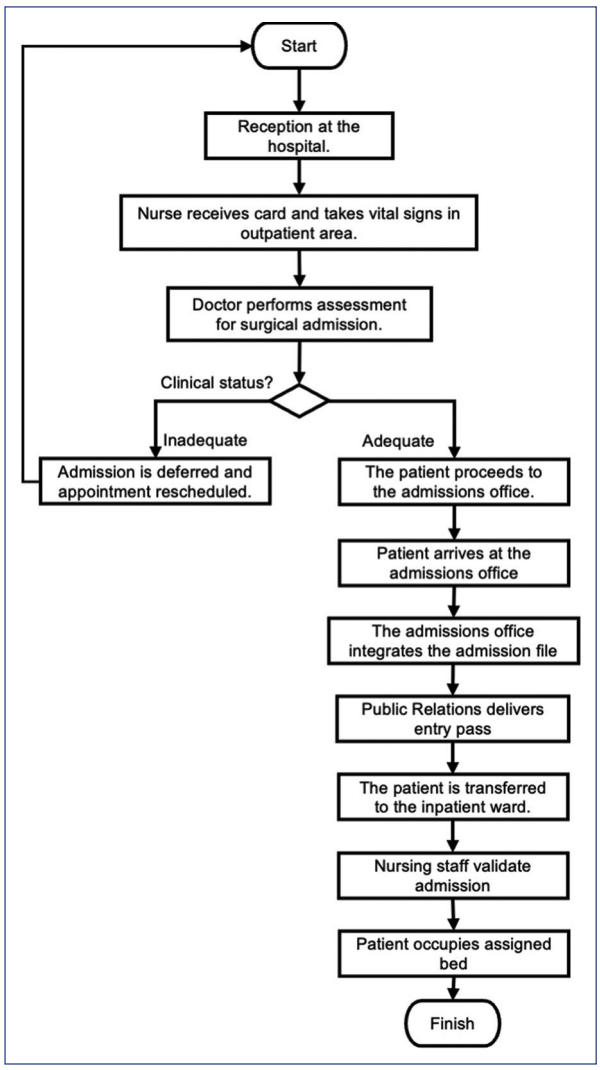


Figure 1. Simplified flowchart of the elective surgery admission process.

Transfer to admission

Following medical and surgical assessment, the children and their companions proceeded to the admission office. In cohort A, a resident pediatrician accompanied the patient and caregiver to the admission area. In cohort B, other specialties directed patients to the admission office, typically at 15:00, resulting in extended waiting times. In cohort C, patients were discharged and completed admission procedures over the weekend.

No significant differences were observed in admission procedures. Public relations staff provided information about admission and hospital rules to all scheduled admissions gathered in the admission area between 15:00 and 17:00, regardless of arrival time.

Waiting time for hospital admission

The estimated waiting time in the elective admission process was 6.9 h (± 1.3 h). The 95% CI for this parameter was between 6.6 and 7.2 h (Table 3). Significant differences were observed among the waiting times of cohorts A, B, and C ($p < 0.0001$). The comparison between cohorts B and A showed a significant difference of 1.8 h ($p < 0.0001$), while cohorts B and C differed by 1.9 h ($p < 0.0001$). Direct comparison between waiting times of cohorts A and C revealed no difference (mean difference 0.08 h, $p = 0.956$). Only 6% of total admissions met the WHO recommendation of waiting time ≤ 4 h, while 7.5% of admissions exceeded 9 hours. Most admissions (70.1%) were completed between 16:00 and 18:00.

Stages of the admission process

The two longest stages of the admission process were medical-surgical assessment (3.3 ± 0.9 h) and admission formalities (3.6 ± 1.3 h). No significant difference was found among the three cohorts in the first phase ($p = 0.305$). In the second stage, cohorts A (3.3 ± 0.9 h) and C (2.7 ± 0.9 h) differed significantly from cohort B (4.6 ± 0.9 h) ($p < 0.0001$).

Delay incidents

One hundred delay incidents were identified in the scheduled admission process, including 16 external to the admission process. External incidents comprised leaving care areas (n = 4), arriving hours before scheduled appointments (n = 4), and essential medical procedures during assessment (n = 8) such as cast removal, electrocardiograms, and blood sampling. The remaining 84 delay incidents occurred across 52 follow-ups, with varying distribution per follow-up. Fifteen follow-ups (22.4%) experienced no delays during the admission process.

The most significant delays in terms of duration and frequency occurred during transfer to the admission procedure area (average delay 98 min), unavailability of beds (average delay 88 min), and lack of admission staff due to shift changes (average delay 46 min). These three delay types accounted for 63.9% of total delay time (Table 4).

Delays resulted in three major periods of inactivity: waiting time for surgical consultation (mean 102 min, maximum 238 min), transfer to the admission area for cohort B patients (mean 51 min, maximum 242 min),

Table 3. Waiting times for scheduled surgical admission

Surgical admission process	Waiting time (h)	
	$\bar{x}$ (± SD)	95%CI
Global estimate	6.9 (± 1.3)	6.6-7.2
Cohort A	6.4 (± 0.7)	6.1-6.6
Cohort B	8.1 (± 0.9)	7.7-8.5
Cohort C	6.3 (± 1.5)	5.6-7.0

SD: sample standard deviation; 95%CI: confidence interval with 95% confidence; x: arithmetic mean.
Admission cohort. A: general surgery admission on weekdays. B: other specialties admission on weekdays. C: weekend specialties admission.

and waiting time for admission to the inpatient service (mean 79 min, maximum 166 min).

Delay-free waiting time

The estimated delay-free waiting time was 5.5 h (± 1.5 h), representing a reduction of 1.4 h compared to the actual waiting time ($p < 0.0001$). Some cases with waiting times exceeding 9 h showed no reductions due to non-preventable delay incidents. Delay-free waiting times by cohort were: cohort A, 5.3 ± 1.5 h ($p < 0.0001$); cohort B, 5.9 ± 1.7 h ($p < 0.0001$); and cohort C, 5.3 ± 1.2 h (paired t, $p = 0.004$). Cohort B demonstrated the largest reduction in waiting time, averaging 2.2 h. No significant difference was found in delay-free waiting time among cohorts ($p = 0.336$).

Discussion

This study found that the average time for the elective surgery admission process was 6.9 h, including 1.4 h of cumulative delays. Few studies in Mexico examine the operational attributes of health services, leading to a lack of defined standards or criteria for assessing their appropriateness for users, particularly in pediatric services[20].

Following the WHO recommendation for non-urgent care, only 6% of admissions were completed within the expected 4-h window[28]. Other national estimates indicate that the average waiting time for hospital admission is 7 h, with a maximum of 10 hours. Furthermore, up to 60% of hospital admissions require 5-8 h for completion[10]. This aligns with our findings (68.7% between 5 and 7 h); however, these challenges and their causes are common across international health systems[8,9].

Two aspects encompass the multiple deficiencies and excessive complexity in care processes that result in increased queues and low utilization of resources (human and physical)[10,29,30], even when capacity may be sufficient[7,18]. The first aspect is the organization's functional structure, where clinical and administrative services lack control over patient trajectory beyond their departments. This negatively impacts the adoption of coordination mechanisms between care departments[11,12]. One indicator of this issue is that 77.6% of patients experience delays due to operational deficiencies in the admission process. In addition, patients in the third quartile (Q3) lose an average of 2.3 h during admission. These operational failures result in extended periods of inactivity[17]. Improving patient flow requires adopting a patient-centered process approach[11,12].

The second issue affecting waiting times relates to inefficiencies in hospital bed management. This impacts the hospital's ability to admit new patients, increases non-medical discharges, and results in significant loss of hospitalization days[10,14,16]. Delays in the discharge process indicate poor communication and information mechanisms within the hospital[10], which become more pronounced during high-demand periods[30]. In our study, 14% of incidents were related to bed management, representing the second most common cause of delay and prolonged waiting. Previous studies have identified bed management delays in up to 98% of hospital admissions[10]. The primary issue is bed availability, either due to delayed vacating of beds or extended maintenance procedures (cleaning, disinfection, among others)[10]. Administrative procedures constitute another significant cause of discharge delays. Studies show that clinical causes account for only one-third of delayed discharges, while administrative causes comprise the remaining two-thirds[13].

Additional research is needed to identify factors impeding smooth and timely discharge, particularly those affecting bed availability and admission start times. This includes examining the behavioral patterns of staff involved in these processes, which may be challenging to modify over time. Extended waiting times and negative interactions with staff can adversely affect the relationship between patients, healthcare institutions, and workers[6].

Other relevant aspects include the economic, physical, emotional, and social discomfort experienced by patients and caregivers[10,13]. Long waiting times for medical care are a significant source of dissatisfaction with health services[20] and show a proportional correlation with service saturation and quality of care[29-31]. In

Table 4. Category of delay in the surgical admission process

Category	n = 84 (%)	Cumulated delay (min)	Average delay (min)†
Delayed arrival at the admission office.	17 (20.2)	1658	98
Bed unavailable due to multiple causes.	12 (14.3)	1050	88
Shortage of hospital admissions staff.	20 (23.8)	916	46
Downtime between consultations	13 (15.5)	735	57
Delayed processing at the admissions office	13 (15.5)	665	10
Communication issues between medical and administrative staff.	3 (3.5)	322	107
Administrative delay before surgical assessment	3 (3.6)	258	86
Delays before admission to the inpatient ward	3 (3.5)	60	20

†The delay average was calculated based on the total number of patients studied. This information was then used to estimate the type of delay in each cohort.

addition, other factors influencing hospital delays, such as health status, comorbidities, and socioeconomic factors, need to be studied[20,21].

In recent decades, research has been used to enhance service capacity by redesigning systems and processes to increase service delivery[3,32,33]. This study applied process mapping to identify potential areas of workflow failures[27]. This approach identified appointment scheduling for admissions as a significant issue in the admission process design, as it caused unnecessary waiting between the completion of admission assessment and transfer to the hospital admission area. The mechanism that promotes efficient patient and caregiver flow during the consultation process is appointment scheduling at specific times, separate from outpatient consultations. Furthermore, the patient and caregiver are accompanied to the admission area with their file upon completing the admission assessment. In contrast, a first-come, first-served approach to outpatient consultations and surgical admissions lengthen waiting times and is the least efficient method. This improvement action has the potential to reduce waiting times and initiate hospital admission procedures earlier.

Finally, the central message is to simplify processes and prioritize patient care. However, this work only addressed the operational aspect, leaving strategic and tactical interventions pending[4]. Various options are available, including mathematical models, Markov chains, and artificial intelligence[3]. Another important consideration is the limitation that the quantitative rationality of process optimization in healthcare places on patient preferences and the flexibility required for equity. This paper's scope does not allow for a detailed exploration of these issues.

Conclusions

The waiting time for pediatric patients in the scheduled surgical admission process is 6.9 h (95% CI: 6.6-7.2 h), measured from arrival in the surgical consultation area until occupying the assigned hospital bed. The main issue identified in the process design is the allocation of appointments and surgical assessment schedules. Delays are primarily attributed to patient transfers to the hospital admission area, bed management, and staff availability during shift changes in the admission service. The findings suggest that simplifying the admission process and reducing delays could result in a decrease in waiting times by approximately 1.4 h.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. McIntyre D, Chow CK. Waiting time as an indicator for health services under strain: a narrative review. Inquiry. 2020;57:1-15.
2. OECD. Waiting Times for Health Services: Next in Line. OECD Health Policy Studies. Paris: OECD Publishing; 2020.
3. Ala A, Chen F. Appointment scheduling problem in complexity systems of the healthcare services: a comprehensive review. J Healthc Eng. 2022;2022:5819813.
4. Abdalkareem ZA, Amir A, Al-Betar MA, Ekhan P, Hammouri AI. Healthcare scheduling in optimization context: a review. Health Technol (Berl). 2021;11:445-69.
5. Xie Z, Or C. Associations between waiting times, service times, and patient satisfaction in an endocrinology outpatient department: a time study and questionnaire survey. Inquiry 2017;54:1-10.
6. Guiterrez A, Mendoza P. Tiempo de espera y calidad de atención en pacientes de odontoestomatología intervenidos en sala de operaciones. An Fac Med. 2019;80:183-7.
7. Kreindler SA. Policy strategies to reduce waits for elective care: a synthesis of international evidence. Br Med Bull. 2010;95:7-32.
8. Ballini L, Negro A, Maltoni S, Vignatelli L, Flodgren G, Simera I, et al. Interventions to reduce waiting times for elective procedures. Cochrane Database Syst Rev. 2015;23:CD005610.
9. Siciliani L, Borowitz M, Moran V, editors. Waiting Time Policies in the Health Sector: What Works? OECD Health Policy Studies. Paris: OECD Publishing; 2013.
10. García TG. Análisis de Incidencias Asociadas al Tiempo de Demora Intrahospitalaria en Relación a la Gestión de Camas en un Hospital de Referencia. Mexico City: 25 Congreso Internacional de Ciencias Administrativas; 2021. Available from: https://investigacion.fca.unam.mx/docs/memorias/2021/15.01.pdf [Last accessed on 2024 Feb 26].
11. Vos L, Chalmers SE, Dückers ML, Groenewegen PP, Wagner C, Van Merode GG. Towards an organisation-wide process-oriented organisation of care: a literature review. Implement Sci. 2011;6:8.
12. Dimakou S, Dimakou O, Basso HS. Waiting time distribution in public health care: empirics and theory. Health Econ Rev. 2015;5:61.
13. Zapata Goez LJ, Restrepo Hernández Y. Factores Asociados a las Estancias Hospitalarias Prolongadas no Justificadas de Pacientes Mayores de 18 Años, en Una Institución de III Nivel de Complejidad en el Municipio de Rionegro. [Tesis de Maestría en Administración en Salud, Thesis for a Master's degree in Health Administration]. Medellín: Facultad de Medicina, Universidad Ces; 2019. Available from: https://hdl.handle.net/10946/4692
14. Mendoza Giraldo D, Navarro A, Sánchez-Quijano A, Villegas A, Asencio R, Lissen E. Retraso del alta hospitalaria por motivos no médicos [Impact of delayed discharge for nonmedical reasons in a tertiary hospital internal medicine department]. Rev Clin Esp. 2012;212:229-34.
15. Manzano-Santaella A. From bed-blocking to delayed discharges: precursors and interpretations of a contested concept. Health Serv Manage Res. 2010;23:121-7.
16. Bastero NM, Martínez GL, Olivé CM. La Optimización de los Circuitos Hospitalarios en la Gestión de Camas. [Tesis de Maestría en Administración y Gestión en Cuidados de Enfermería, Thesis for a Master's Degree in Nursing Care Administration and Management]. Barcelona: Universidad de Barcelona; 2009. Available from: https://hdl.handle.net/2445/21568
17. Sánchez HJ. Diseño de Indicadores del uso Eficiente del Quirófano en un Hospital de Segundo Nivel. [Tesis de Maestría en Salud Pública, Thesis of Master's Degree in Public Health]. Mexico City: Instituto Nacional de Salud Pública, Escuela de Salud Pública de México; 2018. Available from: https://catalogoinsp.mx/files/tes/55576.pdf
18. Kreindler SA. Watching your wait: evidence-informed strategies for reducing health care wait times. Qual Manag Health Care. 2008;17:128-35.
19. Lizaur-Utrilla A, Martinez-Mendez D, Miralles-Muñoz FA, Marco-Gomez L, Lopez-Prats FA. Negative impact of waiting time for primary total knee arthroplasty on satisfaction and patient-reported outcome. Int Orthop. 2016;40:2303-7.
20. Centro de Investigación en Sistemas de Salud. Tiempos de Espera y Productividad en Rastreadores Clínicos Seleccionados en Hospitales del Sector Público. Morelos, Mexico: Instituto Nacional de Salud Pública; 2011. Available From: https://www.dged.salud.gob.mx/contenidos/dged/descargas/estudios/if_te_11.pdf [Last accessed on 2024 Feb 26].
21. Diaz-Koo CJ, Fernández-Mogollón J, Hirakata NC. Características de los pacientes con estancia prolongada en el servicio de cirugía general del Hospital Nacional Almanzor Aguinaga Asenjo. Rev Cuerpo Med HNAAA. 2020;13:251-6.
22. NHS England. Consultant-led Referral to Treatment Waiting Times Rules and Guidance. Consultant-led Referral to Treatment Waiting Times; 2021. Available from: https://www.england.nhs.uk/statistics/statistical-work-areas/rtt-waiting-times/rtt-guidance [Last accessed on 2024 Feb 26].
23. Anuario Estadístico del HIMFG 2019. Mexico City: Hospital Infantil de México Federico Gómez; c2024. Available From: https://www.himfg.edu.mx/interior/bioestadistica.html [Last accessed on 2024 Feb 26].
24. Eldh AC, Rycroft-Malone J, Van der Zijpp T, McMullan C, Hawkes C. Using nonparticipant observation as a method to understand implementation context in evidence-based practice. Worldviews Evid Based Nurs. 2020;17:185-92.
25. Busetto L, Wick W, Gumbinger C. How to use and assess qualitative research methods. Neurol Res Pract. 2020;2:14.
26. Ruiz F, Garcia F, Calahorra L, Llorente C, Gonçalves L, Daniel C, et al. Business process modeling in healthcare. Stud Health Technol Inform. 2012;179:75-87.
27. Antonacci G, Lennox L, Barlow J, Evans L, Reed J. Process mapping in healthcare: a systematic review. BMC Health Serv Res. 2021;21:342.
28. Manual Para la Implementación de un Sistema de Triaje Para los Cuartos de Urgencias. Washington DC: Pan American Health Organization; 2011. Catalog Number: OPS/HSS/HP/2010/007. Available from: https://www3.paho.org/hq/index.php?option=com_content&view=article&id=5259:2011-manual-un-sistema-triaje-cuartos-urgencias&Itemid=0&lang=es#gsc.tab=0 [Last accessed on 2024 Feb 26].
29. Hoot NR, Aronsky D. Systematic review of emergency department crowding: causes, effects, and solutions. Ann Emerg Med. 2008;52:126-36.
30. Izco LA. Propuesta de Mejora: Tiempo de Espera Para Ingresar del Paciente a Urgencias [Tesis de Maestría en Administración en Salud, Thesis for a Master's Degree in Health Administration.]. Navarra: Universidad Pública de Navarra; 2014. Available from: https://academica-e.unavarra.es/bitstream/handle/2454/14005/ana%20izco.pdf?sequence=4&isallowed=y
31. Flores C. La saturación de los servicios de urgencias: una llamada a la unidad. Emergencias. 2011;23:59-64.
32. Le DX, Do HT, Bui KT, Hoang TQ, Nguyen GH, Nguyen AV, et al. Lean management for improving hospital waiting times-Case study of a Vietnamese public/general hospital emergency department. Int J Health Plann Manage. 2022;37:156-70.
33. Marin-Garcia JA, Vidal-Carreras PI, Garcia-Sabater JJ. The role of value stream mapping in healthcare services: A scoping review. Int J Environ Res Public Health. 2021;18:951.

Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

RESEARCH ARTICLE

Characteristics of preterm infants in pediatric rehabilitation at a referral hospital in Peru

Roger De la Cerna-Luna[1], Walter Chacon-Obregon[2], Paola Del Carpio-Samaniego[3], Ana Igei-Chiney[1], and Alvaro Taype-Rondan[4]*

[1]Pediatric Rehabilitation Service, Hospital Nacional Edgardo Rebagliati Martins, EsSalud, Lima; [2]Rehabilitation Medicine Service, Hospital Santa Rosa, Ministerio de Salud, Lima; [3]Physical Medicine and Rehabilitation Service, Hospital Nacional Carlos Alberto Seguín Escobedo, EsSalud, Arequipa; [4]Research Unit for the Generation of Health Evidence Synthesis, Vicerrectorado de Investigación, Universidad San Ignacio de Loyola, Lima. Peru

Abstract

Background: *Prematurity is associated with a higher risk of disability. However, no studies on this population in rehabilitation settings in Peru have been found. This study aims to describe the characteristics of preterm infants at the Pediatric Rehabilitation Service of Hospital Nacional Edgardo Rebagliati Martins (SRP-HNERM).* **Method:** *A cross-sectional descriptive study was conducted. Medical records of preterm infants at SRP-HNERM from September 2023 to February 2024 were reviewed. The Hammersmith Infant Neurological Examination (HINE), General Movements Assessment (GMA), and other outcome measures were used for evaluation.* **Results:** *A total of 158 preterm infants were evaluated. During hospitalization, 51.3% were evaluated by a physiatrist, 47.5% received physical therapy, and 51.3% had feeding and swallowing disorders (FSD). After discharge, all patients were evaluated by a physiatrist at SRP-HNERM. Among infants with ≥ 44 weeks of corrected gestational age (CGA), 48.1% showed some degree of developmental delay, with global delay present in 34%. Of those with ≥ 48 weeks of CGA, 54.9% had an optimal HINE score. Normal GMA was observed in 51.2% of infants with ≤ 5 months of CGA. A higher frequency of global developmental delay was found in infants who had FSD during hospitalization and a lower frequency in those who had neonatal jaundice.* **Conclusions:** *Slightly more than half of the preterm infants were evaluated by a physiatrist, had FSD during hospitalization, had an optimal HINE score at ≥ 48 weeks of CGA, and had a normal GMA at ≤ 5 months of CGA. The presence of FSD during hospitalization should alert clinicians to a higher risk of global developmental delay in this population.*

Keywords: *Premature. Newborn. Infant. Physical medicine and rehabilitation. Peru.*

Características de lactantes prematuros en rehabilitación pediátrica de un hospital de referencia en Perú

Resumen

Introducción: *La prematuridad está asociada con mayor riesgo de discapacidad. Sin embargo, no encontramos estudios sobre esta población en entornos de rehabilitación en el Perú. Este estudio tiene como objetivo describir las características de lactantes prematuros en el Servicio de Rehabilitación Pediátrica del Hospital Nacional Edgardo Rebagliati Martins*

***Correspondence:**
Roger De la Cerna-Luna
E-mail: rdelacerna89@gmail.com

Date of reception: 04-09-2024
Date of acceptance: 25-11-2024
DOI: 10.24875/BMHIM.24000113

Available online: 28-02-2025
Bol Med Hosp Infant Mex. 2025;82(1):44-53
www.bmhim.com

(SRP-HNERM). **Método:** *Estudio descriptivo transversal. Se revisaron historias clínicas de lactantes prematuros en el SRP-HNERM desde septiembre 2023 hasta febrero 2024. Para la evaluación, se utilizaron el Hammersmith Examination (HINE), el General Movements Assessment (GMA) y otras medidas de resultado.* **Resultados:** *Se evaluaron 158 lactantes prematuros. Durante la hospitalización, 51.3% fue evaluado por un fisiatra, 47.5% recibió terapia física, y 51.3% presentó trastornos de la succión-deglución (TSD). Posterior al alta, todos fueron evaluados por un fisiatra en el SRP-HNERM. 48.1% de aquellos con ≥ 44 semanas de edad gestacional corregida (EGC) presentó algún grado de retraso del desarrollo, con retraso global presente en el 34%. 54.9% de aquellos con ≥ 48 semanas de EGC tuvo una puntuación HINE óptima. 51.2% de aquellos con ≤ 5 meses de EGC tuvo una GMA normal. Se encontró mayor retraso global del desarrollo en aquellos que tuvieron TSD en hospitalización, y menor en los que tuvieron ictericia neonatal.* **Conclusiones:** *Poco más de la mitad fue evaluado por un fisiatra, tuvo TSD en hospitalización, tuvo una puntuación HINE óptima a ≥ 48 semanas de EGC y tuvo una GMA normal a ≤ 5 meses de EGC. La presencia de TSD en hospitalización debería alertar sobre un mayor riesgo de retraso global del desarrollo en esta población.*

Palabras clave: *Prematuro. Recién nacido. Lactante. Medicina física y rehabilitación. Perú.*

Introduction

Prematurity is defined as birth before 37 weeks of gestational age and is one of the leading causes of neonatal and infant morbidity and mortality[1]. Long-term complications of prematurity can affect the pulmonary, renal, cardiac, neurological, and endocrine systems, among others[2]. According to a 2022 study, global prematurity rates range from 5% to 18%, with high rates observed in industrialized and developing countries[3]. In Peru, the incidence of prematurity varies depending on the source of information: 23% according to the 2020 Demographic and Family Health Survey (ENDES), 8.8% according to the World Health Organization (WHO), and 7% according to the Ministry of Health (MINSA)[4].

Prematurity is associated with a higher risk of disability, particularly motor and intellectual disabilities, making survival without disability an important outcome measure for this population[5]. Current data indicate that approximately 80% of preterm infants born between 22 and 32 weeks survive without any form of disability[5]. However, infants born very preterm (between 28 and 32 weeks) or with very low birth weight (≤ 1500 g) are at higher risk of having a lower health-related quality of life in early adulthood[6]. Children with a history of prematurity are at higher risk of developmental delays, poor academic performance, and lower intelligence quotients (IQ)[7-9].

There are highly predictive tests for motor and cognitive impairments in preterm infants, such as the Hammersmith Infant Neurological Examination (HINE) and Prechtl's General Movements Assessment (GMA)[10]. The HINE has the highest predictive accuracy for severe motor delay, whereas the GMA is most accurate for mild-to-moderate motor and cognitive delays[11]. Early developmental assessment in school-aged children with a history of prematurity shows good specificity and negative predictive value for cognitive impairments[12]. In Peru, screening tests such as the *Test Peruano de Evaluación del Desarrollo del Niño* (TPED) and the *Perfil de Evaluación del Desarrollo Infantil del Hospital Rebagliati* (REBA-PED) are used for child development assessment[13].

Predicting disability associated with prematurity is crucial for initiating early rehabilitation that can reduce the progression of motor impairments, prevent complications, and improve long-term independence[14]. Early rehabilitation in preterm infants is significant due to increased brain plasticity during the first months of life and the absence of fixed pathological movement patterns[15]. Previous studies suggest that early rehabilitation in preterm infants can reduce the incidence of motor delays and improve bone mineralization[16,17]. Oral-motor rehabilitation interventions have proven effective in improving oral feeding in preterm infants, who frequently experience feeding and swallowing disorders (FSD)[18,19].

Investigating the characteristics of preterm infants is essential due to their increased risk of long-term disabilities and health complications, as this enables early identification of developmental delays and timely interventions that can improve outcomes and quality of life[3,5,14]. These characteristics have been studied in various countries in Latin America and around the world[10,16-17,19]. However, no studies conducted in Physical Medicine and Rehabilitation (PM&R) settings in Peru have been found. Therefore, this study aims to describe the characteristics of preterm infants in the Pediatric Rehabilitation Service of *Hospital Nacional Edgardo Rebagliati Martins* (SRP-HNERM).

Method

Design and study population

A cross-sectional descriptive study was conducted using data from electronic medical records of preterm infants (born before 37 weeks of gestation) treated at SRP-HNERM over 6 months (September 1, 2023, to February 29, 2024). This timeframe was selected because the study variables were first recorded in SRP-HNERM medical records beginning in September 2023. All patients who met the selection criteria during this period were included.

Context

HNERM, located in Peru's capital, is one of the most important national referral centers for Social Health Insurance (EsSalud) due to its high level of specialization and problem-solving capacity[20]. All patients at SRP-HNERM were referred either from less complex EsSalud health-care facilities (outside Lima or from the Rebagliati Care Network) or through inter-consultation from other HNERM services.

Between September 2023 and February 2024, SRP-HNERM's staff included four physiatrists, 15 physical therapists, one occupational therapist, five speech and language therapists, and two psychologists. Of these, one physiatrist, five physical therapists, one occupational therapist, two speech and language therapists, and one psychologist were part of the Perinatal and Chromosomal Pathology Unit (also known as the "High-Risk Unit") of SRP-HNERM. This team provided both inpatient and outpatient care to preterm infants and their parents and/or responsible family members.

The Neonatology Service of HNERM includes neonatal intensive care units (NICU) and neonatal intermediate care units (NIMCU). In 2003, the perinatal mortality rate was estimated at 10.5/1,000 live births, and in 2018, the survival rate for NICU admissions was reported at approximately 75%.

Preterm infants hospitalized in the Neonatology Service of HNERM receive care from the SRP-HNERM multidisciplinary team, primarily consisting of physical therapy (PT) and speech and language therapy (SLT) interventions. During hospitalization, parents or responsible family members receive emotional support from the psychology team. Upon discharge, patients are referred to SRP-HNERM for outpatient care according to HNERM's technical guide for the follow-up of high-risk children.

During the initial outpatient medical consultation at SRP-HNERM, the physiatrist prescribes 10 PT sessions for all preterm infants. The prescription for SLT depends on the presence of FSD. When signs of possible neurological damage are observed during the consultation, patients are referred to Pediatric Neurology (part of the Pediatric Clinical Specialties Service at HNERM) at the physiatrist's choice.

SLT interventions for both hospitalized patients with FSD and outpatients include therapeutic techniques such as orofacial massage for tone normalization, extraoral massage to stimulate the rooting reflex, intraoral massage for non-nutritive sucking, orofacial and full-body stimulation to normalize altered sensitivity, and initiation of taste stimulation, among others.

Procedures

Following ethics committee approval, a list of all preterm infants seen in medical consultations between September 2023 and February 2024 was obtained from SRP-HNERM. Subsequently, 158 electronic medical records were manually reviewed to extract relevant information using a custom collection form, which was then imported into a Microsoft Excel database.

Preterm infants seen in medical consultations at SRP-HNERM were included because this facility has standardized the evaluation of all patients through a pediatric rehabilitation protocol[21], enabling better characterization of this group.

Variables

Based on a literature review, variables collected included demographic, anthropometric, comorbidity-related, hospitalization care, outpatient medical consultation care, and clinical evaluation data.

For FSD diagnosis (a disorder of nutritive sucking leading to feeding difficulties) during hospitalization, the Premature Oral Feeding Readiness Assessment Scale (POFRAS) was used[19]. This instrument comprises 18 items evaluating five variables with separate scoring: corrected gestational age (CGA), behavioral organization (state of consciousness, overall posture, and overall tone), oral posture (lips and tongue), oral reflexes (rooting, sucking, biting, and gag reflexes), and non-nutritive sucking (tongue movement, tongue grooving, jaw movement, sucking strength, maintenance of rhythm, maintenance of alertness, and signs of stress)[22]. Each item receives 0 to 1 or 2 points, with a

maximum total score of 35 points; a total score below 28 indicates FSD[22].

Child development was assessed using REBA-PED, an instrument evaluating five developmental areas and identifying warning signs in patients aged 1-72 months[13]. Developmental delay is classified as mild if > 0% but < 25% (equivalent to 2 standard deviations in similar instruments) in one or more areas, significant if ≥ 25% in one area, and global if ≥ 25% in two or more areas[20]. Previous studies detail the methodology for creating and applying REBA-PED[13,20].

HINE consists of 26 items assessing five neurological aspects in patients aged 2-24 months: cranial nerves (0-15), posture (0-18), movements (0-6), muscle tone (0-24), and reflexes and postural reactions (0-15), totaling a maximum of 78 points[23]. Items score 3 points if matching ≥ 75% of the typical development population, 2 points if matching 10-25%, and 1 or 0 points if matching ≤ 10%[23]. Optimal scores are ≥ 73 at 9 and 12 months and ≥ 67 and ≥ 70 at 3 and 6 months, respectively[10,23].

The GMA was used to assess general movements. This test evaluates the complex motor patterns generated by the fetal and neonatal nervous system, which include variable sequences in the neck, arms, trunk, and legs that fluctuate in intensity, speed, and range of motion[24]. These movements are called writhing movements from term age and gradually disappear at 46-49 weeks of CGA when fidgety movements (FM) begin to appear[24]. Abnormal movements can be classified as poor repertoire, cramped-synchronized, chaotic, absent FM, or abnormal FM. If FM is only sporadically present or absent at 3-5 months of CGA, severe neurological deficits such as cerebral palsy (CP) are likely to develop[24]. The patient must be awake, calm, and alert to perform the GMA[25]. The GMA is considered normal if the patient exhibits writhing movements during the first period (before 46-49 weeks of CGA) and/or FM during the second period (up to 5 months of CGA)[10,24].

The *Escala de Evaluación de la Succión Nutricia* was used to diagnose FSD in outpatient medical consultations. This instrument consists of seven questions: "Does the infant form and maintain a seal with the lips around the nipple?" "Does the infant maintain the sucking motion, lip, and jaw movement during feeding?" "Does the infant spit out or reject the nipple or bottle nipple?" "Does the infant have milk or vomit spill from the corners of the mouth?" "Does the infant have coughing episodes?" "Does the infant show signs of choking, gagging, or nausea?" and "Does the infant show signs of fatigue?"[26] Each item is scored from 1 to 4 points, with a minimum and maximum total score of 7 and 28 points, respectively; a total score of < 25 is considered indicative of FSD[26].

Statistical analysis

The data collected from the Excel spreadsheet were imported into Stata v17 software. Numerical variables were presented as means and standard deviations or medians and interquartile ranges (IQR), depending on the data distribution in normality tests. Categorical variables were presented with absolute and relative frequencies. To assess the factors associated with global developmental delay, crude (RR) and adjusted relative risks (aRR) and their respective 95% confidence intervals (95% CI) were calculated using Poisson regression with robust variance. The adjusted model included variables with a $p < 0.05$ in the crude analysis.

Results

A total of 158 preterm infants were evaluated at SRP-HNERM between September 2023 and February 2024. The median CGA was 52 weeks (IQR 40-72), and the median GA was 33 weeks (IQR 31-35). Most infants were moderately premature (43%), male (53.2%), from Lima (81.7%), new patients (74.4%), and had low birth weight (63.9%). Twins accounted for 25.9% of the sample. The most common comorbidities were neonatal jaundice (59.5%), congenital heart disease (33.5%), and retinopathy of prematurity (ROP) (21.5%). The median length of hospital stay was 19 days (IQR 6-33). Among the infants, 51.3% were evaluated by a physiatrist during hospitalization, and 47.5% received PT while hospitalized. FSD was present in 51.3% during hospitalization, and 85.2% received SLT for this reason. Parents and/or relatives of 36.1% of infants received emotional support during hospitalization (Table 1).

After hospital discharge, all patients were evaluated by the physiatrist at SRP-HNERM, with a median time of 1 month from discharge to the first outpatient medical consultation. All continuing patients received outpatient PT after the first outpatient medical consultation, and the median time from birth to the first session was 2 months (IQR 1-4). Only 5% of the continuing patients received outpatient SLT for FSD, with a median time of 1 month from birth to the first session (Table 1).

Among the infants, 4.4% had macrocephaly, 3.8% had microcephaly, and 9.5% had some form of positional cranial deformity. Asymmetrical skin folds were

Table 1. Demographic, anthropometric, comorbidity-related, and hospitalization care characteristics of preterm infants (n = 158)

Characteristics	n (%)
CGA (in months)*	3 (0-8)
CGA (in weeks)*	52 (40-72)
GA (in weeks)*	33 (31-35)
Classification	
Late preterm	48 (30.4)
Moderate preterm	68 (43.0)
Very preterm	37 (23.4)
Extremely preterm	5 (3.2)
Male sex	84 (53.2)
From Lima	129 (81.7)
New patient	118 (74.4)
Birth weight	
Normal	26 (16.5)
Low weight	101 (63.9)
Very low weight	23 (14.6)
Extremely low weight	8 (5.1)
Twin	41 (25.9)
Comorbidities	
Neonatal jaundice	94 (59.5)
Congenital heart disease	53 (33.5)
Retinopathy of prematurity	34 (21.5)
Congenital hypotonia	12 (7.6)
Bronchopulmonary dysplasia	11 (7.0)
Intraventricular hemorrhage	8 (5.1)
Down syndrome	6 (3.8)
Congenital hypertonia	6 (3.8)
Metabolic bone disease	6 (3.8)
History of abdominal surgery	5 (3.2)
Hypothyroidism	4 (2.5)
Days of hospitalization*	19 (6-33)
Evaluated by the physiatrist during hospitalization	81 (51.3)
Received physical therapy during hospitalization	75 (47.5)
FSD during hospitalization	81 (51.3)
Received speech and language therapy during hospitalization for FSD	69 (85.2)
Emotional support to parents and/or family members during hospitalization	57 (36.1)
Received outpatient physical therapy (continuing patient) (n = 40)	40 (100)
Months elapsed from birth to the first session of outpatient physical therapy for those who received it*	2 (1-4)
Received outpatient speech and language therapy for FSD (continuing patient) (n = 40)	2 (5)

*Median (p25-p75).
CGA: corrected gestational age; GA: gestational age; FSD: feeding and swallowing disorder.

present in 15.8% of cases, whereas no patients exhibited orthopedic deformities. FSD was present in 12.7% of patients at the outpatient medical consultation. Among patients with 44 weeks or more of CGA, 48.1% exhibited some degree of developmental delay, with global delay present in 34%. Greater delays were observed in the gross motor (17.9%), hearing and language (17.9%), and fine motor (13.2%) areas (Table 2).

Among patients with 48 weeks or more of CGA, 54.9% had an optimal HINE score, with a median of 71 (IQR 64-76). Most patients had low HINE scores in muscle tone (80.5%), posture (70.7%), and reflexes and postural reactions (54.9%). In patients aged 5 months or less, 51.2% had a normal GMA. Among those showing abnormal movements, poor repertoire movements were the most common (11.9%). The GMA was deferred in 30.9% of these patients because they were not awake, calm, and alert during the assessment. A referral to Pediatric Neurology was made for 38% of patients (Table 2).

In the analysis of associated factors, a higher frequency of global developmental delay was found in patients with 80 weeks or more of CGA compared to those with less than 60 weeks of CGA (aRR: 1.83, 95% CI: 1.04-3.21), as well as in those who had FSD during hospitalization (aRR: 2.13, 95% CI: 1.17-3.88). In addition, a lower frequency of global delay was found in patients with neonatal jaundice (aRR: 0.47, 95% CI: 0.28-0.78) (Table 3).

Discussion

Most infants in this study were male. A national cohort study from 2016 in the Netherlands reported that male sex was a significant risk factor for spontaneous preterm birth, with a higher risk of neonatal morbidity[27]. However, a 2018 study in the UK involving high-risk pregnant women for preterm birth did not observe a significant increase in the risk of spontaneous or iatrogenic preterm birth when the fetus was male, which contradicts reports in low-risk pregnancies[28]. Regarding the potential implications of prematurity on child development, a systematic review from 2023 found that preterm males did not have greater impairment compared to females[29].

The most frequent comorbidities were neonatal jaundice, congenital heart disease, and ROP. A systematic review from 2021 reported that neonatal morbidities were important risk factors associated with lower IQ in young adults born very preterm or with very low birth weight[9]. Neonatal jaundice is a neurological risk factor

Table 2. Characteristics of preterm infants in outpatient medical consultation (n = 158)

Characteristics	n (%)
Developmental delay in those with ≥ 44 weeks of CGA (n = 106)	51 (48.1)
Delay in gross motor development	19 (17.9)
Delay in hearing and language development	16 (15.1)
Delay in fine motor development	14 (13.2)
Delay in personal-social development	8 (7.6)
Delay in intelligence and learning development	6 (5.7)
Global developmental delay in those with ≥ 44 weeks of CGA (n = 106)	36 (34.0)
Macrocephaly	7 (4.4)
Microcephaly	6 (3.8)
Positional cranial deformation	15 (9.5)
Brachycephaly	5 (3.2)
Dolichocephaly	4 (2.5)
Plagiocephaly	4 (2.5)
Scaphocephaly	2 (1.3)
Asymmetric skin folds	25 (15.8)
Orthopedic deformity	0 (0)
FSD	20 (12.7)
HINE score in those with ≥ 48 weeks of CGA (n = 82)*	71 (64-76)
Low score in muscle tone	66 (80.5)
Low score in posture	58 (70.7)
Low score in reflexes and postural reactions	45 (54.9)
Low score in cranial nerves	24 (29.3)
Low score in movements	12 (14.6)
Optimal HINE score in those with ≥ 48 weeks of CGA (n = 82)	45 (54.9)
GMA in those with ≤ 5 months of CGA (n = 84)	
Normal	43 (51.2)
Poor repertoire	10 (11.9)
Cramped-synchronized	4 (4.8)
Abnormal Fidgety movements	1 (1.2)
Deferred	26 (30.9)
Referral to pediatric neurology	60 (38.0)

*Median (p25-p75).
CGA: corrected gestational age; FSD: feeding and swallowing disorder; HINE: hammersmith infant neurological examination; GMA: prechtl's general movements assessment.

in neonates, associated with hearing, visual, and intellectual disabilities, as well as conditions such as autism spectrum disorder and attention-deficit/hyperactivity disorder[30]. A systematic review from 2024 found that 26% and 19% of preterm infants with congenital heart disease exhibited cognitive impairment and intellectual disability, respectively[31]. A systematic review from 2023 concluded that in preterm infants, ROP was associated with a higher risk of intellectual disability, cerebral palsy, behavioral problems, and developmental delay[32].

Just over half of the infants were evaluated by the physiatrist during hospitalization. The physiatrist typically is part of the multidisciplinary team that examines preterm infants during hospitalization and provides care in outpatient consultations[20,33]. Preterm infants hospitalized in the Neonatology Service of HNERM should be evaluated by the physiatrist at least once. However, many preterm infants were not evaluated, possibly due to a short hospitalization time (median of 19 days), compared to what was reported by studies from 2022 in Brazil (median of 39 days) and Malaysia (medians of 26 and 44 days for each group), and by a 2018 study across various European countries (medians of 52.4 and 76.5 days depending on the region)[34-36].

Just under half of the infants received PT during hospitalization. This could be related to the lack of evaluation of preterm infants by the physiatrist, who is the first in the multidisciplinary team to examine these patients and lead rehabilitation interventions. PT is often necessary for most preterm infants due to psychomotor delays caused by biological immaturity[16]. A systematic review from 2020 suggests that PT during hospitalization could have a significant effect on the mental and motor development of preterm infants, especially during the 1st year of life[37].

Just over half of the infants had FSD during hospitalization, which is higher than reported by a systematic review from 2021 (prevalence of 27%)[19]. A systematic review from 2022 concluded that oral feeding within 72 h after birth in preterm infants and low birth weight infants possibly reduces the risk of mortality, length of hospital stay, risk of sepsis, and weight loss at discharge[38]. A systematic review from 2021 revealed that oral-motor therapy interventions in preterm infants could reduce the time to transition to full oral feeding and the length of hospital stay, as well as increase feeding efficiency and weight gain[18]. More than 85% of infants received SLT during hospitalization for FSD; those who did not receive therapy likely missed it due to a short hospitalization time or because they were not in a condition to receive it.

After hospital discharge, all preterm infants were evaluated by the physiatrist at the SRP-HNERM, and the median time from discharge to the first outpatient medical consultation was 1 month. A consensus from 2023 among physiatrists in South Korea recommended outpatient medical evaluations for preterm infants within the 1st month after hospital discharge if there was at least one high-risk antecedent: brain injury, periventricular leukomalacia, grade 3 or 4 intraventricular hemorrhage, hypoxic-ischemic encephalopathy,

Table 3. Factors associated with global developmental delay in preterm infants with 44 weeks or more of corrected gestational age (n = 106)

Factors	Global developmental delay		
	No	Yes	RR (95% CI)
Sex			
Female	32 (61.5)	20 (38.5)	Ref
Male	38 (70.4)	16 (29.6)	0.77 (0.45-1.32)
CGA (in weeks), in tertiles			
44-59	28 (70.0)	12 (30.0)	Ref
60-79	27 (81.8)	6 (18.2)	0.61 (0.25-1.45)
80-132	15 (45.5)	18 (54.5)	1.82 (1.03-3.21)
GA (in weeks), in tertiles			
24-32	30 (66.7)	15 (33.3)	Ref
33-34	16 (59.3)	11 (40.7)	1.22 (0.66-2.27)
35-36	24 (70.6)	10 (29.4)	0.88 (0.45-1.72)
Birth weight			
Normal	12 (66.7)	6 (33.3)	Ref
Low weight	48 (69.6)	21 (30.4)	0.91 (0.43-1.93)
Very or extremely low weight	10 (52.6)	9 (47.4)	1.42 (0.63-3.20)
Days of hospitalization, in tertiles			
0-9	27 (64.3)	15 (35.7)	Ref
10-28	23 (76.7)	7 (23.3)	0.65 (0.30-1.41)
29-210	20 (58.8)	14 (41.2)	1.15 (0.65-2.05)
Optimal HINE score			
No	37 (60.7)	24 (39.3)	Ref
Yes	33 (73.3)	12 (26.7)	0.68 (0.38-1.21)
FSD during hospitalization			
No	65 (69.1)	29 (30.9)	Ref
Yes	5 (41.7)	7 (58.3)	1.89 (1.07-3.34)
Congenital heart disease			
No	45 (65.2)	24 (34.8)	Ref
Yes	25 (67.6)	12 (32.4)	0.93 (0.53-1.65)
Twin			
No	55 (65.5)	29 (34.5)	Ref
Yes	15 (68.2)	7 (31.8)	0.92 (0.47-1.82)
Neonatal jaundice			
No	22 (52.4)	20 (47.6)	Ref
Yes	48 (75.0)	16 (25.0)	0.53 (0.31-0.89)
Retinopathy of prematurity			
No	56 (65.1)	30 (34.9)	Ref
Yes	14 (70.0)	6 (30.0)	0.86 (0.41-1.79)

CGA: corrected gestational age; GA: gestational age; HINE: hammersmith infant neurological examination; FSD: feeding and swallowing disorder.

meningitis, encephalitis, ventriculomegaly, feeding disorders associated with malnutrition, neonatal sepsis, bronchopulmonary dysplasia with mechanical ventilation up to 36 weeks of CGA, neonatal jaundice, confirmed congenital or neuromuscular disorder, extreme prematurity, extremely low birth weight, high social risk, hypertonia, hypotonia, infantile spasms, or epilepsy[39].

Just under half of the infants with 44 weeks or more of CGA exhibited some degree of developmental delay, with greater delays in gross motor, hearing and language, and fine motor areas. This is consistent with findings from a 2023 study of children under 5 years old treated at the SRP-HNERM, who more frequently exhibited delays in hearing and language, and gross motor areas[20]. A systematic review from 2023 reported that moderate preterm infants had a higher risk of developmental delay compared to term-born infants[7]. The effect of prematurity on child development persists into school

age and beyond[40]. Systematic reviews from 2018 and 2020 concluded that preterm infants had lower scores in cognitive ability tests, as well as in motor skills, behavior, reading, mathematics, and spelling[8,40].

Just over half of the infants with 48 weeks or more of CGA had an optimal HINE score (median of 71). This percentage was lower than that found in a 2023 study of preterm infants in Norway (79.5% with optimal HINE at 3 months of CGA, median of 61.8) but higher than reported in a 2018 study of late preterm infants in Greece (25.4% with optimal HINE at 6 months of CGA, median of 59)[41,42]. The median HINE score was higher than reported by these studies and also higher than that of another study from 2022 in preterm infants in Italy (55.6 at 3 months of CGA)[10].

Just over half of the infants with 5 months or less of CGA exhibited a normal GMA. This percentage was lower than that found in a 2022 study of preterm infants in Italy, where 68.1% had normal FM[10]; in a 2023 study of preterm infants in India with 32 weeks or less of gestational age, where 54.9% and 94.4% had normal general movements and FM, respectively[43]; and in a 2023 study of very preterm infants in Germany, where 93.9% had normal FM[44].

A higher frequency of global developmental delay was found in infants with FSD during hospitalization. In preterm infants, having FSD at 40 weeks of CGA may be a clinically useful and simple marker of developmental delay risk[45]. Extreme preterm infants with FSD should be identified as high risk for motor delay at 4-5 years, compared to those without FSD[46]. Preterm infants with FSD are more likely to present language delays at 18 months of CGA[47].

A lower frequency of global developmental delay was found in infants with neonatal jaundice. A systematic review from 2023 concluded that neonatal jaundice has not been demonstrated to be a unique risk factor for developmental alterations in preterm infants, unlike in term newborns, where it is associated with hearing, neurological, and motor developmental alterations, particularly during the 1st year of life[30]. Therefore, more studies are needed in preterm infants with neonatal jaundice to determine its impact on child development[30].

Limitations and strengths

This study has limitations that should be considered to properly interpret its results: (1) as a retrospective study based on the review of electronic medical records, it is possible that the physiatrists in charge of the outpatient consultations at the SRP-HNERM incorrectly recorded some data. (2) Other relevant variables could not be collected as they were not systematically recorded in the medical records (such as the degree of neonatal jaundice or the receipt of phototherapy during hospitalization). (3) The study was conducted in a referral hospital in Lima, Peru, so the results may not be representative of other facilities. (4) Preterm infants not seen at the SRP-HNERM due to transportation, geographical, or other barriers were not included. (5) In addition, there may be a survival bias since preterm infants who died early were not included in the study.

However, to our knowledge, this is the first study to thoroughly evaluate the characteristics of preterm infants in a PM&R setting in Peru. It provides relevant information to understand the needs of this population and formulate improvement proposals.

Conclusions and recommendations

Slightly more than half of the preterm infants at the SRP-HNERM were evaluated by the physiatrist and had FSD during hospitalization. Slightly less than half received PT during hospitalization. Slightly more than half of infants with 48 weeks or more of CGA had an optimal HINE score. Slightly more than half of those with 5 months or less of CGA had normal GMA. A higher frequency of global developmental delay was found in infants who had FSD during hospitalization and a lower frequency in those who had neonatal jaundice.

These findings highlight the importance of adopting strategies to increase the number of preterm infants evaluated by the physiatrist and those who receive PT and SLT during hospitalization. After hospital discharge, it is necessary to strengthen outpatient care in PM&R for preterm infants, as a significant number showed poor outcomes in the predictive tests used in outpatient medical consultations. Finally, it is essential to recognize and address FSD early, both during hospitalization and on an outpatient basis, due to its association with global developmental delay.

Funding

The authors declare that they have not received funding.

Conflicts of interest

Roger De la Cerna-Luna and Ana Igei-Chiney work at Hospital Nacional Edgardo Rebagliati Martins. The other authors do not report any potential conflicts of interest related to this study.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. This study was approved by the Institutional Ethics Committee for Research of HNERM (Ethical Qualification Certificate AUT No. 082-CE-GHNERM-GRPRESSALUD-2024). All collected information remained strictly confidential and was used exclusively for the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Mitrogiannis I, Evangelou E, Efthymiou A, Kanavos T, Birbas E, Makrydimas G, et al. Risk factors for preterm birth: an umbrella review of meta-analyses of observational studies. BMC Med. 2023;21:494.
2. Pravia CI, Benny M. Long-term consequences of prematurity. Cleve Clin J Med. 2020;87:759-67.
3. Khandre V, Potdar J, Keerti A. Preterm birth: an overview. Cureus. 2022;14:e33006.
4. Guevara-Rios E. La prematuridad: un problema de salud pública. Rev Peru Invest Matern Perinat. 2023;12:7-8.
5. Bourke J, Wong K, Srinivasjois R, Pereira G, Shepherd CC, White SW, et al. Predicting long-term survival without major disability for infants born preterm. J Pediatr. 2019;215:90-7.
6. Bolbocean C, Van Der Pal S, Van Buuren S, Anderson PJ, Bartmann P, Baumann N, et al. Health-related quality-of-life outcomes of very preterm or very low birth weight adults: evidence from an individual participant data meta-analysis. Pharmacoeconomics. 2023;41:93-105.
7. Pettinger KJ, Copper C, Boyle E, Blower S, Hewitt C, Fraser L. Risk of developmental disorders in children born at 32 to 38 weeks gestation: a meta-analysis. Pediatrics. 2023;152:e2023061878.
8. McBryde M, Fitzallen GC, Liley HG, Taylor HG, Bora S. Academic outcomes of school-aged children born preterm: a systematic review and meta-analysis. JAMA Netw Open. 2020;3:e202027.
9. Eves R, Mendonça M, Baumann N, Ni Y, Darlow BA, Horwood J, et al. Association of very preterm birth or very low birth weight with intelligence in adulthood: an individual participant data meta-analysis. JAMA Pediatr. 2021;175:e211058.
10. Dicanio D, Spoto G, Alibrandi A, Minutoli R, Nicotera AG, Di Rosa G. Long-term predictivity of early neurological assessment and developmental trajectories in low-risk preterm infants. Front Neurol. 2022;13:958682.
11. Caesar R, Colditz PB, Cioni G, Boyd RN. Clinical tools used in young infants born very preterm to predict motor and cognitive delay (not cerebral palsy): a systematic review. Dev Med Child Neurol. 2021;63:387-95.
12. Wong HS, Santhakumaran S, Cowan FM, Modi N, Medicines for Neonates Investigator Group. Developmental assessments in preterm children: a meta-analysis. Pediatrics. 2016;138:e20160251.
13. De la Cerna-Luna R, Casas-Flores N, Igei-Chiney A, Taype-Rondan A. REBA-PED: propuesta de una herramienta para evaluar el desarrollo infantil en el contexto peruano. Rev Cuerpo Med HNAAA. 2023;16(2).
14. Palisano RJ, Orlin MN, Schreiber J. Campbell's Physical Therapy for Children. 6th ed. St. Louis, MO: Elsevier; 2023.
15. Taczała J, Latalski M, Dmoszyńska-Graniczka M, Aftyka A, Majcher P. Neurodevelopmental outcome and early rehabilitation of premature babies - is it needed in the first 2 years of life? Ann Agric Environ Med. 2021;28:172-8.
16. Parau D, Todoran AB, Balasa R. Physiotherapy intervention on premature infants-a pilot study. Medicina (Kaunas). 2024;60:138.
17. Torró-Ferrero G, Fernández-Rego FJ, Gómez-Conesa A. Physical therapy to prevent osteopenia in preterm infants: a systematic review. Children (Basel). 2021;8:664.
18. Chen D, Yang Z, Chen C, Wang P. Effect of oral motor intervention on oral feeding in preterm infants: a systematic review and meta-analysis. Am J Speech Lang Pathol. 2021;30:2318-28.
19. Weeks CL, Marino LV, Johnson MJ. A systematic review of the definitions and prevalence of feeding intolerance in preterm infants. Clin Nutr. 2021;40:5576-86.
20. De la Cerna-Luna R, Fernandez-Guzman D, Alvarado-Gamarra G, Taype-Rondan A. Developmental delay assessment in children < 5 years of age attended in the pediatric rehabilitation service of a reference hospital in Peru. Bol Med Hosp Infant Mex. 2023;80:189-201.
21. De la Cerna-Luna R, Aleman-Del Castillo A, Rado-Triveno J. Pediatric rehabilitation evaluation protocol. PM R. 2024;16:521-3.
22. Muñoz-Zambrano I, Cárdenas-Camayo Y, Cháves-Peñaranda MC. Evaluación del inicio de la alimentación oral en prematuros con "POFRAS" en instituciones hospitalarias: fiabilidad interobservador. Popayán Colombia. Acta Pediátr Méx. 2022;43:270-9.
23. Romeo DM, Apicella M, Velli C, Brogna C, Ricci D, Pede E, et al. Hammersmith infant neurological examination in low-risk infants born very preterm: a longitudinal prospective study. Dev Med Child Neurol. 2022;64:863-70.
24. Einspieler C, Bos AF, Libertus ME, Marschik PB. The general movement assessment helps us to identify preterm infants at risk for cognitive dysfunction. Front Psychol. 2016;7:406.
25. Abbasi H, Mollet SR, Williams SA, Lim L, Battin MR, Besier TF, et al. Deep-learning markerless tracking of infant general movements using standard video recordings. Annu Int Conf IEEE Eng Med Biol Soc. 2023;2023:1-4.
26. Rendon-Macias ME, Villasis-Keever MA, Martinez-Garcia MC. Validación de una escala clínica de la succión nutricia. Rev Med Inst Mex Seguro Soc. 2016;54:318-26.
27. Peelen MJ, Kazemier BM, Ravelli AC, De Groot CJ, Van Der Post JA, Mol BW, et al. Impact of fetal gender on the risk of preterm birth, a national cohort study. Acta Obstet Gynecol Scand. 2016;95:1034-41.
28. Teoh PJ, Ridout A, Seed P, Tribe RM, Shennan AH. Gender and preterm birth: is male fetal gender a clinically important risk factor for preterm birth in high-risk women? Eur J Obstet Gynecol Reprod Biol. 2018;225:155-9.
29. Christians JK, Ahmadzadeh-Seddeighi S, Bilal A, Bogdanovic A, Ho R, Leung EV, et al. Sex differences in the effects of prematurity and/or low birthweight on neurodevelopmental outcomes: systematic review and meta-analyses. Biol Sex Differ. 2023;14:47.
30. Solis-Garcia G, Raghuram K, Augustine S, Ricci MF, St-Hilaire M, Louis D, et al. Hyperbilirubinemia among infants born preterm: peak levels and association with neurodevelopmental outcomes. J Pediatr. 2023;259:113458.
31. Derridj N, Calderon J, Bonnet D, Khoshnood B, Monier I, Guedj R. Neurodevelopmental outcomes of preterm and growth-restricted neonate with congenital heart defect: a systematic review and meta-analysis. Eur J Pediatr. 2024;183:1967-87.
32. Diggikar S, Gurumoorthy P, Trif P, Mudura D, Nagesh NK, Galis R, et al. Retinopathy of prematurity and neurodevelopmental outcomes in preterm infants: a systematic review and meta-analysis. Front Pediatr. 2023;11:1055813.
33. Ferrara PE, Gatto DM, Codazza S, Zordan P, Stefinlongo G, DI Polito A, et al. PEP mask therapy for the rehabilitation of a pre-term infant with respiratory distress syndrome: a case report. Eur J Phys Rehabil Med. 2023;59:436-9.
34. Costa LP, Costa GA, Valete CO, Machado JK, Silva MH. In-hospital outcomes in preterm and small-for-gestational-age newborns: a cohort study. Einstein (Sao Paulo). 2022;20:eAO6781.
35. Yun WZ, Kassab YW, Yao LM, Khairuddin N, Ming LC, Hadi MA. Effectiveness and safety of early versus late caffeine therapy in managing apnoea of prematurity among preterm infants: a retrospective cohort study. Int J Clin Pharm. 2022;44:1140-8.
36. Maier RF, Blondel B, Piedvache A, Misselwitz B, Petrou S, Van Reempts P, et al. Duration and time trends in hospital stay for very preterm infants differ across European regions. Pediatr Crit Care Med. 2018;19:1153-61.
37. Soleimani F, Azari N, Ghiasvand H, Shahrokhi A, Rahmani N, Fatollahierad S. Do NICU developmental care improve cognitive and motor outcomes for preterm infants? A systematic review and meta-analysis. BMC Pediatr. 2020;20:67.
38. Chitale R, Ferguson K, Talej M, Yang WC, He S, Edmond KM, et al. Early enteral feeding for preterm or low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150:e2022057092E.
39. Hyun SE, Kwon JY, Hong BY, Yoon JA, Choi JY, Hong J, et al. Early neurodevelopmental assessments of neonates discharged from the neonatal intensive care unit: a physiatrist's perspective. Ann Rehabil Med. 2023;47:147-61.
40. Allotey J, Zamora J, Cheong-See F, Kalidindi M, Arroyo-Manzano D, Asztalos E, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. BJOG. 2018;125:16-25.
41. Paulsen H, Ljungblad UW, Riiser K, Evensen KA. Early neurological and motor function in infants born moderate to late preterm or small for gestational age at term: a prospective cohort study. BMC Pediatr. 2023;23:390.
42. Chatziioannidis I, Kyriakidou M, Exadaktylou S, Antoniou E, Zafeiriou D, Nikolaidis N. Neurological outcome at 6 and 12 months corrected age in hospitalised late preterm infants -a prospective study. Eur J Paediatr Neurol. 2018;22:602-9.
43. Kadam AS, Nayyar SA, Kadam SS, Patni BC, Khole MC, Pandit AN, et al. General movement assessment in babies born preterm: motor optimality score-revised (MOS-R), trajectory, and neurodevelopmental outcomes at 1 Year. J Pediatr X. 2022;8:100084.

44. Teschler U, Dathe AK, Heuser-Spura KM, Bialas J, Cordier LJ, Albayrak B, et al. General movements trajectories and outcome at 12 months in very preterm infants: an analysis of tendencies and pathological persistence. Sci Rep. 2023;13:21825.
45. Lainwala S, Kosyakova N, Power K, Hussain N, Moore JE, Hagadorn JI, et al. Delayed achievement of oral feedings is associated with adverse neurodevelopmental outcomes at 18 to 26 months follow-up in preterm infants. Am J Perinatol. 2020;37:483-90.
46. Rinat S, Mackay M, Synnes A, Holsti L, Zwicker JG. Early feeding behaviours of extremely preterm infants predict neurodevelopmental outcomes. Early Hum Dev. 2022;173:105647.
47. Adams-Chapman I, Bann CM, Vaucher YE, Stoll BJ, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Association between feeding difficulties and language delay in preterm infants using bayley scales of infant development-third edition. J Pediatr. 2013;163:680-5.e1-3.

Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

RESEARCH ARTICLE

Hemodynamic phenotypes in congenital diaphragmatic hernia and their association with morbidity and mortality

Daniel Ibarra-Ríos[1], José G. Mantilla-Uresti[2], Diana M. Barrios-Bautista[3], Alejandro Peñarrieta-Daher[4], Cristian R. Zalles-Vidal[4], Deneb A. Morales-Barquet[1], and Horacio Márquez-González[5]*

[1]Department of Neonatology, Instituto Nacional de Perinatología Isidro Espinosa de los Reyes, Mexico City; [2]Department of Neonatology, Hospital General de Soledad de Graciano Sánchez, San Luis Potosí; [3]Department of Neonatology, Unidad Médica de Alta Especialidad, Hospital de Gineco Obstetricia No. 4 Luis Castelazo Ayala, Mexico City; [4]Department of Surgery, Hospital Infantil de México Federico Gómez, Mexico City; [5]Clinical Research Service, Hospital Infantil de México Federico Gómez, Mexico City. Mexico

Abstract

Background: *Congenital diaphragmatic hernia (CDH) is a severe condition associated with high morbidity and mortality. Its severity correlates with the degree of pulmonary hypoplasia. Recent literature has emphasized the importance of identifying distinct hemodynamic phenotypes (HP) to guide physiology-based management.* **Method:** *We included all CDH patients evaluated by targeted neonatal echocardiography from January 2017 to April 2022. HPs were classified into three groups: HP1 (mild pulmonary hypertension [PH] without ventricular dysfunction), HP2 (pre-capillary PH), and HP3 (post-capillary PH). We compared differences between survivors and non-survivors using the Mann–Whitney U-test, analyzed baseline and pre/post-surgical echocardiographic parameters using the Wilcoxon test, estimated survival curves using Kaplan–Meier analysis, and compared length of stay using the Kruskal–Wallis test.* **Results:** *Among 28 included neonates, 24 survived (86%). HP distribution was: HP1 9 patients (32%), HP2 8 patients (29%), and HP3 11 patients (39%). Four patients died, two post-surgery and two without surgical intervention. Mortality-associated factors included higher pCO_2, lower left ventricular (LV) output, decreased LV compliance, and elevated pulmonary vascular resistance (PVR). Survival analysis revealed a non-significant trend toward higher mortality in HP2 (one death) and HP3 (three deaths). Follow-up demonstrated progressive increases in biventricular output, PVR reduction, and compensatory cerebral vasodilation.* **Conclusion:** *HP correlated with patient mortality, particularly in cases with greater pulmonary hypoplasia (higher CO_2) and compromised ventricular performance. Echocardiographic monitoring revealed improvements in biventricular performance, decreased PVR facilitating surgical intervention, and cerebral perfusion adaptation.*

Keywords: *Congenital diaphragmatic hernia. Echocardiography. Mortality. Hemodynamics. Hemodynamic monitoring. Phenotype.*

Fenotipos hemodinámicos en hernia diafragmática congénita y su asociación con morbilidad y mortalidad

Resumen

Introducción: *La hernia diafragmática congénita (HDC) es una patología grave y de alta morbimortalidad. Su gravedad está relacionada con el grado de hipoplasia pulmonar; Recientemente, se ha descrito la importancia de reconocer diferentes fenotipos hemodinámicos (FH) para el manejo fisiopatológico.* **Método:** *Se incluyeron pacientes con HDC evaluados mediante*

***Correspondence:**
Daniel Ibarra-Ríos
E-mail: ibarraneonato@gmail.com

Date of reception: 04-07-2024
Date of acceptance: 25-11-2024
DOI: 10.24875/BMHIM.24000093

Available online: 28-02-2025
Bol Med Hosp Infant Mex. 2025;82(1):54-62
www.bmhim.com

ecocardiografía funcional desde enero 2017 hasta abril 2022. Los FH se clasificaron en 3: FH1: Hipertensión pulmonar (HP) leve sin disfunción ventricular; FH2: HP precapilar; y FH3: HP postcapilar. Diferencias entre sobrevivientes y no sobrevivientes se compararon con U Man Whitney; parámetros ecocardiográficos basales, pre y post quirúrgicos con Wilcoxon. Las curvas de supervivencia se estimaron con Kaplan-Meier y la duración de la estancia hospitalaria se comparó con Kruskal Wallis. **Resultados:** *Se incluyeron 28 neonatos, 24 supervivientes (86%). Los FH encontrados fueron: 9 FH1 (32%), 8 FH2 (29%) y 11 FH3 (39%). Dos murieron tras cirugía y dos sin cirugía. Factores asociados a mortalidad fueron mayor pCO2, menor gasto cardiaco y distensibilidad del ventrículo izquierdo, y mayores resistencias vasculares pulmonares (RVP). Las curvas de supervivencia mostraron una tendencia no significativa hacia una mayor mortalidad en el FH2 y FH3. En seguimiento, se observó un aumento gradual del gasto biventricular, disminución de la RVP y vasodilatación cerebral compensatoria.* **Conclusión:** *Los FH se relacionaron con la mortalidad de los pacientes con mayor hipoplasia pulmonar y rendimiento ventricular subóptimo. El seguimiento ecocardiográfico mostró un aumento del gasto biventricular, una disminución de la RVP que permitió la cirugía y una adaptación de la perfusión cerebral.*

Palabras clave: *Hernia diafragmática congénita. Ecocardiografía. Mortalidad. Hemodinamia. Monitoreo hemodinámico. Fenotipo.*

Introduction

Congenital diaphragmatic hernia (CDH) is a developmental defect of the diaphragm, usually posterolateral, through which abdominal viscera migrate into the chest during fetal life, causing compression and hypoplasia with mainly ipsilateral lung involvement, but also contralateral damage. The herniation of abdominal viscera yields a complex pathophysiology (two-hit theory) characterized by pulmonary hypoplasia (arrest of both lungs) and compression (abnormal pulmonary parenchymal and vascular development); this generates aberrant pulmonary vasoreactivity and pulmonary hypertension (PH), and ventricular dysfunction (right ventricular [RV] hypertrophy and dilatation and different spectrum of left ventricular [LV] hypoplasia), which can lead to pulmonary venous hypertension.

It represents a serious pathology with high morbidity and mortality. Population-based studies have reported that the prevalence of CDH is between 1 in 2500 and 1 in 3000 live births. Approximately 80% of CDH cases are left-sided, 15% are right-sided, and < 5% are bilateral[1].

Despite advances in neonatal resuscitation and intensive care, newborns with CDH continue to have high mortality, with increasing recognition that cardiac dysfunction plays an important role. Current survival rates in population-based studies are around 55% to 80%. Highly specialized centers report up to 90% survival but rule out hidden mortality, mainly in the prenatal period[2].

Targeted neonatal echocardiography (TnECHO) programs have been established in several Neonatal Intensive Care Units (NICUs) with comprehensive guidelines, a training framework, and robust clinical governance processes[3]. This modern hemodynamic monitoring method includes anatomical assessment for congenital heart disease, PH assessment, and ventricular size and function evaluation, including shunts across the patent ductus arteriosus (PDA) and *foramen ovale* (PFO). Systolic and diastolic dysfunction have been described, correlating with mortality and the need for extracorporeal membrane oxygenation (ECMO)[4-9].

Recently, three main hemodynamic phenotypes (HPs) have been described[1,10,11]: 1. Mild or no PH with normal cardiac function; 2. Pulmonary arterial hypertension (pre-capillary PH) with either no cardiac dysfunction or primary RV dysfunction; and 3. Pulmonary venous hypertension (post-capillary PH) with primary LV dysfunction with or without RV dysfunction.

Method

The study was conducted in a Pediatric Tertiary Level Referral NICU with a Hemodynamic Consultation (HC) team in Mexico City. All patients with CDH consulted from January 2017 to April 2022 were included in the study. The Institutional Research Ethics Committee approved this retrospective study, and the requirement for informed consent was waived. All patients had a basal TnECHO study performed within 8 h of admission. Irrespective of the number of patients' studies, the closest pre-surgical TnECHO was considered; post-surgical TnECHO was taken after post-surgical stability was obtained. TnECHO and middle cerebral artery (MCA) Doppler were performed with the available equipment using a standardized imaging protocol based on the American Society of Echocardiography guidelines[12]: Acuson ×300™ (Siemens Healthcare, Munich, Germany; LU with a 9 MHz phased array transducer) during 2018-2019 and Vivid E90™ (GE Medical Systems, Milwaukee, WI, USA; with a 7-12 MHz phased

array transducer) during 2020-2022. After a comprehensive Hemodynamic Consultation (HC), a physiology-based recommendation was formulated; the attending team ultimately decided on the patient's treatment.

Vital signs were obtained from the cardiorespiratory monitor at the time of HC. The highest CO_2 in the first 72 h was recorded.

The study analyzed cardiac images using apical, subcostal, short axis, and RV 3-chamber (RV-3C) projections with M-mode, color Doppler, pulsed wave Doppler, and continuous wave Doppler. It evaluated pulmonary artery pressure, right and LV function, pulmonary vascular resistance (PVR), and cerebral circulation, with PH classified into three phenotypes.

For pulmonary artery pressure, right ventricular systolic pressure was determined by identifying regurgitant flow with color Doppler and applying the Bernoulli equation. The interventricular septum's motion, specifically its curvature during systole and diastole, was assessed at the papillary muscle level.

PVR was evaluated through pulmonary artery acceleration time (PAAT), right ventricular ejection time (RVET), and the velocity time integral (VTI) of the pulmonary Doppler profile[13]. Right ventricular function included right ventricular output (RVO), tricuspid annular plane systolic excursion (TAPSE), and fractional area change (FAC). RVO was calculated as the product of VTI, heart rate, and half the cross-sectional area of the pulmonary artery squared[14,15].

For LV systolic function, left ventricular output (LVO) was calculated similarly to RVO using aortic valve measurements. The Simpson's biplane method was applied to calculate the LV ejection fraction using two orthogonal imaging planes. LV diastolic performance involved calculating the E/A ratio of mitral valve flow and assessing pulmonary venous return at the pulmonary vein confluence using pulsed Doppler in the four-chamber view[16].

MCA Doppler was performed through the trans-temporal window.

HPs were classified into three groups (Fig. 1):

- HP1: Mild PH without ventricular dysfunction; PDA and PFO shunt predominantly left to right.
- HP2 (Pre-capillary PH phenotype): Moderate-to-severe PH with right ventricular dysfunction; PDA and FO shunt right to left.
- HP3 (Post-capillary PH phenotype): Moderate-to-severe PH with LV dysfunction/biventricular dysfunction; PDA shunt right to left, FO shunt left to right.

The differences between survivors and non-survivors were compared using the Mann–Whitney U-test. Baseline, pre-surgical, and post-surgical echocardiographic parameters were analyzed using the Wilcoxon test. Survival analysis was performed, and Kaplan–Meier survival curves were plotted. Length of stay was compared using the Kruskal–Wallis test.

Results

A total of 28 neonates were included, with 24 survivors (86%). The median maternal age was 24 years, with a low rate of prenatal diagnosis (25%). Only one patient had fetal surgery (survivor). Six patients (21%) were inborn with prenatal diagnosis included as a program to avoid postnatal transport (5 survivors and one death). From the overall population, 57% were intubated at birth, and only one patient required chest compressions and adrenaline at birth (out born, deceased). A left anatomical defect was found in 22 patients (78.5%), one left eventration (3.5%); four patients showed right-sided hernias (14.5%), and in one patient, the defect was bilateral (3.5%). Demographics are depicted in table 1.

At the time of HC, 20 patients were assessed on conventional mechanical ventilation and 8 (29%) under high-frequency oscillatory ventilation (HFOV). The HP encountered were 9 HP1 (32%), 8 HP2 (29%), and 11 HP3 (39%). Treatment recommendations were made according to the physiology found (Fig. 2).

Mild or no PH with normal cardiac function usually responded to appropriate ventilatory settings, lung recruitment, early switch to HFOV, and adequate sedation. TnECHO showed predominantly left-to-right flow through the PDA and PFO. In pre-capillary PH with either no cardiac dysfunction or primary RV dysfunction, management focused on reducing PVR with adequate ventilation, sedation, and pulmonary vasodilators (iNO and/or milrinone). TnECHO showed right-to-left flow through the PDA and PFO. In the third HP showing post-capillary PH with primary LV dysfunction, treatment was directed toward improving LV function (iNO could lead to clinical deterioration). TnECHO showed right-to-left flow through the PDA and left-to-right flow through the PFO.

When systemic vasoconstrictors were needed, norepinephrine was used; in the setting of high FiO_2, vasopressin was preferred for its theoretical benefit of reducing PVR[17] (norepinephrine was not recommended as it might increase PVR)[18]. In cases of right or biventricular dysfunction with a restrictive PDA, Prostaglandin

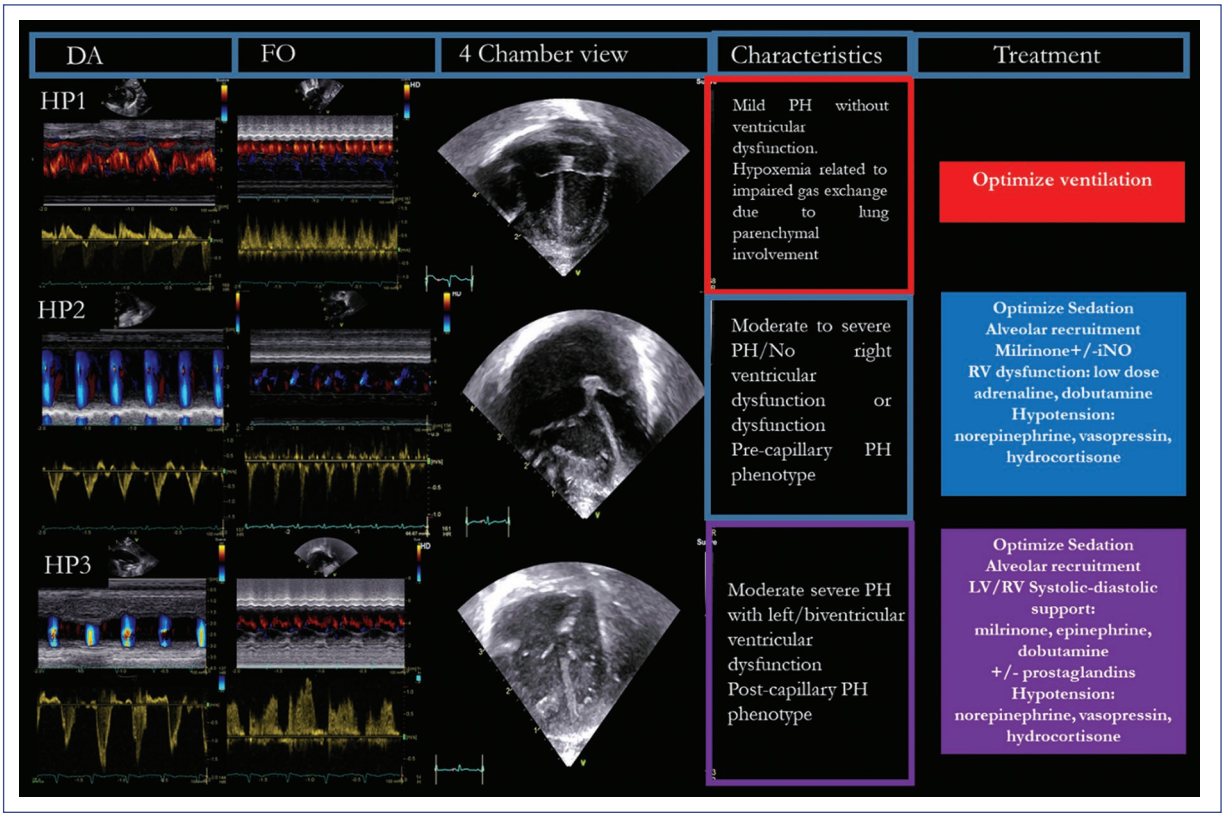


Figure 1. Hemodynamic phenotypes and standardized clinical management. DA: ductus arteriosus; FO: foramen ovale; HP: hemodynamic phenotype; PH: pulmonary hypertension; iNO: inhaled nitric oxide.

E1 (PGE1) was prescribed as a potent pulmonary vasodilator and acted as a "pop-off" valve for RV dysfunction[19]. Low-dose epinephrine infusion was indicated in six patients with HP3 (54%) and three patients with HP2 (37%). Hydrocortisone was used in six cases (two survivors and four non-survivors).

Two patients died after surgery, and two without surgery. Surgery occurred at a median of 6 (3, 7) days after hemodynamic stability was obtained. All patients with HP1 underwent thoracoscopic intervention. Clinical and hemodynamic differences between survivors and non-survivors were compared. Gestational age and birth weight between groups were similar. RVSP [available in 13 patients (46%)] showed no difference between groups. Factors associated with mortality were higher pCO_2, lower LVO, less compliant left ventricle depicted by the E/A ratio, and higher PVR demonstrated by the PAAT/RVET ratio (Table 2).

Survival curves were computed, finding a non-significant trend toward higher mortality in HP2 (one death) and HP3 (three deaths) (Fig. 3). HP2, followed by HP3, showed longer length of stay ($p < 0.05$) (Fig. 4).

At follow-up, a gradual increase in biventricular output, a decrease in PVR, and compensatory cerebral vasodilation were observed ($p < 0.05$) (Table 3).

Discussion

As described in the literature, CDH newborns with mild/no PH (HP1) tend to maintain stability without worsening of PH severity and have a good prognosis. In our cohort, all patients underwent thoracoscopic surgery, experienced no mortality, and had a reduced length of stay. Patients with severe PH at any point have a significantly higher risk for ECMO and mortality[20]. Patients who died were classified as HP2 and HP3 and had higher mortality and longer length of stay.

Of the seven patients with prenatal diagnosis in our study, only one patient with severe pulmonary hypoplasia (defined as liver herniation and observed/expected lung-to-head circumference ratio below 26%) underwent fetal surgery (survivor). In our population, it has been demonstrated that temporary endotracheal

Table 1. Demographic characteristics (n = 28)

Birth history	n = 28	
Maternal age (years), median (IQR)	24 (21, 30)	
Prenatal diagnosis, n (%)	7 (25)	
Fetal surgery, n (%)	1 (3.5)	
Female, n (%)	11 (39)	
Gestational age (weeks), median (IQR)	38.5 (37.8, 39)	
Inborn, n (%)	6 (21)	
Vaginal delivery, n (%)	11 (39)	
5-minute Apgar score, median (IQR)	8 (7, 9)	
Birthweight, median (IQR)	3022 (2897, 3200)	
Intubated at birth, n (%)	16 (57)	
Chest compressions, n (%)	1 (3.5)	
Associated malformations	7 (25)	
Anatomical defect, n (%)	Left: 22 (78.5) Left eventration 1 (3.5) Right: 4 (14.5) Bilateral: 1 (3.5)	Defect size: A: 7 (28) B: 10 (40) C: 7 (28) D: 1 (4)
Liver herniation, n (%)	10 (35)	
Hernia sac, n (%)	10 (35)	
Days of conventional mechanical ventilation, median (IQR)	7 (5, 12)	
HFOV, n (%)	8 (29%)	
Days of HFOV, median (IQR)	3 (1, 5)	
Days of iNO, median (IQR)	3 (2, 7)	
Days of life at surgery, median (IQR)	6 (3, 7)	
Thoracoscopic repair, n (%)	17 (61)	
Thoracoscopic converted to open, n (%)	2 (7)	
Open repair, n (%)	7 (25)	
No surgery, n (%)	2 (7)	
Patch repair, n (%)	8 (28)	
Survivors' length of stay, median (IQR)	21 (16, 30)	
Non survivors' length of stay, median (IQR)	4 (1, 7)	

IQR: interquartile range; CMV: mechanical ventilation; HFOV: high frequency oscillatory ventilation; iNO: inhaled nitric oxide.

occlusion of the fetus prevents the leakage of lung fluid, favoring its growth and improving survival by 32%[21].

Most protocols recommend immediate intubation at birth with gentle ventilation, avoiding mask ventilation to minimize air entry into the stomach, as well as gastric tube decompression. Recently, the consensus has suggested allowing spontaneous breathing of low-risk patients (mild CDH)[22]. In our study, 57% required advanced neonatal resuscitation, including intubation at birth (100% of inborn and 45% of outborn) and chest compressions in one patient (outborn, deceased). Inborn babies had moderate and severe CDH, so spontaneous breathing was not attempted with inborn babies had moderate and severe CDH, so spontaneous breathing was not attempted.

In the present study, we found that 80% of the neonates had left diaphragmatic hernia. As reported in a study by Kotecha et al., of the total number of CDH, about 90% correspond to hernias affecting the left side, and only 10% occur on the right side[23]. Poor prognostic factors have been described, including prematurity and low birth weight[24]. In our study, most of our patients were full-term (38.5 [37.8-39 weeks), with only one being a late-preterm at 35 weeks of gestation (survivor).

CDH is a condition that, despite advances in its diagnosis and management, has high mortality rates due to PH secondary to pulmonary hypoplasia. Among the biochemical variables that allow monitoring of pulmonary hypoplasia are the pCO_2 values in the first 72 h. Permissive hypercarbia is recommended[25]. Salas et al. found that $pCO_2 \geq 80$ mmHg in the first arterial blood gas and/or before ECMO may indicate severe pulmonary hypoplasia[26]. In addition, it has been reported that $PaCO_2 \geq 60$ mmHg in the first 24 h of life is associated with higher mortality[27]. Our study also found a significant association between increased pCO_2 values and mortality (66 [51,71] vs. 120 [85,182]).

As there are no randomized trials regarding optimal cardiovascular management, the correct diagnosis and effective management of PH and cardiac dysfunction are necessary for optimizing outcomes. HC with TnECHO is fundamental in delineating the pathophysiology-targeted treatment of CDH[28]. In our study, treatment recommendations were made based on the physiology assessed by a trained neonatologist using TnECHO and Neonatal Hemodynamics[29].

Milrinone, a phosphodiesterase-3 inhibitor that leads to pulmonary and systemic vasodilation, providing positive inotropism and lusitropism, was the most common vasoactive drug used in our population (68%). Given elevated PVR and frequent ventricular dysfunction, it is

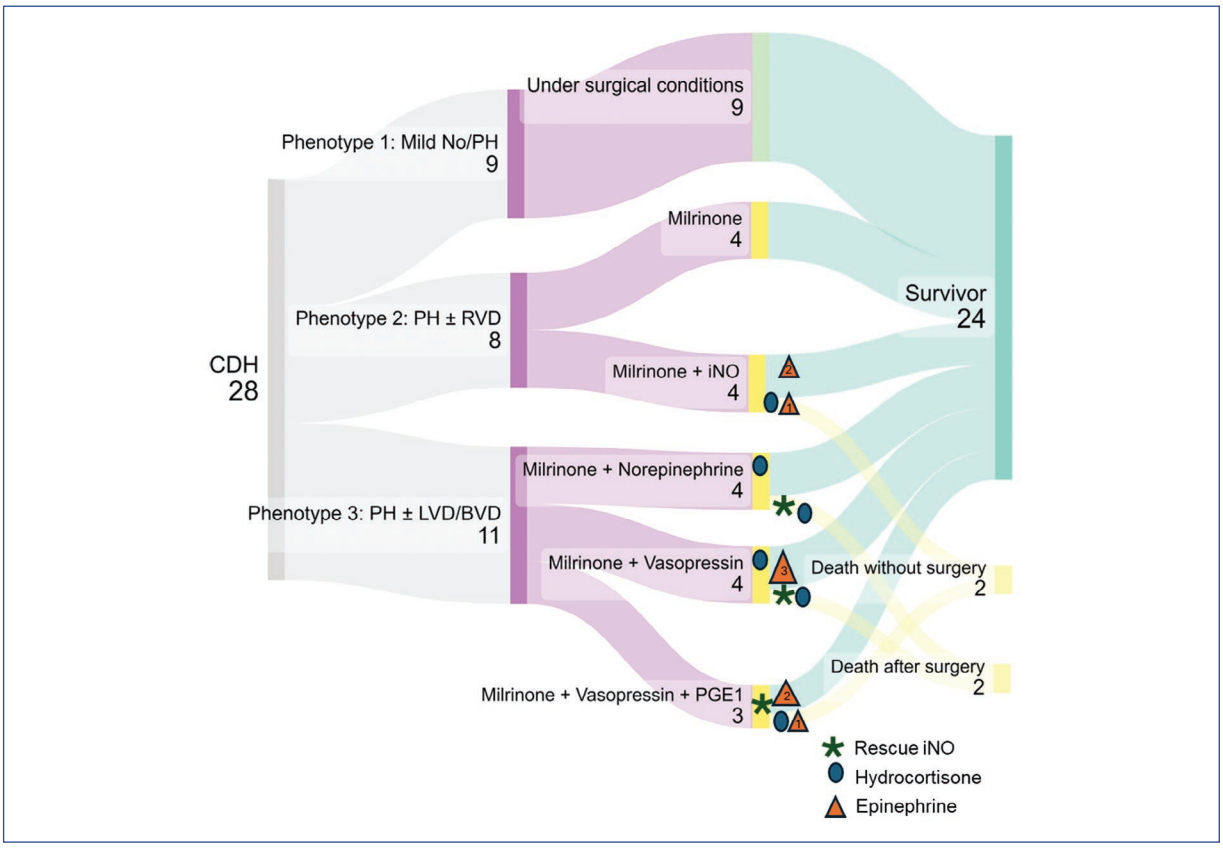


Figure 2. Sankey diagram depicting hemodynamic phenotypes, initial management, and survival.
*Rescue iNO. CDH: Congenital diaphragmatic hernia; PH: pulmonary hypertension; RVD: right ventricular dysfunction; LVD: left ventricular dysfunction; BVD: bi-ventricular dysfunction; iNO: inhaled nitric oxide; PGE_1: prostaglandin-E1.

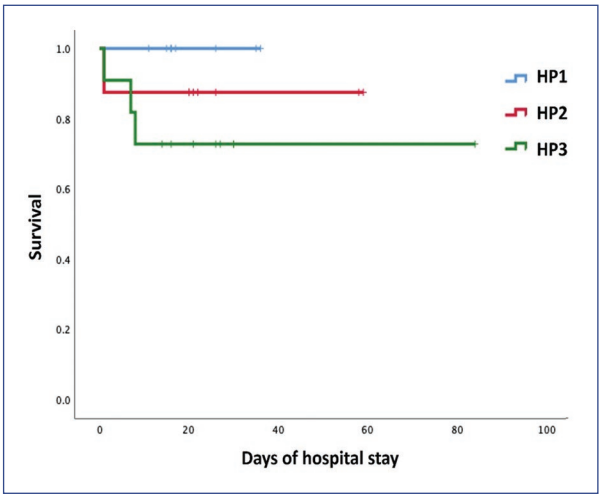


Figure 3. Kaplan–Meyer curves, survival probability according to hemodynamic phenotype.

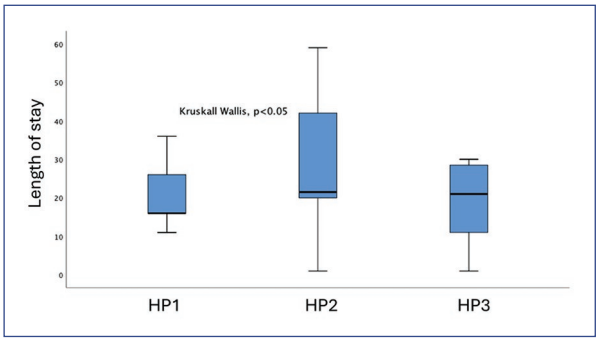


Figure 4. Length of stay between hemodynamic phenotypes.

a compelling agent for HP2 and HP3[30,31]. Nevertheless, it is still understudied in CDH. At present, there is an ongoing randomized phase 2 trial[32].

Hemodynamic variables associated with mortality were a lower LVO, less compliant left ventricle depicted by the E/A ratio, and higher PVR demonstrated by the PAAT/RVET ratio. Hemodynamically, prognostic markers of CDH have been described, including severe PH, LV dimensions, and dysfunction. In CDH patients, pulmonary vascular disease starts *in utero*, causing circulatory changes and LV hypoplasia that generates

Table 2. Clinical and hemodynamic differences between survivors and non-survivors

Clinical and echocardiographic parameters	Survivors		Non-survivors		p
	Median	P25-75	Median	P25-75	
Clinical parameters					
Gestational age (weeks)	39	38-40	38	37-39	0.4
Birth weight (g)	3020	2895-3203	3145	2755-3200	0.7
Maximum CO_2 (first 72 h)	66	51-71	120	85-182	0.01
Hemodynamic consultation					
SAP (mm Hg)	67	59-81	58	51-82	0.5
DAP (mm Hg)	43	38-47	49	26-53	0.7
HR (lpm)	138	125-152	136	126-160	1
RVO (mL/kg/min)	139	84-159	110	81-147	0.5
TAPSE (mm)	8.4	6.9-8.9	8.3	7.9-8.6	0.9
RV FAC (%)	42	38-44	37	25-41	0.1
RVSP (mm Hg)	62	43-66	67	64-70	0.4
RVET (ms)	192	171-207	186	120-197	0.4
PAAT (ms)	51	41-67	30	23-53	0.09
PAAT/RVET	0.29	0.24-0.33	0.19	0.16-0.26	0.04
PV S (cm/s)	39	33-50	37	25-48	0.5
PV D (cm/s)	55	42-71	47	36-57	0.4
E/A ratio	0.96	0.81-1.12	0.8	0.73-0.88	0.02
LVO (mL/kg/min)	139	108-160	73	48-79	0.001
Simpsons biplane EF (%)	64	57-70	56	54-66	0.3

SAP: systolic arterial pressure; DAP: diastolic arterial pressure; HR: heart rate; RVO: right ventricular output; TAPSE: tricuspid annular plane excursion; RV FAC: right ventricular fractional area change; RVPS: right ventricular systolic pressure; RVET: right ventricular ejection time; PAAT: pulmonary artery acceleration time; PV: pulmonary vein; LVO: left ventricular output; EF: ejection fraction.

Table 3. Baseline, pre-, and post-surgical echocardiographic assessment

Clinical and echocardiographic parameters	Baseline		Pre-surgical		Post-surgical		p
	Median	P25-P75	Median	P25-P75	Median	P25-P75	
SAP (mm Hg)	66	57-82	71	64-82	70	65-77	0.5
DAP (mm Hg)	43	37-49	43	37-52	43	34-51	0.6
HR (bpm)	137	126-152	146	130-158	147	139-163	0.03
RVO (ml/kg/min)	135	84-157	160	134-186	185	135-223	0.005
TAPSE (mm)	8.2	6.7-8.8	8.2	7.1-10.2	9.2	6.8-9.8	0.4
RV FAC (%)	41	38-44	39	37-42	46	39-51	0.2
RSVP (mmHg)	64	45-66	45	41-49	45	38-60	0.5
RVET (ms)	190	163-207	182	170-207	184	170-200	0.6
PAAT (ms)	50	40-64	51	43-64	58	45-73	0.5
PAAT/RVET	0.26	0.24-0.30	0.28	0.25-30	0.31	0.26-0.37	0.005
PV S (cm/s)	39	32-49	39	33-57	45	41-54	0.4
PV D (cm/s)	55	41-71	54	50-60	59	45-69	0.6
E/A ratio	0.82	0.69-1.07	0.88	0.73-1.04	0.96	0.68-1.15	0.6
LVO (ml/kg/min)	134	90-158	150	138-197	169	141-203	0.07
Simpsons biplane EF (%)	70	66-76	68	64-72	71	63-74	0.03
MCA PI	1.30	1.12-1.63	1.18	0.86-1.47	1.28	0.98-1.44	0.1
MCA RI	0.69	0.53-0.77	0.69	0.65-0.81	0.73	0.67-0.77	0.05

SAP: systolic arterial pressure; DAP: diastolic arterial pressure; HR: heart rate; RVO: right ventricular output; TAPSE: tricuspid annular plane excursion; RV FAC: right ventricular fractional area change; RVPS: right ventricular systolic pressure; RVET: right ventricular ejection time; PAAT: pulmonary artery acceleration time; PV: pulmonary vein; LVO: left ventricular output; EF: ejection fraction; MCA: medium cerebral artery; PI: pulsatility index; RI: resistive index.

systolic and diastolic dysfunction after birth[33]. In the largest randomized, double-masked, controlled multicenter study that compared the use of iNO in CDH, there was no difference in the combined endpoint of death/ECMO between patients treated with iNO and controls. ECMO use was higher in the iNO group (80% vs. 54%)[34]. It is possible that patients with HP3 had pulmonary venous hypertension secondary to LV diastolic dysfunction increasing wedge pressure and worsening pulmonary edema. In a recent large single-center cohort, Fraga et al. demonstrated that patients with CDH with LV dysfunction and left heart hypoplasia had the highest risk of ECMO use and death[35].

Based on this, the HC team did not recommend iNO in HP3 in our population. Although it was not part of the HC recommendation, rescue iNO was used in five patients prescribed by the attending team. It has been demonstrated in a large multicenter study that included 1777 CDH infants (863 with early iNO treatment) that iNO in the first 72 h of life was associated with significantly increased mortality and ECMO use. Stratification by HP and defect size did not uncover a subgroup that benefited from early iNO[36].

In three patients with right/biventricular dysfunction with a restrictive PDA, PGE1 was prescribed as a potent pulmonary vasodilator and a "pop-off" valve (2 survivors). It has been shown that PGE1 treatment improves oxygenation and hemodynamics[19,37].

Adrenal insufficiency is prevalent among patients with CDH[38]. Hydrocortisone was used in six cases (two survivors and all four non-survivors). As reported in the literature, steroid use was found in sicker newborns with increased mortality; currently, there are no proper guidelines to identify patients that might benefit, as prolonged steroid use might increase sepsis and mortality. In addition, 9 patients (28%) in HP2 and HP3 received a low-dose epinephrine infusion indicated by the attending team.

Recently, Le et al. reported an association between early systolic dysfunction of any ventricle and the need for ECMO. Failure to normalize biventricular function was associated with adverse outcomes. LV function normalized quicker and consistently with a milrinone infusion universally indicated by guidelines[39]. In our survival follow-up, a gradual increase in biventricular output, a decrease in PVR, and compensatory cerebral vasodilation were observed. Serial TnECHO might help identify cardiac dysfunction, recognizing that early treatment might improve prognosis. A protocolized approach recognizing different HP, assessing ventricular function, and atrial and ductal shunts enhances the understanding of CDH postnatal hemodynamics, allowing pathophysiology-based management[40].

Our study has several limitations. Only the patients with HC were included in the study. Only 21% had a prenatal diagnosis and were inborn. Outborn patients were filtered by time and survival to transport, leading to occult mortality. The strength is that it represents a case series in a middle-income country without ECMO that highlights the importance of hemodynamic phenotyping and depicts clinical and hemodynamic variables related to mortality.

Conclusion

HPs were related to patient mortality, which was higher in those with greater pulmonary hypoplasia (higher CO_2) and suboptimal ventricular performance. The post-capillary PH phenotype had higher mortality. Patients were treated according to pathophysiology; nevertheless, despite recent evidence discouraging its early use, rescue iNO was indicated in severe cases. Echocardiographic follow-up showed an increase in biventricular performance, a decrease in PVR that allows the repair of the defect, and an adaptation of cerebral perfusion.

Acknowledgments

The authors thank Dr. José Alberto García Aranda, his Board of Directors and the Board of Trustees from the *Hospital Infantil de México Federico Gómez*, for their support in establishing the Hemodynamic Consultation an Ultrasound Evaluation Program in Neonates in Critical Condition, 2017-2023.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's

confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. McHoney M. Congenital diaphragmatic hernia, management in the newborn. Pediatr Surg Int. 2015;31:1005-13.
2. Lally KP, Lasky RE, Lally PA, Bagolan P, Davis CF, Frenckner BP, et al. Standardized reporting for congenital diaphragmatic hernia--an international consensus. J Pediatr Surg. 2013;48:2408-15.
3. Singh Y. Echocardiography in the neonatal unit: current status and future prospects. Expert Rev Med Devices. 2024;21:307-16.
4. Evers PD, Scottoline B, Armsby LB. Acute right ventricular failure associated with pulmonary hypertension in pediatrics: understanding the hemodynamic profiles. J Perinatol. 2022;42:139-42.
5. Moenkemeyer F, Patel N. Right ventricular diastolic function measured by tissue Doppler imaging predicts early outcome in congenital diaphragmatic hernia. Pediatr Crit Care Med. 2014;15:49-55.
6. Altit G, Bhombal S, Van Meurs K, Tacy TA. Diminished cardiac performance and left ventricular dimensions in neonates with congenital diaphragmatic hernia. Pediatr Cardiol. 2018;39:993-1000.
7. Dao DT, Patel N, Harting MT, Lally KP, Lally PA, Buchmiller TL. Early left ventricular dysfunction and severe pulmonary hypertension predict adverse outcomes in "Low-Risk" congenital diaphragmatic hernia. Pediatr Crit Care Med. 2020;21:637-46.
8. Patel N, Lally PA, Kipfmueller F, Massolo AC, Luco M, Van Meurs KP, et al. ventricular dysfunction is a critical determinant of mortality in congenital diaphragmatic hernia. Am J Respir Crit Care Med. 2019;200: 1522-30.
9. Altit G, Bhombal S, Van Meurs K, Tacy TA. Ventricular performance is associated with need for extracorporeal membrane oxygenation in newborns with congenital diaphragmatic hernia. J Pediatr. 2017;191:28-34.e1.
10. Bhombal S, Patel N. Diagnosis and management of pulmonary hypertension in congenital diaphragmatic hernia. Semin Fetal Neonatal Med. 2022;27:101383.
11. Chaudhari T, Schmidt Sotomayor N, Maheshwari R. Diagnosis, management and long term cardiovascular outcomes of phenotypic profiles in pulmonary hypertension associated with congenital diaphragmatic hernia. Front Pediatr. 2024;12:1356157.
12. McNamara PJ, Jain A, El-Khuffash A, Giesinger R, Weisz D, Freud L, et al. Guidelines and recommendations for targeted neonatal echocardiography and cardiac point-of-care ultrasound in the neonatal intensive care unit: an update from the American Society of Echocardiography. J Am Soc Echocardiogr. 2024;37:171-215.
13. Yared K, Noseworthy P, Weyman AE, McCabe E, Picard MH, Baggish AL. Pulmonary artery acceleration time provides an accurate estimate of systolic pulmonary arterial pressure during transthoracic echocardiography. J Am Soc Echocardiogr. 2011;24:687-92.
14. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, Gamillscheg A, et al. Right ventricular function in infants, children and adolescents: reference values of the Tricuspid Annular Plane Systolic Excursion (TAPSE) in 640 healthy patients and calculation of z score values. J Am Soc Echocardiogr. 2009;22:715-9.
15. Jain A, Mohamed A, El-Khuffash A, Connelly KA, Dallaire F, Jankov RP, et al. A comprehensive echocardiographic protocol for assessing neonatal right ventricular dimensions and function in the transitional period: normative data and z scores. J Am Soc Echocardiogr. 2014;27:1293-304.
16. Schmitz L, Stiller B, Pees C, Koch H, Xanthopoulos A, Lange P. Doppler-derived parameters of diastolic left ventricular function in preterm infants with a birth weight <1500 g: reference values and differences to term infants. Early Hum Dev. 2004;76:101-14.
17. Mohamed AA, Louis D, Surak A, Weisz DE, McNamara PJ, Jain A. Vasopressin for refractory persistent pulmonary hypertension of the newborn in preterm neonates - a case series. J Matern Fetal Neonatal Med. 2022;35:1475-83.
18. Lakshminrusimha S, Russell JA, Wedgwood S, Gugino SF, Kazzaz JA, Davis JM, et al. Superoxide dismutase improves oxygenation and reduces oxidation in neonatal pulmonary hypertension. Am J Respir Crit Care Med. 2006;174:1370-7.
19. Hari Gopal S, Patel N, Fernandes CJ. Use of prostaglandin E1 in the management of congenital diaphragmatic hernia-a review. Front Pediatr. 2022;10:911588.
20. Leyens J, Schroeder L, Geipel A, Berg C, Bo B, Lemloh L, et al. Dynamics of pulmonary hypertension severity in the first 48 h in neonates with prenatally diagnosed congenital diaphragmatic hernia. Front Pediatr. 2023;11:1164473.
21. Cruz-Martínez R, Martínez-Rodríguez M, Gámez-Varela A, Nieto-Castro B, Luna-García J, Juárez-Martínez I, et al. Survival outcome in severe left-sided congenital diaphragmatic hernia with and without fetal endoscopic tracheal occlusion in a country with suboptimal neonatal management. Ultrasound Obstet Gynecol. 2020;56:516-21.
22. Horn-Oudshoorn EJ, Knol R, Cochius-den Otter SC, Te Pas AB, Hooper SB, Roberts CT, et al. Spontaneous breathing approach in mild congenital diaphragmatic hernia: a resuscitation algorithm. Front Pediatr. 2022;10:945090.
23. Kotecha S, Barbato A, Bush A, Claus F, Davenport M, Delacourt C, et al. Congenital diaphragmatic hernia. Eur Respir J. 2012;39:820-9.
24. Nam CP, Campos CV, Leal GN, Tannuri U, Ceccon ME, de Carvalho WB. Post-natal prognostic factors in CDH: experience of 11 years in a referral center in Brazil. Clinics (Sao Paulo). 2023;78:100217.
25. Snoek KG, Reiss IK, Greenough A, Capolupo I, Urlesberger B, Wessel L, et al. Standardized Postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO consortium consensus - 2015 update. Neonatology. 2016;110:66-74.
26. Salas AA, Bhat R, Dabrowska K, Leadford A, Anderson S, Harmon CM, et al. The value of $Pa(CO_2)$ in relation to outcome in congenital diaphragmatic hernia. Am J Perinatol. 2014;31:939-45.
27. Patel MJ, Bell CS, Lally KP, Lally PA, Katakam LI. Lowest $PaCO_2$ on the first day of life predicts mortality and morbidity among infants with congenital diaphragmatic hernia. J Perinatol. 2019;39:229-36.
28. Surak A, Mahgoub L, Ting JY. Hemodynamic management of congenital diaphragmatic hernia: the role of targeted neonatal echocardiography. World J Pediatr Surg. 2024;7:e000790.
29. Ibarra-Ríos D, Márquez-González H, Quiroga-Valdés A, Guzmán-Arce AE, Villanueva-García D. Analysis of the results of the neonatal functional echocardiography program in a third-level pediatric hospital. Bol Med Hosp Infant Mex. 2020;77:178-85.
30. Patel N. Use of milrinone to treat cardiac dysfunction in infants with pulmonary hypertension secondary to congenital diaphragmatic hernia: a review of six patients. Neonatology. 2012;102:130-6.
31. Kumar VH, Dadiz R, Koumoundouros J, Guilford S, Lakshminrusimha S. Response to pulmonary vasodilators in infants with congenital diaphragmatic hernia. Pediatr Surg Int. 2018;34:735-42.
32. Lakshminrusimha S, Keszler M, Kirpalani H, Van Meurs K, Chess P, Ambalavanan N, et al. Milrinone in congenital diaphragmatic hernia - a randomized pilot trial: study protocol, review of literature and survey of current practices. Matern Health Neonatol Perinatol. 2017;3:27.
33. Kinsella JP, Steinhorn RH, Mullen MP, Hopper RK, Keller RL, Ivy DD, et al. The left ventricle in congenital diaphragmatic hernia: implications for the management of pulmonary hypertension. J Pediatr. 2018;197:17-22.
34. Finer NM. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. The Neonatal Inhaled Nitric Oxide Study Group (NINOS). Pediatrics. 1997;99:838-45.
35. Fraga MV. Hedrick HL, Rintoul NE, Wang Y, Ash D, Flohr SJ, et al. Congenital diaphragmatic hernia patients with left heart hypoplasia and left ventricular dysfunction have highest odds of mortality. J Pediatr. 2024;271:114061.
36. Noh CY, Chock VY, Bhombal S, Danzer E, Patel N, Dahlen A, et al. Early nitric oxide is not associated with improved outcomes in congenital diaphragmatic hernia. Pediatr Res. 2023;93:1899-906.
37. Le Duc K, Mur S, Sharma D, Aubry E, Recher M, Rakza T, et al. Prostaglandin E1 in infants with Congenital Diaphragmatic Hernia (CDH) and life-threatening pulmonary hypertension. J Pediatr Surg. 2020;55:1872-8.
38. Robertson JO, Criss CN, Hsieh LB, Matsuko N, Gish JS, Mon RA, et al. Steroid use for refractory hypotension in congenital diaphragmatic hernia. Pediatr Surg Int. 2017;33:981-7.
39. Le LS, Kinsella JP, Gien J, Frank BS. Failure to normalize biventricular function is associated with extracorporeal membrane oxygenation use in neonates with congenital diaphragmatic hernia. J Pediatr. 2023;260:113490.
40. Lakshminrusimha S, Fraga MV. Longitudinal trajectory of ventricular function and pulmonary hypertension in congenital diaphragmatic hernia. J Pediatr. 2023;260:113550.

Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

CLINICAL CASE

Hydrocele of the canal of Nuck: a case report of an unusual disease

Bruna Suda-Rodrigues[1], Ma. Beatriz Ferraz-Cabral da Ponte[2], Márcio L. Duarte[3,4], and Élcio R. Duarte[1]*

[1]Department of Ultrasonography, Irmandade da Santa Casa de Misericórdia de Santos, Santos (SP); [2]Department of Internal Medicine, Universidade Metropolitana de Santos, Santos (SP); [3]Department of Radiology, Universidade de Ribeirão Preto – Campus Guarujá, Guarujá (SP); [4]Department of Radiology, Diagnósticos da América S.A., São Paulo (SP). Brazil

Abstract

Background: *Hydrocele of the canal of Nuck is a rare pathology with a prevalence of approximately 1% in females aged 0-16 years. Its prevalence in adults remains unknown. The condition develops due to persistent patency or failed obliteration of the canal of Nuck. Several factors may contribute to its development, including lymphatic disorders, trauma, infection, inflammation, or idiopathic causes. Clinically, it presents as edema in the groin or genital region without additional symptoms. Ultrasonography is the preferred diagnostic modality for hydrocele of the canal of Nuck.* **Case report:** *We present the case of a 20-month-old female patient who presented with pain and a "lump" in the right inguinal region for 3 days. The patient was diagnosed with type 1 hydrocele of the canal of Nuck through ultrasonography, which was subsequently confirmed during surgery. The patient was discharged on the same day as the procedure and remains asymptomatic.* **Conclusions:** *Although rare, hydrocele of the canal of Nuck should be considered in the differential diagnosis of groin or genital region edema presenting without additional symptoms. Its diagnosis can be challenging due to several common differential diagnoses, including indirect inguinal hernia, tumors, cysts, abscesses, and lymphadenopathies, which occur more frequently. Therefore, ultrasonography plays a crucial role in evaluating these differential diagnoses and confirming the hydrocele of the canal of Nuck.*

Keywords: *Ultrasonography. Hydrocele of the canal of Nuck. Diagnosis. Case report.*

Hidrocele del canal de Nuck: informe de caso de una enfermedad poco común

Resumen

Introducción: *El hidrocele del canal de Nuck es una patología rara con una prevalencia aproximada del 1% en mujeres de 0 a 16 años. Su prevalencia en adultos aún se desconoce. La afección se desarrolla debido a una permeabilidad persistente o a una obliteración fallida del canal de Nuck. Varios factores pueden contribuir a su desarrollo, como trastornos linfáticos, traumatismos, infecciones, inflamaciones o causas idiopáticas. Clínicamente, se presenta como un edema en la ingle o en la región genital sin síntomas adicionales. La ecografía es la modalidad diagnóstica preferida para el hidrocele del canal de Nuck.* **Caso clínico:** *Presentamos el caso de una paciente de 20 meses de edad que presentó dolor y un "bulto" en la región inguinal derecha durante tres días. Se le diagnosticó hidrocele del canal de Nuck de tipo 1 mediante ecografía, que se confirmó posteriormente durante la intervención quirúrgica. El paciente fue dado de alta el mismo día de la intervención y permanece asintomático.* **Conclusiones:** *Aunque poco frecuente, el hidrocele del canal de Nuck debe considerarse en el*

***Correspondence:**
Márcio L. Duarte
E-mail: marcioluisduarte@gmail.com

Date of reception: 08-06-2024
Date of acceptance: 04-10-2024
DOI: 10.24875/BMHIM.24000078

Available online: 28-02-2025
Bol Med Hosp Infant Mex. 2025;82(1):63-66
www.bmhim.com

diagnóstico diferencial del edema inguinal o de la región genital que se presenta sin síntomas adicionales. Su diagnóstico puede ser difícil debido a varios diagnósticos diferenciales comunes, incluida la hernia inguinal indirecta, tumores, quistes, abscesos y linfadenopatías, que se presentan con mayor frecuencia. Por lo tanto, la ecografía desempeña un papel crucial en la evaluación de estos diagnósticos diferenciales y la confirmación del hidrocele del canal de Nuck.

Palabras clave: *Ultrasonografía. Hidrocele del canal de Nuck. Diagnóstico. Reporte de caso.*

Introduction

The female hydrocele or cyst of the canal of Nuck is a rare pathology with a prevalence of approximately 1% in females aged 0-16 years. The pathophysiology can be explained by embryological development. During embryogenesis, an evagination of the parietal peritoneum accompanies the round ligament, forming the vaginal process that extends to the genital tubercle, giving rise to the inguinal canal. The segment of the vaginal process within the inguinal canal is known as the canal of Nuck. Pathology develops when this canal fails to obliterate or persists[1].

The female hydrocele appears to develop due to an imbalance between fluid secretion and absorption by the secretory membranes of the canal of Nuck[1]. Several factors may contribute to its development, including lymphatic disorders, trauma, infection, inflammation, or idiopathic causes. Clinically, it presents as edema in the groin or genital region without additional symptoms, making diagnosis challenging due to various differential diagnoses, including indirect inguinal hernia, tumors, cysts, abscesses, and lymphadenopathies[2,3]. While ultrasonography is the preferred diagnostic imaging modality, additional imaging studies may be employed to delineate the patient's anatomy better[1].

Herein, we present the case of a 20-month-old female patient who presented with pain and a "lump" in the right inguinal region for 3 days.

Clinical case

Our case is a 20-month-old female patient presented with pain and a "lump" in the right inguinal region that had lasted for 3 days. The parents reported no history of previous illnesses or surgical procedures. At the time of her visit, the patient tested positive for COVID-19, confirmed by reverse transcription polymerase chain reaction testing.

Physical examination revealed a mobile, non-tender swelling in the right inguinal region, which showed no changes with the Valsalva maneuver. Ultrasonographic examination demonstrated a well-defined cystic lesion with anechoic content and a thin neck communicating with the right inguinal canal, consistent with type 1 hydrocele of the canal of Nuck (Fig. 1).

The patient was managed conservatively at home until the COVID-19 resolution. Three weeks after recovery, surgical intervention was performed, confirming the ultrasonographic diagnosis. The patient was discharged on the same day of surgery and remains asymptomatic.

Discussion

Hydrocele of the canal of Nuck is a rare pathology in the literature[4,5]. Paperela *et al*. reported a prevalence of 0.74% among 353 female patients aged 1-14 years with compatible clinical presentation[6]. Similarly, Akkoyun et al.[7] documented a prevalence of 0.76% in a cohort of girls aged 0-16 years[7], while Huang et al. found a prevalence of 1% in girls aged 1 month-14 years[4]. The prevalence in adults remains undocumented. This rarity highlights the need for increased awareness and training among clinicians, surgeons, and radiologists regarding this condition.

The pathophysiology is rooted in embryological development. The formation of the inguinal canal, including the canal of Nuck, involves two primary structures: the gubernaculum and the vaginal process[2]. In males, the distal portion of the gubernaculum continues to develop under androgenic hormone influence, facilitating testicular descent through the inguinal canal into the scrotal sac[3]. In females, the absence of androgenic and anti-Müllerian hormones arrests gubernacular development, with its caudal portion forming the round ligament, which enables proper positioning of the pelvic organs[2,3].

The vaginal process, an evagination of the parietal peritoneum forming during the first trimester of gestation, attaches to the ventral portion of the gubernaculum[2]. While in males, it facilitates testicular descent to the scrotal sac, in females, its inguinal canal portion becomes the canal of Nuck[1,3]. Normal obliteration of the canal of Nuck typically occurs in a craniocaudal

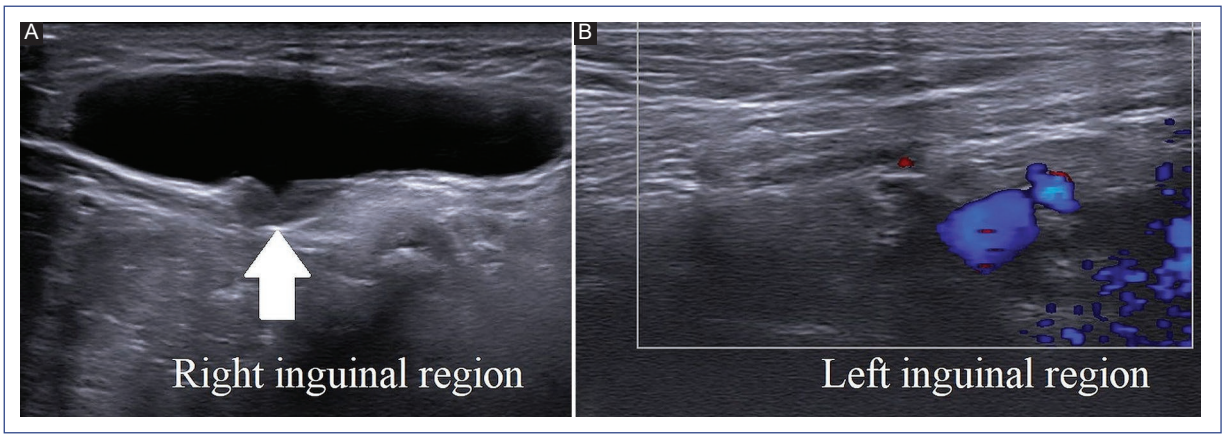


Figure 1. Point-of-care ultrasound examination of the inguinal regions using a linear probe. **A:** transverse plane image of the right inguinal region demonstrates a cystic lesion with a thin neck communicating with the inguinal canal (white arrow), characteristic of hydrocele of the canal of Nuck (female hydrocele). **B:** left inguinal region showing normal anatomy.

direction between the 8th month of gestation and the 1st year of life. Failed obliteration results in canal persistence, potentially leading to hydrocele of the canal of Nuck –also termed Nuck's cyst– through accumulation of fluid secreted by mesothelial cells[3].

Hydrocele of the canal of Nuck can be classified into three types[2]:

Type 1: this is the most common variant, resulting from partial obliteration of the proximal portion of the canal, with no communication with the peritoneal cavity. It typically presents as an irreducible, translucent, and painless mass and is frequently misdiagnosed as an incarcerated hernia. On ultrasonography, the lesion's size remains unchanged with transducer pressure, appearing as an anechoic collection with posterior acoustic enhancement bounded by a thin wall. The content may appear hypoechoic if protein-rich.

Type 2: this variant features communication between the cyst and the peritoneal cavity through a small posterior canal, increasing susceptibility to contamination by pus or blood in the presence of concurrent pathology. It develops due to the complete failure of canal obliteration and presents as a reducible mass, often becoming apparent only during the Valsalva maneuver. Ultrasonographic visualization of this type is typically possible only during strain.

Type 3: this variant exhibits a characteristic hourglass configuration resulting from deep inguinal canal compression. The inferior portion extends into the canal of Nuck within the inguinal canal and labia majora, while the superior portion remains intra-abdominal.

Clinical manifestations and findings are scarce, thus necessitating differentiation and exclusion of other pathologies such as indirect inguinal hernia, tumors, cysts, abscesses, and lymphadenopathy[3]. In the present report, the patient presented with a fluctuating inguinal mass without other associated symptoms, which is highly characteristic of this disease that is more prevalent in childhood[1]. However, during the physical examination, the patient exhibited mobile and painless bulging in the right inguinal region without changes during the Valsalva maneuver, which differs from the literature as it typically reports that the mass can extend to the labia majora[3]. Another evaluation method would be transluminescence to aid in diagnosis, which may be positive if the herniation is large enough and not reducible[3].

The diagnosis is challenging to establish. The preferred initial investigative method for Nuck canal abnormalities is ultrasonography, which shows a well-defined anechoic lesion with posterior acoustic reinforcement[5]. Computed tomography (CT) should not be routinely used due to radiation exposure. In cases of diagnostic uncertainty, magnetic resonance imaging can be used for better analysis of the anatomy and extent of the lesion, showing the hydrocele as an elongated cystic structure in the inguinal canal with low-signal intensity on T1-weighted sequences and high-signal intensity on T2-weighted sequences[5]. Another diagnostic method, which also serves as a treatment option, is laparoscopy, which determines the hydrocele and anatomical conditions more definitively[3].

To date, there is no defined standard therapeutic procedure for the disease. If the patient is asymptomatic, expectant management can be undertaken with monitoring alone, although conservative therapies such as aspiration or sclerotherapy are described in the literature[3]. However, when symptomatic, surgical treatment should be performed, involving excision of the cystic structure with concurrent closure of the inguinal canal defect to reduce the chance of recurrence[2,5]. Surgical treatment presents various technical possibilities that differ according to the patient's anatomical and pathological conditions, such as necrosis of the round ligament[1]. Some authors suggest correcting intraoperative defects with polyurethane mesh[1]. If the condition extends to the labia majora, esthetic correction of the vulva can be performed[1]. Therefore, the surgical intervention should be carefully selected and analyzed according to the patient's anatomical conditions and the surgeon's expertise, considering the risk-benefit ratio before surgery[1].

After the improvement of imaging methods enabling adequate visualization of this pathology and its anatomical characteristics, the number of published cases has increased significantly[1]. Consequently, as more healthcare professionals understand the hydrocele of the canal of Nuck, its reported prevalence increases, as it becomes more easily diagnosed, allowing for the establishment of appropriate standards of care for affected patients[1].

Conclusions

Hydrocele of the canal of Nuck, although rare, should be included among the differential diagnoses of groin or genital region edema without other associated symptoms. Its diagnosis is challenging since there are several differential diagnoses such as indirect inguinal hernia, tumors, cysts, abscesses, and lymphadenopathies, which are diseases with a much higher incidence. Therefore, ultrasonography is essential in analyzing these differential diagnoses and the hydrocele of the canal of Nuck itself.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Kohlhauser M, Pirsch JV, Maier T, Viertler C, Fegerl R. The cyst of the canal of nuck: anatomy, diagnostic and treatment of a very rare diagnosis-a case report of an adult woman and narrative review of the literature. Medicine (Kaunas). 2022;58:1353.
2. Saguintaah M, Eulliot J, Bertrand M, Prodhomme O, Béchard N, Bolivar-Perrin J, et al. Canal of nuck abnormalities in pediatric female patients. Radiographics. 2022;42:541-58.
3. Keeratibharat N, Chansangrat J. Hydrocele of the canal of nuck: a review. Cureus. 2022;14:e23757.
4. Huang CS, Luo CC, Chao HC, Chu SM, Yu YJ, Yen JB. The presentation of asymptomatic palpable movable mass in female inguinal hernia. Eur J Pediatr. 2003;162:493-5.
5. Rees MA, Squires JE, Tadros S, Squires JH. Canal of nuck hernia: a multimodality imaging review. Pediatr Radiol. 2017;47:893-8.
6. Papparella A., Vaccaro S., Accardo M., DE Rosa L., Ronchi A., Noviello C. Nuck cyst: A rare cause of inguinal swelling in infancy. Minerva Pediatr. 2021;73:180–183.
7. Akkoyun I., Kucukosmanoglu I., Yalinkilinc E. Cyst of the canal of Nuck in pediatric patients. N. Am. J. Med. Sci. 2013;5:353–356.