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Contenido

Boletín Médico del Hospital Infantil de México

Vol. 82 • No. 2 • March-April 2025 www.bmhim.com Indexed in Scopus and MEDLINE

Contents

Boletín Médico del
Hospital Infantil de México

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REVIEW ARTICLE

Pediatric arrhythmias: a comprehensive integrative review, symptom-based conceptual framework, and practical care guide

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Abstract

Pediatric arrhythmia encompass a diverse array of conditions, ranging from asymptomatic cases to severe life-threatening episodes. Effective management of these conditions, especially for non-specialist physicians, is crucial to improving patient outcomes and reducing the risk of sudden cardiac death (SCD). This integrative review aims to synthesize the present evidence on the strategies for diagnosing and treating pediatric arrhythmias, providing a practical, symptom-based guide for non-specialist physicians. Following Cooper's methodological framework, we conducted a comprehensive literature search using electronic databases (PubMed/MEDLINE and Cochrane Library) up to August 7, 2024. Inclusion criteria focused on studies published between 2019 and 2024, involving pediatric patients aged 2-18 years with several types of arrhythmias, excluding those with congenital heart disease or other systemic conditions. Quality appraisal was performed using the GRADE and CONSORT methodologies. From 176 initially selected studies, 69 met the inclusion criteria. The evidence was synthesized into a symptom-based conceptual framework, categorizing arrhythmias into asymptomatic, paroxysmal tachycardia, and those associated with low cardiac output or syncope. Common arrhythmias, such as sinus arrhythmia, sinus bradycardia, and wandering atrial pacemaker typically do not require treatment. In contrast, conditions, such as supraventricular tachycardia, ventricular tachycardia, and inherited arrhythmias (e.g., long QT syndrome, Brugada syndrome) necessitate specific diagnostic and therapeutic strategies. This review provides a practical guide for non-specialist physicians to diagnose and manage pediatric arrhythmias, aiming to improve patient outcomes and reduce SCD incidence in children. Future research should focus on pediatric-specific studies and the development of novel therapeutic interventions.

Keywords: *Pediatric arrhythmias. Arrhythmias in children. Supraventricular tachycardia. Ventricular tachycardia. Sudden cardiac death. Integrative review.*

Arritmias pediátricas: una revisión integrativa de variaciones comunes e inusuales

Resumen

Las arritmias pediátricas abarcan una amplia gama de condiciones, desde casos asintomáticos hasta episodios potencialmente mortales. La gestión efectiva es crucial para mejorar los resultados y reducir el riesgo de muerte súbita cardiaca (MSC). Esta revisión integrativa tiene como objetivo sintetizar la evidencia sobre las estrategias para diagnosticar y tratar las arritmias pediátricas, proporcionando una guía práctica basada en los síntomas. Siguiendo el marco metodológico de

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Cooper, realizamos una búsqueda exhaustiva de la literatura utilizando bases de datos electrónicas (PubMed/MEDLINE y Cochrane Library) hasta el 7 de agosto de 2024. Los criterios de inclusión se centraron en estudios publicados entre 2019 y 2024, que involucraban a pacientes pediátricos de 2 a 18 años con diversos tipos de arritmias, excluyendo aquellos con cardiopatías congénitas u otras condiciones sistémicas. La evaluación de calidad se realizó utilizando las metodologías GRADE y CONSORT. De 176 estudios, 69 cumplieron los criterios de inclusión. La evidencia se sintetizó en un marco conceptual basado en síntomas, categorizando las arritmias en asintomáticas, taquicardias paroxísticas y con bajo gasto cardíaco o síncope. Las arritmias comunes, como la arritmia sinusal, la bradicardia sinusal y el marcapasos auricular errante, generalmente no requieren tratamiento. En contraste, condiciones como la taquicardia supraventricular, la taquicardia ventricular y las arritmias hereditarias requieren estrategias diagnósticas y terapéuticas específicas. Esta revisión proporciona una guía práctica para que los médicos no especialistas diagnostiquen y manejen las arritmias pediátricas, con el objetivo de mejorar los resultados y reducir la MSC en niños.

Palabras clave: *Palabras clave: Arritmias pediátricas. Arritmias en niños. Taquicardia supraventricular. Taquicardia ventricular. Muerte súbita Cardíaca. Revisión integrativa.*

Introduction

Pediatric arrhythmias encompass a diverse array of conditions that present along a broad spectrum-from asymptomatic cases to sporadic or frequent episodes of paroxysmal tachycardia, and even sudden cardiac death (SCD) as the initial manifestation of severe disorders caused by genetic mutations in cardiac ion channels or associated proteins[1]. Although the literature on cardiac electrical disorders is extensive, research focused on children is relatively sparse. Consequently, the management and treatment protocols often mirror those established for adults, which are underpinned by a more robust body of evidence regarding their efficacy[2,3].

Cardiac diseases in both adults and children may exhibit similar morphological and clinical characteristics, yet their prognoses differ markedly. Non-specialist physicians, who are typically the first to engage with affected children, are primarily guided by the presenting symptoms that prompt medical consultations. An initial survey of the literature reveals a significant gap in practical, accessible management guides for non-specialists that comprehensively address the full spectrum of pediatric electrical diseases based on patient symptoms[4,5].

This review aimed is to synthesize the present evidence regarding the strategies for approaching and managing pediatric arrhythmias, from the most common and benign to those capable of causing SCD. It seeks to equip non-specialist physicians with a clear and pragmatic guide for treating these conditions, tailored to the observed symptoms in pediatric patients. It is important to clarify that this review focuses on pediatric arrhythmias in the context of a normal heart and in hemodynamically stable patients.

Method

Design

We conducted an integrative review (IR) following Cooper's methodological framework (Fig. 1)[6-10]. The IR was driven by the central research question: 'What are the effective strategies for diagnosing and treating pediatric arrhythmias, ranging from benign to life-threatening conditions, with an emphasis on practical, symptom-based approaches suitable for non-specialist physicians?'

Search strategy

The literature search, which concluded on August 7, 2024, used databases, such as PubMed/MEDLINE and Cochrane Library, with keywords and Boolean operators as specified in table 1. PRISMA guidelines[11] were followed, and EndNote managed citations.

Inclusion and exclusion criteria

We included diverse study designs-quantitative, qualitative, methodological, and theoretical-focused on pediatric arrhythmias[7,8,12,13]. Inclusion was restricted to studies published in English from 2019 to 2024, involving patients aged 2-18 years. Studies related to congenital heart disease (CHD) or other systemic conditions were excluded.

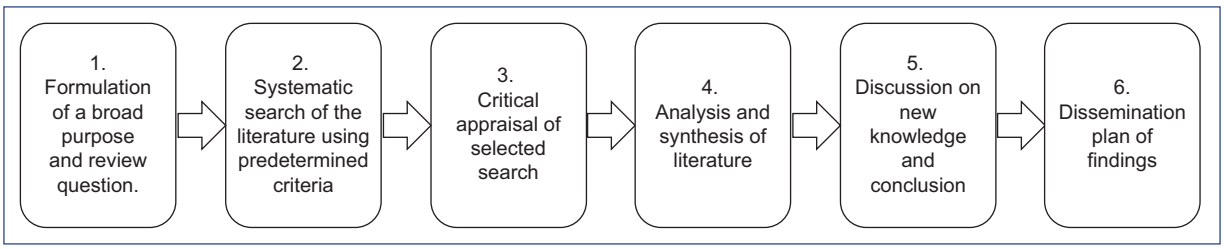

Figure 1. The six steps of the integrative review process.

Table 1. Keywords and Boolean operators used in the search strategy for electronic databases

Arrhythmias OR Rhythm abnormalities OR Rhythm disturbances OR Rhythm alterations OR Electrical abnormalities OR electrical alterations OR Electrical disturbances OR Tachycardia OR Bradycardia OR Sinus arrhythmia OR Sinus bradycardia OR Wandering atrial pacemaker OR Atrial extrasystoles OR Premature atrial contractions OR Ventricular Extrasystoles OR Premature ventricular contractions OR Syncope OR Channelopathies OR Hereditary Arrhythmogenic Syndromes OR Long QT syndrome OR Brugada syndrome OR Catecholaminergic polymorphic ventricular tachycardia OR Short QT syndrome OR Atrioventricular block OR AV block OR Ablation OR Pacing OR Pacemaker OR Cardioverter defibrillator OR Implantable Electronic Devices OR Inherited Arrhythmias AND (Pediatric OR Paediatric OR Young OR Children).

Selection of articles

Two researchers independently assessed the eligibility of studies, screening titles, abstracts, and full texts, as documented in the PRISMA flow diagram (Fig. 2). Out of 176 studies, 79 were initially included, with 31 additional articles found through reference checks. After further screening, 41 studies were excluded, leaving 69 studies that met the criteria for this review.

Quality appraisal

Two independent reviewers assessed each study's methodological strengths and weaknesses using GRADE[14] and CONSORT[15] principles. Discrepancies were resolved through discussion. All studies were included post-evaluation, with 64 scoring high and five moderate. Table 2 shows all scores, while tables 3 and 4 provide examples of moderate and high-quality assessments.

Data abstraction and synthesis

A data matrix (Table 2) was created to integrate concepts across the literature, streamlining data analysis and supporting narrative syntesis[1-5,16-86]. Inductive content analysis was conducted in three phases: preparation, organizing, and reporting. Qualitative analysis identified unifying themes, which are summarized in figure 3. The process involved identifying common meanings and refining categories through collaborative discussion, ultimately consolidating them into synthesized themes that form the foundation of the findings.

Results

To ensure the comprehensive integration of the organized synthesis of evidence into practice, we developed an innovative symptom-based conceptual framework, designed to serve as a practical guide for the management of pediatric arrhythmias, as summarized in figures 4 and 5.

Practical guide for the care of children with arrhythmias based on symptomatology

Asymptomatic or nearly asymptomatic children

Common arrhythmias in asymptomatic children typically do not require treatment. However, some conditions, such as pre-excitation syndrome and long QT syndrome (LQTS)[16], can be asymptomatic for some time but may still pose a risk and require special diagnostic attention and follow-up. The most common asymptomatic arrhythmias in children include sinus arrhythmia, sinus bradycardia, wandering pacemaker, and infrequent premature atrial and ventricular contractions.

Sinus arrhythmia

Prevalence and mechanism: sinus arrhythmia is a common electrocardiographic finding in children[5], characterized by heart rate (HR) variations with respiration

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature search

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Abbasi et al., 2023[34]	Canada	Review	Review the management of acute SVT in children	High	SVT	T, L	ECG, clinical evaluation	Adenosine therapy, electrical therapy	Y
Amedro et al., 2021[62]	France	Prospective multicenter controlled study	Study the health-related quality of life and physical activity in children with inherited cardiac arrhythmia or cardiomyopathy	High	IA, IC	A, L	ECG, physical activity assessment	Lifestyle modifications, medications	Y
Babayiğit et al., 2020[33]	Turkey	Review	Review the European Society of Cardiology guidelines on SVT	High	SVT	A, L	ECG	Ablation	Y
Bieganowska et al., 2021[16]	Poland	Cohort study	Evaluate the usefulness of long-term telemetric ECG monitoring in the diagnosis of tachycardia in children with palpitations	High	Tachycardia	T, L	Long-term telemetric ECG monitoring	Medication, ablation	Y
Cano-Hernández et al., 2018[80]	Mexico	Cohort study	Analyze prevalence and diseases causing sudden cardiac death in children	High	SCD	L	Clinical evaluation	ICD	Y
Cepeda-Nieto et al., 2021[68]	Mexico	Case report	Identify polygenetic variants in Jervell and Lange-Nielsen syndrome	High	Jervell and Lange-Nielsen syndrome	L	Genetic testing	ICD	Y
Cheng et al., 2022[57]	China	Cohort study	Evaluate biomarkers and hemodynamic parameters in the diagnosis and treatment of POTS and vasovagal syncope in children	High	POTS, vasovagal syncope	T, S	Tilt test, biomarkers	Lifestyle modifications, medications	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Chhabra et al., 2023[38]	USA	Review	Overview of WPW syndrome	High	WPW syndrome	T	ECG	Ablation	Y
Chugh et al., 2009[82]	USA	Population-based study	Study sudden death in children	High	SCD	L	Clinical evaluation	ICD	Y
Cioffi et al., 2021[41]	USA	Review	Review the etiology and device therapy in pediatric and young adult population with complete AV block	High	Complete AV block	A, L, B	ECG, Holter monitoring	Pacemaker implantation	Y
Coban-Akdemir et al., 2020[42]	USA	Genetic study	Study genetic variants in WPW syndrome	High	WPW syndrome	T	Genetic testing	Ablation	Y
Cohen and Thurber, 2022[1]	USA	Review	Review the history of cardiac pacing in young patients and future directions	High	Cardiac pacing-related arrhythmias	A, L, T, B	ECG, device interrogation	Pacemaker implantation, programming	Y
Corcia MCG, 2022[75]	UK	Review	Review strategies to minimize overdiagnosis and overtreatment of Brugada syndrome in children	High	BrS	A, L	ECG, genetic testing	Lifestyle modifications, medications	Y
Cruz-Cardentey et al., 2009[82]	Cuba	Review	Overview of short QT syndrome	High	SQTS	L	ECG	ICD	Y
Cui et al., 2023[49]	China	Cohort study	Evaluate baroreflex sensitivity and its implication in neurally mediated syncope in children	High	Vasovagal syncope	S	Tilt test, clinical evaluation	Lifestyle modifications, medications	Y
Danon S, 2023[2]	USA	Review	Review the prevention of sudden cardiac death in children with chest pain, palpitations, and syncope	High	SCD	A, L	ECG, clinical evaluation	Lifestyle modifications, medications	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Dewi and Dharmadjati, 2020[78]	Indonesia	Review	Review diagnosis and management of short QT syndrome	High	SQTS	A	ECG	ICD	Y
Ebrahim et al., 2024[73]	USA	Review	Evaluate bidirectional ventricular tachycardia in pediatric and familial genetic arrhythmia syndromes	High	IA	A, L, T	Genetic testing, ECG	Beta-blockers, ICDs	Y
El-Battrawy et al., 2020[76]	Germany	Cohort study	Evaluate the clinical profile and long-term follow-up of children with Brugada syndrome	High	BrS	A, L	ECG, genetic testing	Beta-blockers, ICDs	Y
Endres et al., 2022[31]	USA	Multicenter retrospective study	Evaluate specialized laboratory investigations in pediatric patients with new-onset SVT	High	SVT	T, L	ECG, specialized labs	Medication, electrical therapy	Y
Groffen et al., 2024[67]	Netherlands	Review	Overview of long QT syndrome	High	LQTS	A, L	ECG, genetic testing	Beta-blockers, ICDs	Y
Hill et al., 2019[39]	USA	Randomized controlled trial	Compare the effectiveness of oral flecainide versus amiodarone for treating recurrent supraventricular tachycardia in children	High	SVT	T, L	ECG, clinical evaluation	Oral flecainide, amiodarone	Y
Howard and Vinocur, 2023[79]	USA	Review	Translate tools and techniques from adult electrophysiology to pediatric CIEDs	High	CIED-related arrhythmias	A, L, T	ECG, device interrogation	CIED implantation, programming	Y
Hu et al., 2021[3]	China	Cohort study	Investigate the incidence of syncope in children and adolescents aged 2-18 years in Changsha	High	Syncope	S	ECG, clinical evaluation	Lifestyle modifications, medications	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Ilkjaer et al., 2021[22]	Denmark	Retrospective clinical study	Evaluate the effectiveness and safety of radiofrequency catheter ablation in children with supraventricular tachyarrhythmia	High	SVT	T, L	ECG, electrophysiology study	Radiofrequency catheter ablation	Y
Janson et al., 2023[23]	USA	Registry study	Analyze the association of weight with ablation outcomes in pediatric WPW	High	WPW syndrome	T, L	ECG, electrophysiology study	Catheter ablation	Y
Kafalı and Ergül, 2022[30]	Turkey	Review	Review common SVT and VT in children	High	SVT, VT	T, L	ECG, clinical evaluation	Ablation, medications	Y
Kallas et al., 2021[28]	Canada	Multicenter cohort study	Evaluate age at symptom onset, proband status, and sex as predictors of disease severity in pediatric CPVT	High	CPVT	T, L	Genetic testing, ECG	Beta-blockers, ICDs	Y
Kallas et al., 2021[29]	Canada	Review	Provide a translational perspective on pediatric catecholaminergic polymorphic ventricular tachycardia for the clinician-scientist	High	CPVT	T, L	Genetic testing, ECG	Beta-blockers, ICDs	Y
Kim et al., 2020[36]	Korea	Cohort study	Evaluate the association between delayed adenosine therapy and refractory supraventricular tachycardia in children	High	SVT	T, L	ECG, clinical evaluation	Adenosine therapy	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Knight et al., 2020[65]	USA	Genetic study	Evaluate genetic testing and cascade screening in pediatric long QT syndrome and hypertrophic cardiomyopathy	High	LQTS, HCM	A, L	Genetic testing, ECG	Beta-blockers, ICDs	Y
Kotadia et al., 2020[37]	UK	Review	Overview of SVT diagnosis and management	High	SVT	T, L	ECG, clinical evaluation	Ablation, medications	Y
Krahn et al., 2022[77]	Canada	Review	Review Brugada syndrome	High	BrS	L	ECG, genetic testing	ICD, medications	Y
Krause et al., 2021[43]	Germany	Multicenter registry study	Evaluate the outcomes of pediatric catheter ablation at the beginning of the 21st century	High	Various arrhythmias	T, L	Electrophysiology study	Catheter ablation	Y
Lee et al., 2021[63]	UK	Cohort study	Compare pediatric/ young versus adult patients with long QT syndrome	High	LQTS	A, L	Genetic testing, ECG	Beta-blockers, ICDs	Y
Li et al., 2021[56]	China	Review	Review advancements in understanding vasovagal syncope in children and adolescents	High	Vasovagal syncope	S	Tilt test, clinical evaluation	Lifestyle modifications, medications	Y
Li et al., 2019[53]	China	Retrospective clinical study	Assess the efficacy of oral rehydration salts in children with neurally mediated syncope of different hemodynamic patterns	High	Vasovagal syncope	S	ECG, clinical evaluation	Oral rehydration salts	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Liao and Du, 2020[54]	China	Review	Update on the pathophysiology and individualized management of vasovagal syncope and postural tachycardia syndrome in children and adolescents	High	Vasovagal syncope, POTS	S	Tilt test, clinical evaluation	Lifestyle modifications, medications	Y
Mallya and Whitehouse, 2021[55]	UK	Retrospective clinical study	Audit the use of slow sodium in children and young people with syncope and/or orthostatic intolerance	High	Syncope, orthostatic intolerance	S	ECG, clinical evaluation	Lifestyle modifications, medications	Y
Mariani et al., 2024[4]	Italy	Review	Provide an updated overview of inherited arrhythmias in the pediatric population	High	IA	A, L, T	Genetic testing, ECG	Beta-blockers, ICDs	Y
Meyer et al., 2012[83]	USA	Review	Review incidence, causes, and trends in survival from sudden cardiac arrest in young population	High	SCA	L	Clinical evaluation, genetic testing	ICD, medications	Y
Moltedo et al., 2020[20]	Argentina	Retrospective clinical study	Study on HAV pattern in pediatric AVNRT	High	AVNRT	T	ECG, electrophysiology study	Ablation	Y
Oliveira et al., 2023[58]	Brasil	Cohort study	Examine clinical and autonomic profiles and validate the Modified Calgary Score in children with presumed vasovagal syncope	High	Vasovagal syncope	S	Tilt test, Modified Calgary Score	Lifestyle modifications, medications	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Oner et al., 2018[84]	Turkey	Prospective clinical study	Evaluate the effect of omega-3 polyunsaturated fatty acid supplementation on cardiac function in children with premature ventricular contractions	High	PVCs	A, T	ECG, clinical evaluation	Omega-3 polyunsaturated fatty acid supplementation	Y
Osama and Delpire, 2024[59]	USA	Review	Review insights into channelopathies	High	IA	A, L	Genetic testing, ECG	Medications, ICDs	Y
Patsiou et al., 2023[17]	Greece	Systematic review and meta-analysis	Compare epicardial versus endocardial pacing in pediatric patients with AV block or sinus node dysfunction	High	AV block, SND	L	ECG, Holter monitoring	Epicardial and endocardial pacing	Y
Peltenburg et al., 2022[72]	Netherlands	Multicenter cohort study	Evaluate the efficacy of β-blockers in treating children with CPVT	High	CPVT	T, L	ECG, genetic testing	Beta-blockers	Y
Ploneda-Valencia et al., 2022[18]	Mexico	Case report	Report a case of short QT syndrome presenting with supraventricular tachyarrhythmia and sinus node dysfunction	Moderate	SQTS	A, T	ECG, genetic testing	Beta-blockers, ICDs	Y
Przybylski et al., 2021[35]	USA	Review	Review the care of children with supraventricular tachycardia in the emergency department	High	SVT	T, L	ECG, clinical evaluation	Medication, electrical therapy	Y
Ramoğlu et al., 2022[40]	Turkey	Retrospective clinical study	Single-center experience with WPW syndrome in children	High	WPW syndrome	T	ECG, clinical evaluation	Ablation, medications	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Rohit and Kasinadhuni, 2020[5]	India	Review	Review the management of pediatric arrhythmias in emergency settings	High	Various arrhythmias	A, L, T	ECG, clinical evaluation	Medication, electrical therapy	Y
Romanov et al., 2019[24]	Russia	Randomized study	Compare catheter ablation versus medical therapy for treating symptomatic frequent ventricular premature complexes in children	High	PVCs	T, L	ECG, clinical evaluation	Catheter ablation, medication	Y
Sabaté Rotés et al., 2020[32]	Spain	Cohort study	Examine supraventricular tachycardia in children managed by a specialized transport team	Moderate	SVT	T, L	ECG, Holter monitoring	Medication, ablation	Y
Shimamoto and Aiba, 2024[70]	Japan	Review	Discuss strategies to evaluate arrhythmic risk in children with long QT syndrome	High	LQTS	A, L	Genetic testing, ECG	Beta-blockers, ICDs	Y
Shkolnikova et al., 2019[69]	Russia	Prospective clinical study	Evaluate new perspectives of holter monitoring in diagnostics of the long QT syndrome in the young	High	LQTS	A, L	Holter monitoring	Holter monitoring	Y
Silka et al., 2021[19]	USA	Expert consensus	Provide expert consensus on the indications and management of cardiovascular implantable electronic devices in pediatric patients	High	Various arrhythmias	A, L, T, B	ECG, clinical evaluation	Implantable devices, follow-up	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Siurana et al., 2020[47]	Spain	Case report	Report a case of asystole triggered by hair grooming in children and review related literature	Moderate	Asystole	L	ECG, clinical history	Avoiding triggers, pacemaker	Y
Sohinki and Mathew, 2018[85]	USA	Review	Review ventricular arrhythmias in structurally normal heart	High	VA	A, L	ECG, clinical evaluation	Medications	Y
Song et al., 2020[48]	China	Pilot study	Evaluate the association between reduced 24-h sodium excretion and plasma acylcarnitine profile in vasovagal syncope children	High	Vasovagal syncope	S	ECG, clinical evaluation	Sodium intake modifications	Y
Song et al., 2021[74]	Korea	Multicenter cohort study	Evaluate outcomes of ICDs in pediatric patients in a Korean cohort	High	Various arrhythmias	T, L	ICD implantation, follow-up	ICDs	Y
Steinberg L, 2023[44]	USA	Review	Overview of congenital heart block	High	Congenital heart block	L, B	ECG, clinical evaluation	Pacemaker	Y
Stewart et al., 2023[46]	Netherlands	Review	Develop a framework for diagnosing pediatric syncope	High	Syncope	A, L	Clinical evaluation, diagnostic framework	Tailored management strategies	Y
Tardo et al., 2023[66]	Australia	Systematic review	Systematic review on T wave biomarkers in long QT syndrome	High	LQTS	A, L	ECG, genetic testing	Beta-blockers, ICDs	Y
Uysal et al., 2024[21]	Turkey	Prospective clinical study	Evaluate the effect of magnesium on ventricular extrasystoles in children	High	PVCs	A, T	ECG, clinical evaluation	Magnesium supplementation	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Vidya et al., 2022[25]	India	Randomized clinical study	Evaluate the use of implantable loop recorder in unexplained palpitations or syncope in young patients with structurally normal heart	High	Unexplained palpitations, syncope	P, S	Implantable loop recorder	Implantable loop recorder	Y
Vogler et al., 2012[86]	Germany	Review	Review bradyarrhythmias and conduction blocks	High	Bradyarrhythmia	A, L	ECG, clinical evaluation	Pacemaker	Y
Wallace et al., 2019[64]	Ireland	Review	Review genetics and future perspectives of long QT syndrome	High	LQTS	A, L	ECG, genetic testing	Beta-blockers, ICDs	Y
Walsh et al., 2021[26]	UK	Systematic review	Review outcomes of pediatric ablation over 20 years	High	Various arrhythmias	T, L	Electrophysiology study	Catheter ablation	Y
Wang et al., 2020[50]	China	Cohort study	Investigate the association between neurally mediated syncope and allergic diseases in children	Moderate	Vasovagal syncope	S	Clinical evaluation, allergy tests	Management of allergies, lifestyle modifications	Y
Weiner and Shah, 2023[45]	USA	Case series	Review of nonsurgical complete AV block in children and its management	High	Complete AV block	L, B	ECG, Holter monitoring	Pacemaker implantation	Y
Wilde et al.; EHRA/HRS/APHRS/LAHRS; 2022[71]		Consensus Statement	Consensus statement on genetic testing for cardiac diseases	High	Various arrhythmias	A, L	Genetic testing, ECG	Medications, ICDs	Y
Xinxing et al., 2020[52]	China	Cohort study	Evaluate the safety and efficacy of RF ablation in pediatric patients with arrhythmias	High	Various arrhythmias	T, L	Electrophysiology study	RF ablation	Y

(*Continues*)

Table 2. Data matrix for concept integration and thematic synthesis from comprehensive literature review *(continued)*

Authors, year (ref)	Country	Design	Purpose/Aim	Quality appraisal data	Arrhythmias included	Symptoms	Strategies of diagnosis	Strategies of treatment	Strategies based on symptoms
Xu et al., 2022[51]	China	Observational study	Explore individual management strategies for pediatric vasovagal syncope	Moderate	Vasovagal syncope	S	Tilt table test, clinical evaluation	Lifestyle modifications, medications	Y
Yan et al., 2023[27]	China	Cohort study	Examine clinical and genetic characteristics of CPVT in Chinese pediatric patients	High	CPVT	T, L	Genetic testing, ECG	Beta-blockers, ICDs	Y
Zavala et al., 2020[60]	USA	Systematic review	Review of pediatric syncope, its causes, and management	High	Syncope	A, L	Clinical evaluation, tilt table test	Lifestyle modifications, medications	Y
Zou et al., 2024[61]	China	Systematic review	Investigate the association between PFO and unexplained syncope in pediatric patients	High	PFO, Syncope	S	Echocardiography, clinical evaluation	Medical management, follow-up	Y

A: asymptomatic; APHRS: Asia Pacific Heart Rhythm Society; AV: atrioventricular; AVNRT: atrioventricular nodal reentrant tachycardia; B: symptoms associated to bradycardia; BrS: Brugada syndrome; CIED: cardiac implantable electronic devices; CPVT: catecholaminergic polymorphic ventricular tachycardia; ECG: electrocardiogram; EHRA: European Heart Rhythm Association; HCM: hypertrophic cardiomyopathy; HRS: Heart Rhythm Society; IA: inherited arrhythmias; IC: inherited cardiomyopathies; ICD: implantable cardioverter defibrillator; L: life threating symptoms including malignant syncope; LAHRS: Latin American Heart Rhythm Society; LQTS: long QT syndrome, N: no; PFO: patent foramen ovale; POTS: postural orthostatic tachycardia syndrome; PVCs: premature ventricular contractions; S: benign syncope; SCA: sudden cardiac arrest; SCD: sudden cardiac death; SND: sinus node disfunction; SQTS: short QT syndrome; SVT: supraventricular tachycardia; T: paroxysmal tachycardia; VA: ventricular arrythmias; VT: ventricular tachycardia; WPW: Wolff-Parkinson-White; Y: yes.

Table 3. Example of the quality assessment of a study with a moderate quality rating

Article evaluation "Asystole in a syncope by hair grooming in children: case report and literature review"		
Criterion	Description	Evaluation
Study type	Determine the study design (clinical trial, cohort study, etc.).	Case report and literature review
Internal validity	Evaluate sample selection, allocation, and follow-up.	Sample Selection: case report based on specific clinical observation. Allocation: not applicable. Follow-up: detailed follow-up of the individual case.
External validity	Consider the generalizability of the results to other populations and settings.	Results are specific to a unique case and context, limiting generalizability. A literature review provides a broader context but remains limited in direct applicability.
Precision and consistency	Review measurement, statistical analysis, and consistency with previous studies.	Measurement: detailed clinical measurements were provided for the case. Statistical analysis: not applicable in case reports. Consistency: supported by literature review, though direct comparisons are limited.
Results	Analyze the magnitude of the effect and its clinical relevance.	Impact: clinically relevant insights into a rare phenomenon. Consistency: unique case but contextualized within the literature.
Transparency and ethics	Verify the completeness of reporting, ethical approval, and informed consent.	Complete reporting: methodology and case details are well reported. Ethical approval: ethical considerations and informed consent obtained.
Conclusion	The article is assessed as having moderate quality. It excels in transparency, detailed reporting, and ethical considerations, which are crucial in case reports. However, its inherent limitations in generalizability and the absence of statistical analysis reduce its overall robustness. The literature review component adds valuable context but does not fully mitigate the limitations associated with the single-case study design.	

(increasing during inspiration and decreasing during exhalation) due to vagal influence (Fig. 6). This pattern may disappear with intense exercise as sympathetic activity increases.

Symptoms: asymptomatic.

Diagnostic strategies: diagnosed through electrocardiogram (ECG) or Holter monitoring.

Treatment strategies: no specific treatment required.

Special considerations: Non-respiratory sinus arrhythmia, potentially linked to mild sinus node dysfunction caused by increased vagal tone, may warrant long-term follow-up[17,18].

Sinus bradycardia

Prevalence and mechanism: significant sinus bradycardia (HR < 60 beats/min [bpm]) is common in healthy children, often due to parasympathetic dominance or long-term sports participation, both typically benign.

Symptoms: usually asymptomatic.

Diagnostic strategies: diagnosed through ECG; more pronounced during deep sleep, as shown by Holter monitoring (Fig. 6). Normal HR response in exercise tests indicates normal sinus function.

Treatment strategies: no treatment required for asymptomatic patients.

Special considerations: symptomatic bradycardia with chronic low cardiac output symptoms requires evaluation by an electrophysiology team to assess the need for a pacemaker[19].

Wandering atrial pacemaker

Prevalence and mechanism: common in children, involving atrial foci generating impulses from lower atrial or perinodal regions.

Symptoms: asymptomatic.

Diagnostic strategies: ECG shows QRS complexes similar to sinus beats but with varying P

Table 4. Example of the quality assessment of a study with a high-quality rating

Article evaluation: "Health-related quality of life and physical activity in children with inherited cardiac arrhythmia or inherited cardiomyopathy: The prospective multicenter controlled QUALIMYORYTHM study rationale design and methods"		
Criterion	**Description**	**Evaluation**
Study type	Determine the study design (clinical trial, cohort study, etc.).	Prospective multicenter controlled study
Internal validity	Evaluate sample selection, allocation, and follow-up.	Sample Selection: randomly selected samples from multiple centers. Allocation: use of control and intervention groups with random allocation. Follow-up: adequate follow-up with minimal loss of participants.
External validity	Consider the generalizability of the results to other populations and settings.	Results applicable to children with inherited cardiac arrhythmias or cardiomyopathy in similar contexts.
Precision and consistency	Review measurement, statistical analysis, and consistency with previous studies.	Measurement: use of validated tools to measure quality of life and physical activity. Statistical analysis: adequate statistical methods with reported confidence intervals.
Results	Analyze the magnitude of the effect and its clinical relevance.	Impact: significant effect on quality of life and physical activity. Consistency: results consistent with previous studies in the same area.
Transparency and ethics	Verify the completeness of reporting, ethical approval, and informed consent.	Complete reporting: detailed methodology and results. Ethical approval: Ethical approval obtained and informed consent given.
Conclusion	By following these steps, it can be determined that the article has a high-quality evaluation ("High") based on its design, internal and external validity, precision, consistency, impact, and ethical compliance.	

wave morphologies. Holter monitoring may reveal competition between multiple pacemakers (Fig. 7).

Treatment strategies: no specific treatment required; the condition usually resolves as atrial foci disappear.

Special considerations: often observed as escape beats during increased vagal tone, such as in deep sleep. Although typically benign, monitoring HR variability and rhythm changes during sleep is advised.

Premature atrial contractions (PACs)

Prevalence and mechanism: PACs are common in newborns and young children, caused by pre-mature atrial depolarization leading to ventricular contraction[5,20]. They generally have an excellent prognosis.

Symptoms: asymptomatic.

Diagnostic strategies: diagnosed through ECG or Holter monitoring, showing pre-mature beats with QRS complexes similar to sinus beats (Fig. 8).

Treatment strategies: no special treatment required.

Special considerations: In rare cases with high arrhythmic burden or symptoms, antiarrhythmic treatment may be necessary.

Premature ventricular contractions (PVCs)

Prevalence and mechanism: PVCs arise from pre-mature ventricular depolarization, leading to a systolic contraction and compensatory pause. They are less frequent in childhood but increase during adolescence[21], often occurring in bigeminy (Fig. 9) or trigeminy patterns.

Symptoms: usually asymptomatic or cause mild symptoms, such as palpitations.

Diagnostic Strategies: diagnosed through ECG or Holter monitoring, showing wide QRS complexes with repolarization abnormalities (Fig. 9).

Treatment strategies: infrequent, asymptomatic PVCs typically require no treatment. Frequent PVCs (over 10% of total beats in 24 h) may need antiarrhythmic drugs or catheter ablation[22-26].

Special considerations: frequent or polymorphic PVCs, or a family history of sudden death, warrant close attention due to the risk of malignant arrhythmias, such as catecholaminergic polymorphic ventricular tachycardia (CPVT) or arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)[27-29].

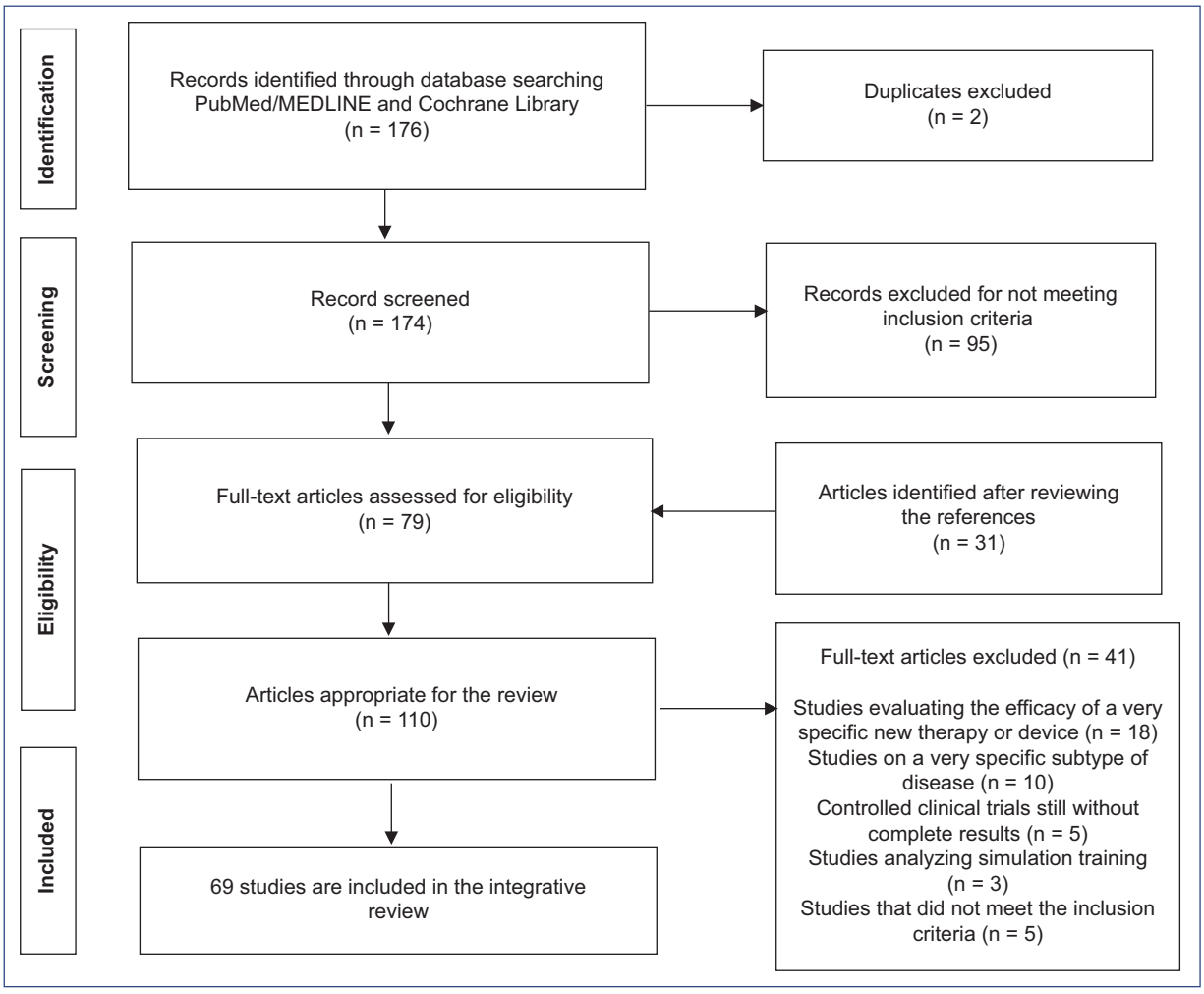

Figure 2. PRISMA flow diagram illustrating the progression of information through the four phases of the integrative review.

Children with episodes of paroxysmal tachycardia

Supraventricular tachycardia (SVT)

Prevalence and Mechanism: SVT is the most common pediatric arrhythmia, affecting 0.1%-0.4% of children, primarily due to re-entry mechanisms. Around 50%-70% of cases are diagnosed within the 1st year, with 30%-50% resolving by 18 months[30-32]. Later childhood SVT has a lower chance of spontaneous resolution[18,30,33,34].

Symptoms: young children may show crying and irritability, while older children report palpitations.

Diagnostic strategies: diagnosis involves a 12-lead ECG and assessing hemodynamic status. HR ranges from 200-300 bpm in younger children and 160-250 bpm in older ones. Basal ECG is usually normal unless ventricular pre-excitation is present[35].

Treatment strategies: hemodynamically stable cases are first treated with vagal maneuvers; if ineffective, intravenous adenosine is used. Adenosine blocks the AV node and helps diagnose other SVT types[23,36-38]. If adenosine fails, esmolol, amiodarone, or verapamil (not for children under 1 year)[39] may be used. Hemodynamically unstable cases require synchronized electrical cardioversion at 1-2 J/kg.

Special considerations: the main re-entry tachycardias in children are atrioventricular reentrant tachycardia (AVRT), including Wolff-Parkinson-White (WPW) syndrome, and atrioventricular nodal reentrant tachycardia (AVNRT)[20,33,40,41].

a) AVRT. AVRT using accessory pathways (APs) is the most common subtype of SVT in children, with the

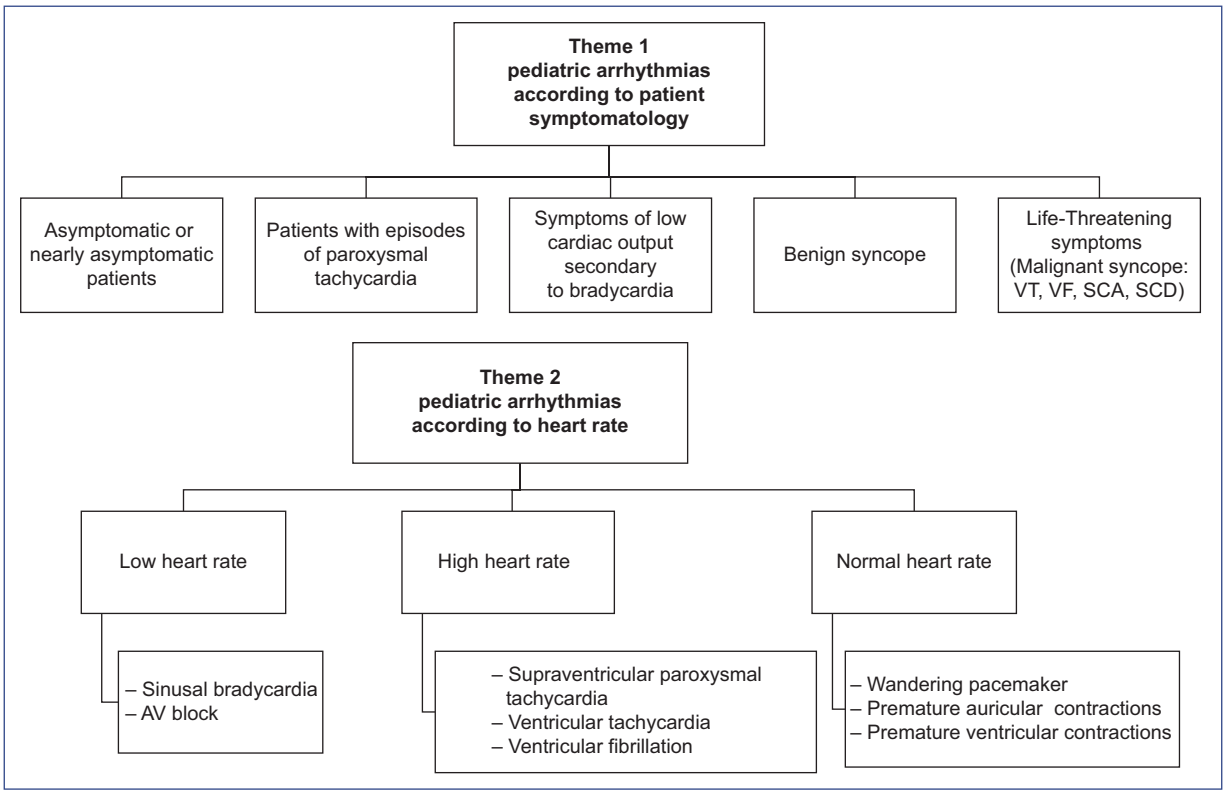

Figure 3. Overview of themes derived from inductive content analysis. SCA: sudden cardiac arrest; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

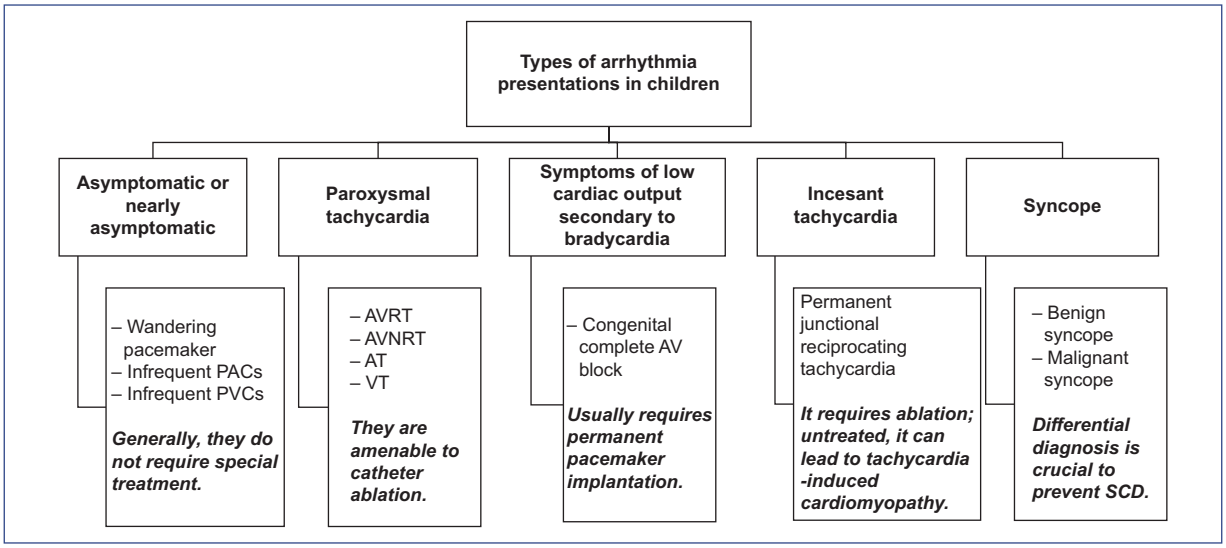

Figure 4. Classification of pediatric arrhythmia presentations. The figure categorizes types of arrhythmias in children based on symptom severity and clinical presentation, ranging from asymptomatic cases to those requiring intervention. It highlights the importance of differential diagnosis in syncope cases to prevent sudden cardiac death (SCD). AT: atrial tachycardia; AVNRT: atrioventricular nodal reentrant tachycardia; AVRT: atrioventricular reentrant tachycardia; PACs: premature auricular contractions, PVCs: premature ventricular contractions; VT: ventricular tachycardia.

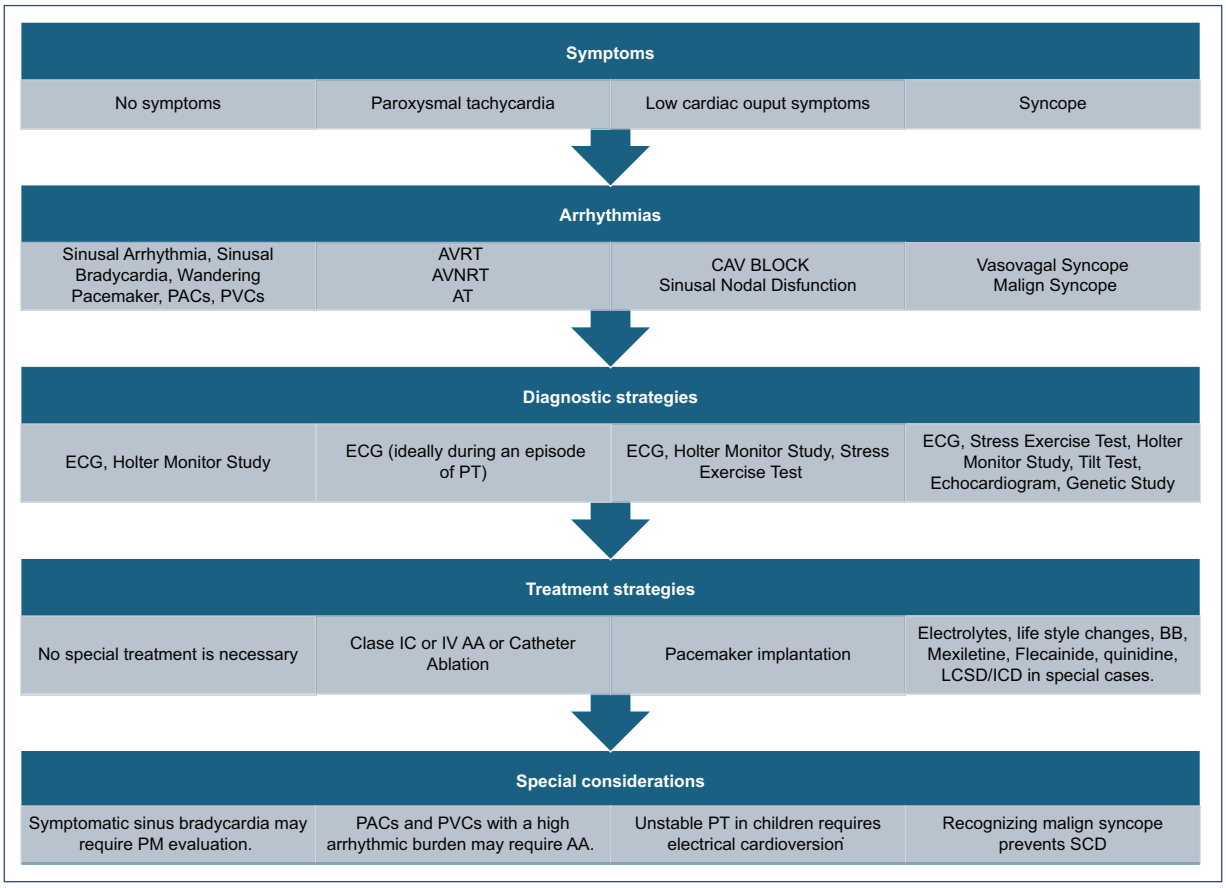

Figure 5. Symptom-based conceptual framework developed for the practical management of pediatric arrhythmias, integrating the organized synthesis of evidence into clinical practice. AA: antiarrhythmic agents; AT: atrial tachycardia; AVNRT: atrioventricular nodal reentrant tachycardia; AVRT: atrioventricular reentrant tachycardia; BB: betablocker; CAV: complete atrioventricular; ECG: electrocardiogram; ICD: implantable cardioverter defibrillator; LCSD: left cardiac sympathetic denervation; PACs: premature atrial contractions; PM: pacemaker; PT: paroxysmal tachycardia; PVCs: premature ventricular contractions; SCD: sudden cardiac death.

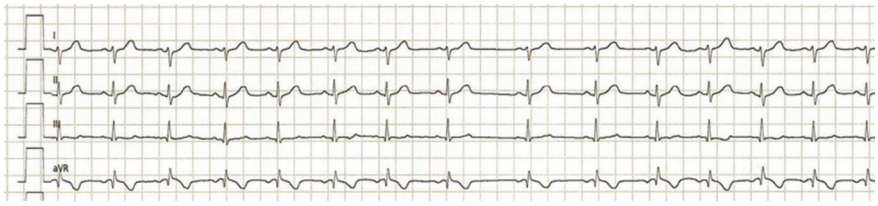

Figure 6. 4-lead electrocardiogram showing sinus arrhythmia in a pediatric patient. The tracing displays normal P wave morphology and a regular sinus rhythm with varying R-R intervals, characteristic of sinus arrhythmia.

left lateral AV groove and postero-septal region being the most common sites. The prevalence is estimated at 1-3/1,000 children[20]. In cases with manifest AP, the QRS complex shows a sloping delta wave, short PR interval, and wide QRS complex, known as the WPW pattern (Fig. 10)[38,40]. WPW syndrome includes this pattern along with symptoms such as palpitations and SVT, and less commonly, syncope or sudden cardiac arrest. Treatment ranges from only vagal maneuvers to transcatheter ablation. Familial WPW syndrome, associated with mutations in the *PRKAG2* gene and conditions, such as

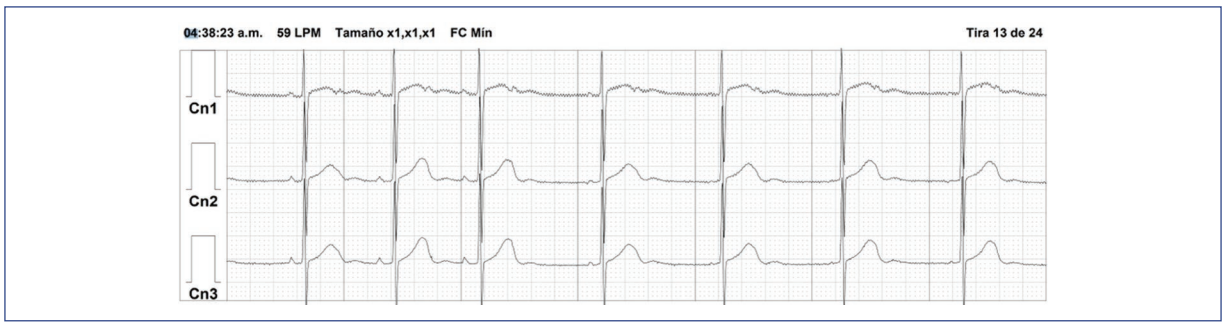

Figure 7. 24-h Holter monitoring ECG tracing in a 4-year-old girl showing sinus bradycardia followed by low atrial beats at a slower heart rate with a different P-wave morphology during deep sleep. The tracing highlights the transition from sinus rhythm to ectopic atrial rhythm, which is common during periods of increased vagal tone, such as in deep sleep.

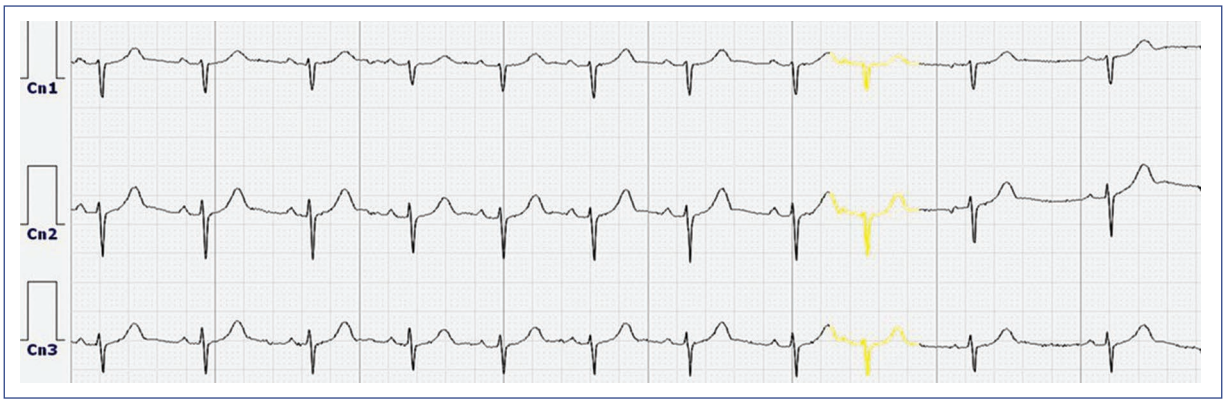

Figure 8. Electrocardiogram trace from a Holter monitor study illustrates the presence of a premature atrial contraction in channels 1, 2, and 3, characterized by the early occurrence of a P wave (highlighted in yellow) with a distinct morphology, followed by a QRS complex similar to that of a sinus beat and a compensatory pause. The normal sinus rhythm is interrupted by this ectopic beat originating from the atria, which resets the timing of subsequent cardiac cycles.

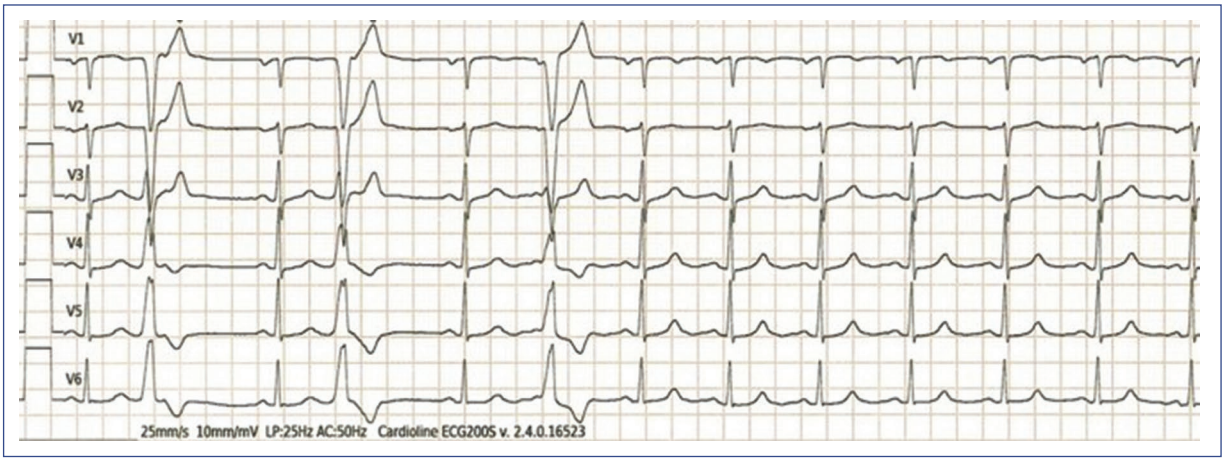

Figure 9. 6-lead Electrocardiogram showing pre-mature, broad QRS complexes not preceded by P waves, with morphology different from the sinus beats, characteristic of ventricular ectopic beats. These pre-mature ventricular contractions interrupt the regular sinus rhythm in a pattern consistent with bigeminy.

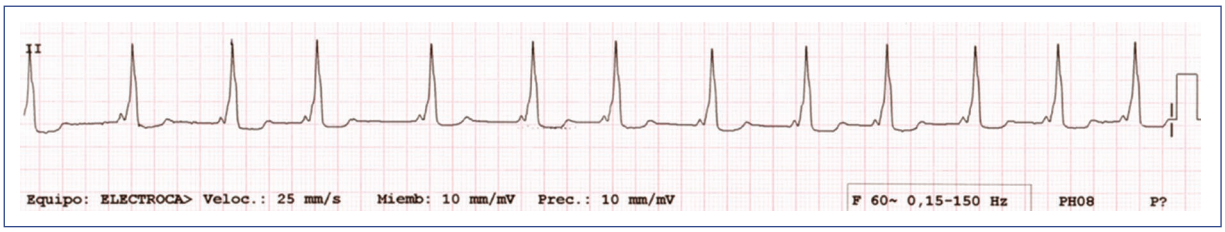

Figure 10. Electrocardiogram demonstrating Wolff-Parkinson-White pattern with characteristic findings, including a short PR interval, delta wave, wide QRS complex, and repolarization abnormalities indicative of pre-excitation due to an accessory pathway.

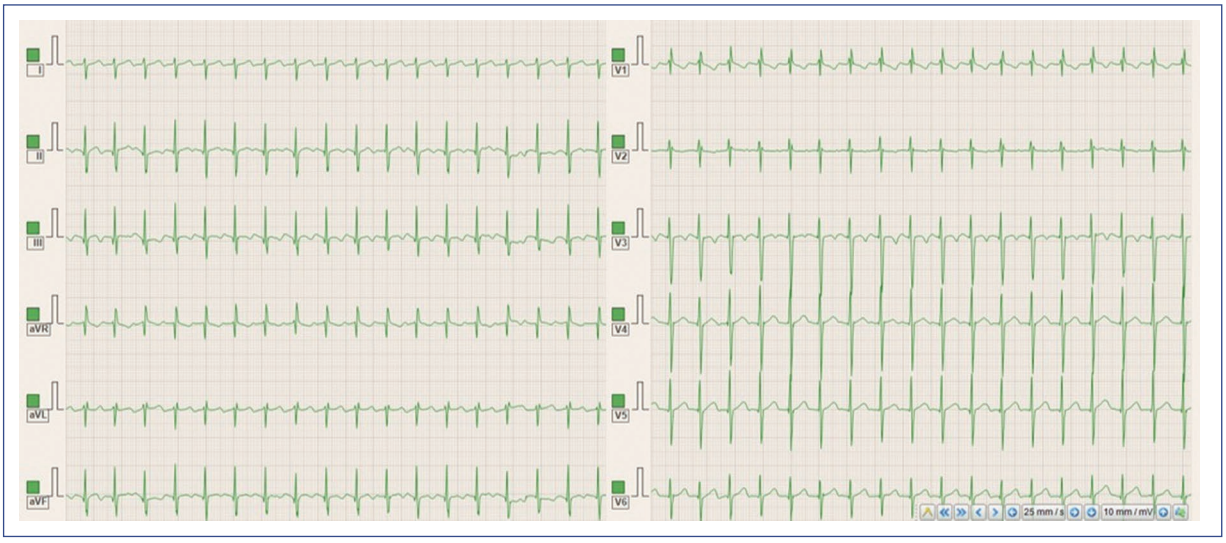

Figure 11. 12-lead electrocardiogram demonstrating orthodromic AVRT in a child with a high heart rate. The ECG shows a narrow complex tachycardia with a rapid ventricular rate, consistent with AVRT. The P waves are typically retrograde and may not be clearly visible, as they are often buried within or immediately following the QRS complexes, reflecting conduction through an accessory pathway. AVRT: atrioventricular reentrant tachycardia.

cardiomyopathy, has been reported[38]. Rare variants in genes linked to atrial fibrillation (AF) and cardiomyopathy have also been identified in WPW syndrome[42].

Variants of AVRT[41]:

- Orthodromic AVRT: the most common AVRT mechanism, with antegrade conduction through the AV node and retrograde conduction up the AP, resulting in narrow QRS complex tachycardia (Fig. 11).
- Antidromic AVRT: an uncommon form (< 5% of cases) where impulses travel antegrade down an AP and retrograde up the AV node, leading to wide QRS complex tachycardia (Fig. 12).
- Permanent Junctional Reciprocating Tachycardia (PJRT): a variant of orthodromic AVRT with slow retrograde AP conduction, creating a stable, often incessant reentrant circuit.

b) Atrioventricular nodal reentrant tachycardia. AVNRT involves a re-entering loop within or near the AV node, utilizing "fast" and "slow" pathways with distinct conduction rates. In typical AVNRT, antegrade conduction is through the slow pathway and retrograde through the fast pathway, leading to a very short RP interval tachycardia (< 70 ms)[20,30]. Catheter ablation is the preferred treatment for recurrent cases[20,26,30,43].

c) Atrial Tachycardia (AT). AT is an organized atrial rhythm from a discrete site, accounting for 11%-16% of SVTs in children and often leading to incessant tachycardias and tachycardia-induced cardiomyopathy.

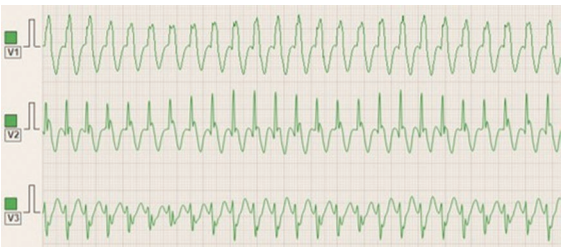

Figure 12. 3-lead electrocardiogram shows a regular, rapid tachycardia with broad QRS complexes, indicating that the reentrant circuit is utilizing an accessory pathway in the antegrade direction (antidromic), leading to a wider QRS morphology compared to orthodromic AVRT. This type of tachycardia is less common but can occur in pediatric patients with pre-excitation syndromes, such as Wolff-Parkinson-White. AVRT: atrioventricular reentrant tachycardia.

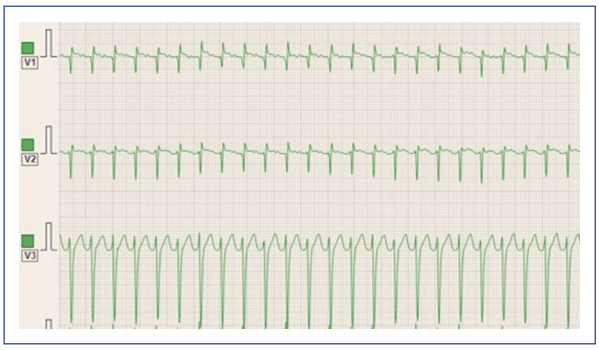

Figure 13. 3-lead ECG demonstrating atrial tachycardia in a young child. The ECG shows a rapid, regular atrial rhythm with narrow QRS complexes and distinct P waves preceding each QRS complex. The P waves exhibit an abnormal morphology, suggesting a focal atrial origin rather than the sinus node. ECG: electrocardiogram.

It presents as a long RP tachycardia on ECG with a distinct P-wave morphology (Fig. 13). Conservative treatment with antiarrhythmic drugs is recommended, as AT often resolves over time in young children[30].

Ventricular tachycardia

Prevalence and mechanism: VT originates in the ventricular myocardium and is less common than SVT, with an incidence of 1/100,000 in children[31]. It can be benign (idiopathic) or malignant (risk of SCD). Idiopathic VT, especially from the right ventricular outflow tract, is common in children, triggered by beta-adrenergic stimuli like exercise[30,33,35].

Symptoms: similar to SVT, young children may show irritability, while older children report abnormal heartbeats.

Diagnostic strategies: defined by three or more PVCs with a rate 20%-25% faster than the basal sinus rate, characterized by wide QRS complexes observed on an ECG, Holter monitor study (Fig. 14), or stress exercise test.

Treatment strategies: idiopathic VT responds to IV verapamil and may be terminated with IV adenosine. Transcatheter ablation is also effective[30,43].

Special considerations: idiopathic left ventricular posterior fascicular VT, involving the left posterior fascicle and partially using the His-Purkinje system, results in a relatively narrow QRS complex.

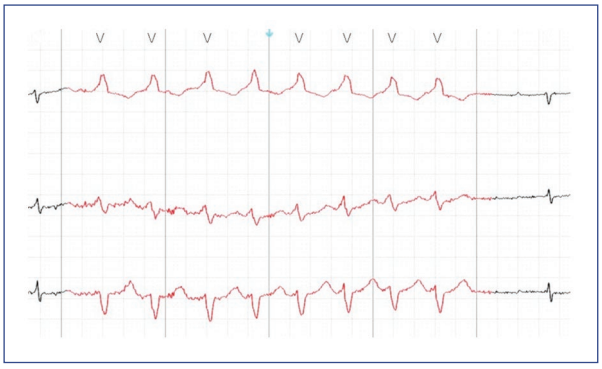

Figure 14. Holter monitor study demonstrating ventricular tachycardia in an adolescent. The electrocardiogram shows a rapid, wide-complex tachycardia with a monomorphic appearance, indicative of ventricular tachycardia. The absence of preceding P waves and the broad QRS complexes are characteristic of VT, suggesting that the origin of the arrhythmia is within the ventricles.

Children with symptoms of low cardiac output secondary to bradycardia

Congenital atrioventricular block

Prevalence and mechanism: congenital AV block, often caused by maternal lupus (60-90%), results from anti-RO-SSA and anti-LA-SSB antibodies crossing to the baby during pregnancy. Other causes include myocarditis and CHD[17,30,44].

Symptoms: common symptoms include fatigue, reduced physical capacity, drowsiness, loss of appetite,

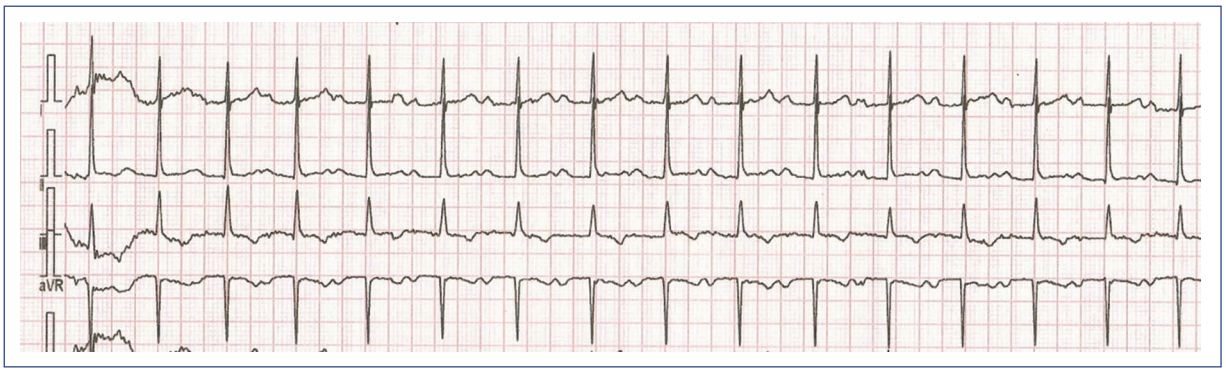

Figure 15. 3-lead ECG demonstrating first-degree AV block in a 13-year-old girl. The ECG shows a prolonged PR interval > 200 ms, consistent with first-degree AV block. Despite the delay in atrioventricular conduction, every P wave is followed by a QRS complex, indicating that conduction through the AV node is intact. This condition is generally benign, especially in young patients, but monitoring may be required if there are symptoms or if the condition progresses. AV: atrioventricular; ECG: electrocardiogram.

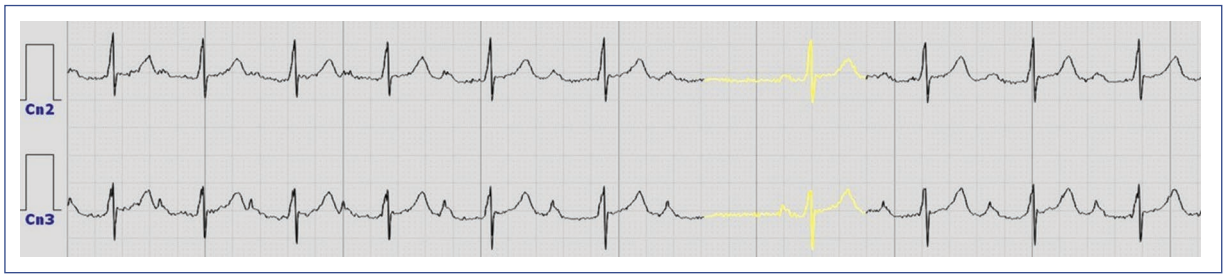

Figure 16. Holter monitor study demonstrating second-degree atrioventricular (AV) block. The ECG shows intermittent failure of conduction from the atria to the ventricles, as evidenced by the dropped QRS complex after some P waves, indicative of second-degree AV block. In this trace, a P wave is not followed by a QRS complex, suggesting a Mobitz type II AV block, where the PR intervals remain constant before the block. This type of AV block can be more serious and may require further evaluation and management. AV: atrioventricular; ECG: electrocardiogram

abdominal pain, and failure to thrive. In newborns, it may present as heart failure (HF)[44].

Diagnostic strategies:

- First-degree AV block. Characterized by a prolonged PR interval on ECG (Fig. 15), usually asymptomatic and benign, with treatment focused on the underlying cause[30,44].
- Second-degree AV block. Occurs when the atrial impulse fails to reach the ventricle correctly and is further divided into two categories:

Mobitz type I (with Wenckebach phenomenon): progressive PR prolongation until a P wave fails to conduct, often asymptomatic and benign[30,44].

Mobitz type II: unchanged PR interval with the sudden failure of P wave conduction (Fig. 16), indicating more severe disease and risk of complete block[30,44].

- Second-degree high-Grade AV Block. Diagnosed when two consecutive P waves fail to reach the ventricles (Fig. 17)[30,44,45].
- Third grade or complete AV Block. Complete AV block with no synchrony between atrial and ventricular activity (Fig. 18) [30,44,45].

Treatment strategies: symptomatic patients may require permanent pacemaker implantation to improve quality of life and prevent bradycardiomyopathy.

Special considerations: patients with complete AV block and CHD are at increased risk of HF and SCD[45]. Acquired complete AV block can result from myocarditis, Lyme disease, rheumatic disease, trauma, or cardiomyopathy[45].

Children with syncope

Syncope, a sudden loss of consciousness due to insufficient cerebral perfusion, is common in children,

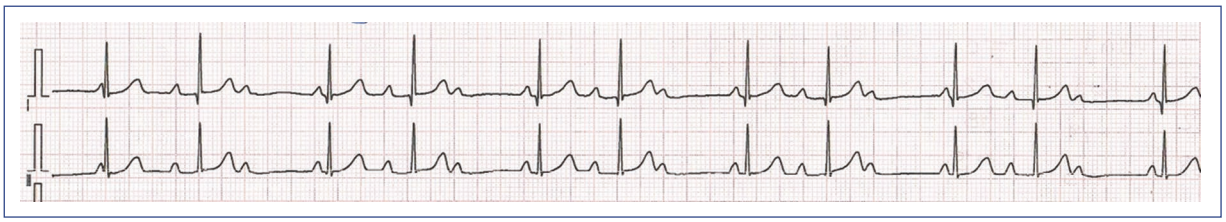

Figure 17. ECG of a 4-year-old girl with congenital high-grade atrioventricular (AV) block, recorded before pacemaker implantation. The ECG shows a high-grade AV block with intermittent conduction. Some P waves are followed by QRS complexes, indicating that occasional atrial impulses are successfully conducted to the ventricles. However, many P waves do not result in QRS complexes, reflecting the impaired conduction through the AV node. The ventricular rate is slow due to this intermittent conduction, and the QRS complexes are narrow, suggesting they originate from above the His bundle when conduction occurs. This degree of conduction abnormality prompted the decision to implant a pacemaker to prevent symptomatic bradycardia and ensure stable cardiac output. AV: atrioventricular; ECG: electrocardiogram.

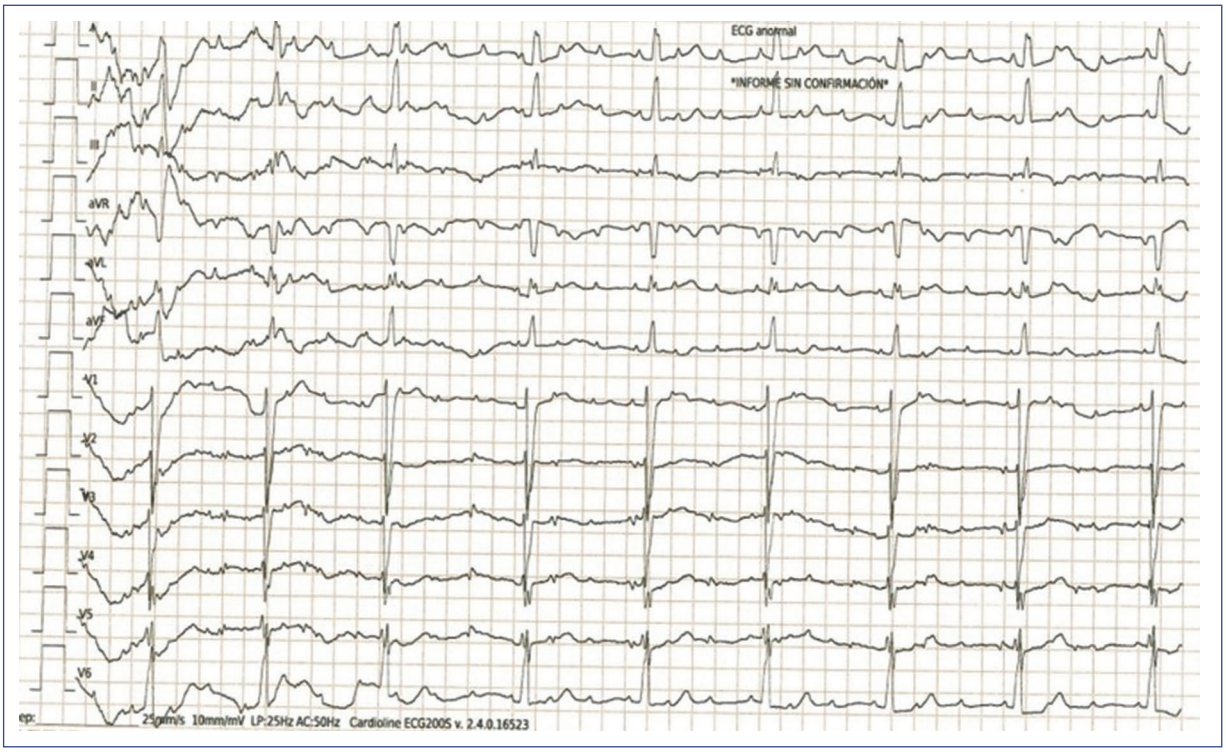

Figure 18. ECG of a 2-year-old boy with congenital complete AV block. The ECG demonstrates a complete dissociation between atrial and ventricular activities, characteristic of third-degree AV block. The P waves occur regularly but have no consistent relationship with the QRS complexes, which also appear at a regular but much slower rate. The QRS complexes are narrow, indicating a junctional escape rhythm as the ventricles independently generate their own rhythm due to the absence of atrial conduction. This severe conduction abnormality often requires early intervention, such as pacemaker implantation, to manage the risk of significant bradycardia and its associated symptoms in a small child. AV: atrioventricular; ECG: electrocardiogram

with a 40% lifetime prevalence and accounting for 1% of emergency department admissions[2,3]. The causes of syncope vary widely and require a systematic approach to identify high-risk patients and manage them appropriately[46-55]. While some arrhythmias, such as bradycardia from complete AV block or tachycardia in WPW syndrome, can cause syncope, the primary concerns are benign vasovagal or situational syncope

and malignant syncope from ventricular fibrillation (VF) due to genetic channelopathies[54,56,57]. Prompt recognition and treatment are critical to prevent SCD.

Benign vasovagal and situational syncope

Classified as benign based on specific criteria (Table 5), it is common and typically managed with lifestyle adjustments such as increased electrolyte intake and avoidance of triggers[56,57]. Tilt-table testing may help diagnose and refine treatment strategies[58].

Malignant syncope

Requires careful analysis to identify cases secondary to diseases that cause SCD, primarily inherited arrhythmias (IAs) that alter ion channel function and predispose to VT and VF (Table 5)[59-61].

The importance of genetic factors in pediatric arrhythmias

Genetic factors play a crucial role in pediatric arrhythmias, particularly in IAs, such as LQTS, Brugada syndrome (BrS), and CPVT. These channelopathies, characterized by ion channel dysfunction despite normal heart structure, carry high mortality risks in children[59]. Next-generation sequencing (NGS) has improved the detection of pathogenic mutations in over 200 genes, increasing the identification of disease-causing mutations, though many variants remain classified as uncertain significance (VUSs)[62]. Channelopathies contribute to approximately 10% of SCD cases, with an incidence of 0.5-20/100,000 person-years from birth to age 35.

a) Congenital LQTS

Prevalence and Mechanism: LQTS is a heritable condition characterized by a prolonged QT interval, abnormal T waves (Fig. 19), recurrent syncope, and SCD. It affects 1 in 2,000 individuals, with an annual SCD rate of 0.5%, increasing to 5% in those with a history of syncope[63]. LQTS is linked to mutations in 17 genes, primarily involving potassium and sodium channels, leading to prolonged action potentials and risk of torsades de pointes (Fig. 20) and SCD.

Loss-of-function mutations in voltage-gated potassium channels are major contributors to LQTS, impairing the outward potassium current crucial during phase 3 of the action potential. LQTS1 is linked to mutations in *KCNQ1* (Kv7.1), LQTS2 to *KCNH2* (Kv11.1), and LQTS5 and LQTS6 to β-subunit mutations (*KCNE1, KCNE2*). LQTS3 is caused by a gain-of-function mutation in *SCN5A*, enhancing the inward sodium current[59,64]. These autosomal dominant mutations prolong action potential duration, predisposing individuals to early afterdepolarizations and torsades de pointes (Fig. 20), while also increasing QT interval variability with HR changes. Additional genes (e.g., *CALM1, CALM2, AKAP9*) are also linked to LQTS[65-68]. A recessive form, caused by homozygous or compound heterozygous mutations in *KCNQ1* and *KCNE1*, leads to

Table 5. Common clinical criteria to differentiate benign from malignant syncope in children

Benign syncope in children	
There is no family history of channelopathy or sudden death.	√
Normal 12-lead ECG (without Brugada pattern and a normal corrected QT interval).	√
Normal physical examination (no murmurs or other abnormalities in heart sounds).	√
Syncope duration and recovery are rapid.	√
Syncope did not occur during physical exertion or stress.	√
A typical trigger for benign syncope can be identified, such as prolonged standing, abdominal pain, urination, defecation, hair brushing, exposure to intense smells (e.g., chemicals or medications), or seeing blood, syringes, or needles during blood draws or vaccine administration, extreme heat.	√
It is very important to rule out inherited arrhythmias: LQTS, BrS, CPVT, and SQTS.	√
Malignant syncope in children	
There is a family history of channelopathy and/or sudden death.	√
The 12-lead ECG is abnormal* (QTc prolongation, Brugada pattern, Conduction abnormalities, Increased QRS complex voltages, abnormalities in repolarization, etc.).	√
Physical examination may be normal.	√
Syncope duration and recovery are slower than in benign syncope.	√
Syncope occurs during physical exertion or stress, or while swimming or after an intense noise.	√
Commonly associated triggers for vasovagal syncope are generally absent.	√
Malignant syncope in children is caused by inherited arrhythmias: LQTS, BrS, CPVT, SQTS.	√

*Except for catecholaminergic polymorphic ventricular tachycardia that usually presents a normal resting ECG. CPVT: catecholaminergic polymorphic ventricular tachycardia; LQTS: long QT syndrome; BrS: Brugada syndrome; SQTS: short QT syndrome.

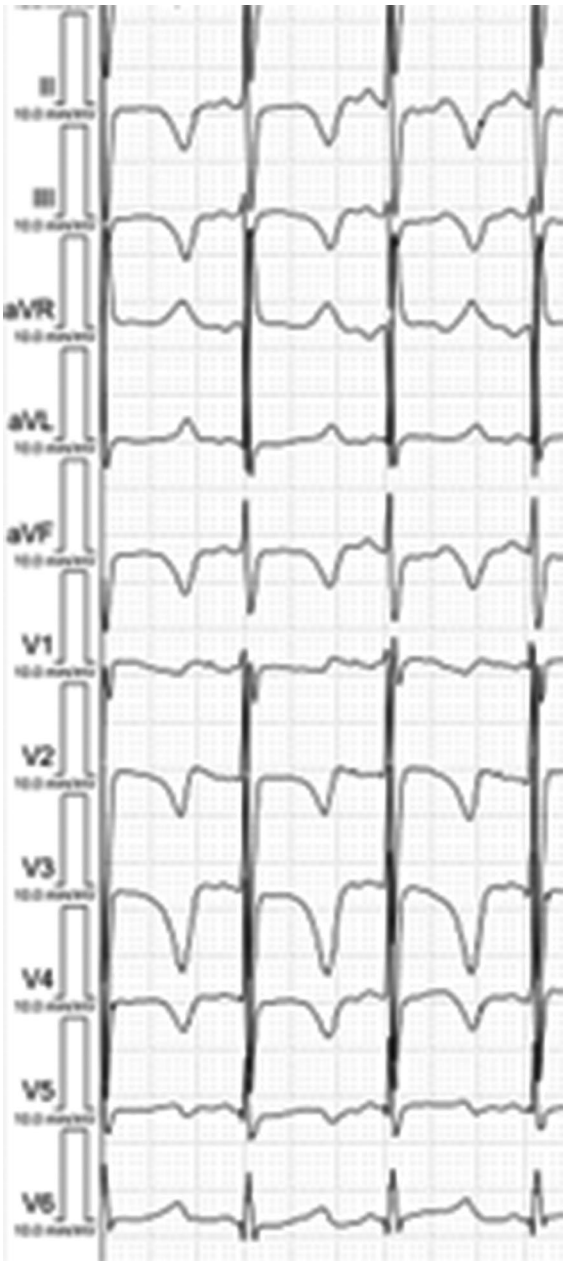

Figure 19. ECG of a young child with LQTS. The ECG displays a markedly prolonged QT interval (measured at 526 ms), evident in all leads, which is characteristic of Long QT Syndrome. The T waves are broad and abnormally shaped, with some leads showing notched or biphasic T waves. This prolonged repolarization increases the risk of life-threatening arrhythmias, such as torsades de pointes, in affected individuals. Early diagnosis and appropriate management, including lifestyle modifications and possibly medication, are crucial to reduce the risk of sudden cardiac events in children with LQTS. LQTS: long QT syndrome.

Jervell and Lange-Nielsen syndrome, characterized by very prolonged QT intervals, high risk of sudden death, congenital deafness, and poor beta-blocker response[68].

Symptoms: symptoms often emerge in childhood or adolescence and include fainting, seizures, and SCD, typically due to VT and VF.

Diagnostic strategies: diagnosis is based on the Schwartz score (Table 6), with LQTS confirmed by QTc ≥ 480 ms, the presence of a pathogenic mutation, or an LQTS score > 3[69,70].

Treatment strategies: all children with LQTS should avoid QT-prolonging medications (www.qtdrugs.org.), competitive sports, and correct electrolyte imbalances[69,70]. Beta-blockers are the first-line treatment, particularly effective in LQTS1[71]. Left cardiac sympathetic denervation (LCSD) and sodium channel blockers, such as mexiletine may be considered in specific cases[71]. Implantable cardioverter-defibrillators (ICDs) are reserved for those who survive VF or have arrhythmogenic syncope despite treatment[71].

Special considerations: genetic counseling and continuous education are recommended for affected families to manage the condition effectively.

b) CPVT

Prevalence and mechanism: CPVT is an inherited channelopathy characterized by polymorphic ventricular arrhythmias triggered by exercise or emotional stress. Its prevalence is estimated at 1/10,000 but may be higher due to increased detection of *RYR2* mutations in SCD cases[27,28,71]. Mutations in *RYR2* (autosomal dominant) and *CASQ2* (autosomal recessive) disrupt calcium handling in the sarcoplasmic reticulum, leading to stress-induced arrhythmias[27-29,71].

Symptoms: symptoms of CPVT include syncope, pre-syncope, seizures, and SCD, often triggered by physical activity or emotional stress[28].

Diagnostic strategies: most patients have normal resting ECGs, but the stress exercise test is the gold standard for diagnosis, revealing ventricular ectopic beats that escalate to monomorphic or bidirectional VT (Fig. 21). Genetic testing for *RYR2* and *CASQ2* mutations is crucial for confirmation and family screening[27].

Treatment strategies: management includes exercise restriction and beta-blockers (nadolol or propranolol)[72,73]. Flecainide may be added if beta-blockers are insufficient. ICD placement is recommended for those resuscitated from CA, but its benefits are debated due

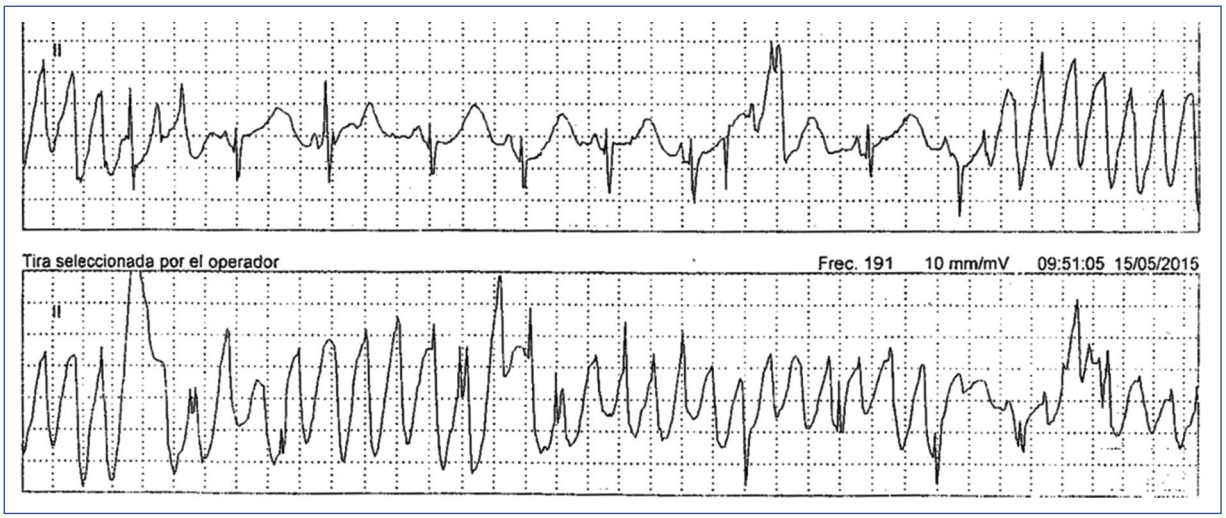

Figure 20. 24-h Holter monitoring ECG tracing in a child diagnosed with LQTS. The tracing reveals episodes of torsades de pointes, a polymorphic ventricular tachycardia characteristic of LQTS, with fluctuating QRS axis and amplitude. These arrhythmic episodes are preceded by a prolonged QT interval, which is the hallmark of the syndrome. The presence of these life-threatening arrhythmias underscores the high risk associated with LQTS in children, necessitating immediate medical intervention. LQTS: long QT syndrome.

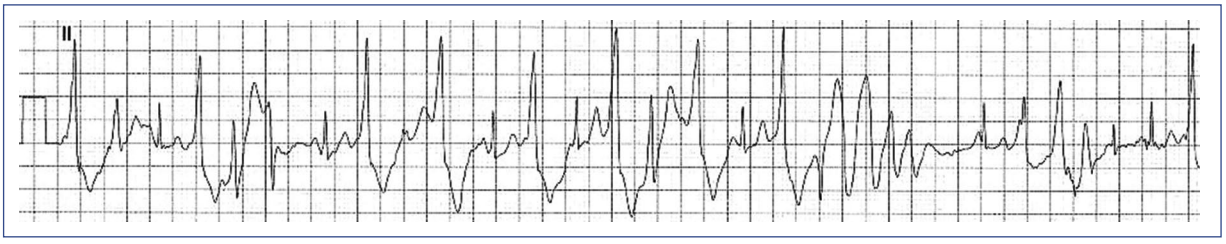

Figure 21. ECG tracing during an exercise stress test in a 14-year-old patient with CPVT. The tracing begins with ventricular extrasystoles, which progressively increase in frequency and culminate in episodes of polymorphic ventricular tachycardia. This pattern, characterized by varying QRS complex morphology and a rapid, irregular rhythm, is typical of CPVT during adrenergic stimulation, such as physical exertion, and underscores the high risk of sudden cardiac arrest associated with this condition. CPVT: catecholaminergic polymorphic ventricular tachycardia.

to the risk of inappropriate shocks in children[25,74]. LCSD is an alternative for reducing arrhythmic events, especially when medical therapy fails.

Special considerations: patients require close monitoring, especially during stress. ICD programming should be carefully managed to avoid triggering arrhythmias. Genetic counseling, family screening, and education about CPVT management are essential.

c) BrS

Prevalence and mechanism: BrS is an autosomal dominant condition characterized by ST-segment elevation in right pre-cordial leads (Fig. 22) and life-threatening ventricular arrhythmias. It has a prevalence of 1 in 2,000-1 in 5,000, contributing to 10-20% of sudden infant deaths and 4-12% of SCD in children and young athletes. The Brugada ECG pattern often emerges post-puberty, even in initially negative cases, with fatal arrhythmias occurring in about 10% of affected children[75-77]. The condition is linked to mutations in *SCN5A* and other genes, with most diagnoses made through family screening[71,77].

Symptoms: children with BrS may experience syncope, palpitations, dizziness, dyspnea, and SCD, often triggered by fever or vaccination[76]. A positive family history is a common initial clue.

Diagnostic strategies: diagnosis involves detecting *SCN5A* mutations, family history, and pediatric ECG, with Holter monitoring to identify ECG abnormalities. Fever can exacerbate ECG abnormalities[77].

Table 6. Schwartz score for the diagnosis of LQTS

Parameter		Points
Electrocardiographic findings		
A	QTc[a] ≥ 480 ms 460 a 479 ms 450 a 459 ms (en varones)	 3 2 1
B	QTc[b] ≥ 480 ms. after 4 min of recovery in the exercise test	1
C	Torsade de Pointes[c]	2
D	T-wave alternans	1
E	Notched T-wave	1
F	Low heart rate for age[d]	0.5
Clinical manifestations		
A	Syncope[c] With stress Without stress	 2 1
B	Congenital deafness	0.5
Family history		
A	Family members with a definite LQTS diagnosis[e]	1
B	Sudden cardiac death in a family member under 30 years	0.5

≤ 1 point: low probability of LQTS.
From 1.5 to 3 points: intermediate probability of LQTS.
≥ 3.5 points: high probability of LQTS.
[a]In the absence of medications or known causes affecting the QT interval.
[b]QTc calculated using Bazett's formula QTc=QTm/√RR.
[c]Mutually exclusive.
[d]Resting heart rate below the second percentile for age.
[e]The same family member cannot be counted in both A and B.

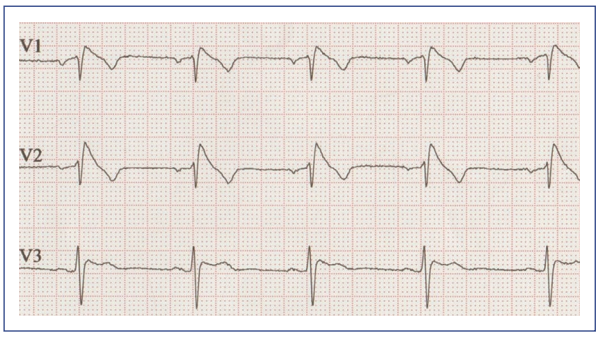

Figure 22. Electrocardiogram of an adolescent with Brugada syndrome showing characteristic coved-type ST-segment elevation in leads V1-V3, indicative of a high risk for ventricular arrhythmias.

Treatment strategies: quinidine is the primary medication, while ICD placement is recommended for those with a history of CA, sustained VT, or spontaneous type 1 ECG patterns (Fig. 22) with syncope. Challenges with ICDs in children include device-related complications and the need for careful programming to prevent inappropriate shocks[75,77].

Special considerations: AF episodes in children may indicate BrS and fever management is crucial. Families should be educated on avoiding medications that increase BrS risks, with guidance available at www.brugadadrugs.org.

d) Short QT syndrome (SQTS)

Prevalence and mechanism: SQTS is a rare inherited channelopathy characterized by abnormally shortened QT intervals (Fig. 23), leading to arrhythmias and SCD. It follows an autosomal dominant inheritance pattern and is associated with mutations in eight genes regulating ionic currents[59,78]. Prevalence ranges from 0.02% to 0.1% in adults and up to 0.05% in children, with a high incidence of arrhythmic events during infancy. The syndrome's fatality rate is significant, with a 40% cumulative risk of cardiac events by age 40, predominantly in males[78].

Symptoms: SQTS manifests in nearly 40% of patients, with symptoms including palpitations, AF, ventricular arrhythmias (VT/VF), syncope, and SCD, especially in infancy and between ages 20 and 40.

Diagnostic strategies: diagnosis is recommended when QTc ≤ 360 ms, along with a pathogenic mutation, family history of SQTS, SCD, or survival from VT/VF[59]. Table 7 shows a diagnostic scoring system for SQTS proposed by Gollob et al. Genetic testing can identify pathogenic variants in approximately 30% of cases, with five genes (*KCNH2, KCNJ2, KCNQ1, CACNA1C, and CACNB2B*) recommended for evaluation. ECG changes include minimal or absent ST segments, tall T waves, and short J-T peak intervals.

Treatment strategies: ICD therapy is indicated for survivors of aborted CA and patients with documented spontaneous VT. In asymptomatic patients, risk stratification is challenging, with ICDs considered for those with arrhythmic syncope[78]. Pharmacological therapies with QTc-prolonging drugs, such as quinidine may be used in patients who cannot receive or decline ICDs. Implantable loop recorders (ILRs) are recommended for monitoring in asymptomatic children.

Special considerations: genetic counseling and family screening are crucial due to the hereditary nature of SQTS. Patients should be educated about the syndrome, its triggers, and management strategies, with a multidisciplinary approach involving cardiologists, geneticists, and electrophysiologists for comprehensive care.

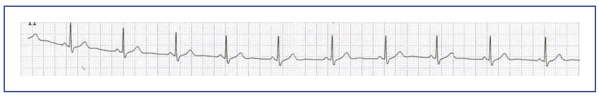

Figure 23. Electrocardiographic tracing of a young child with short QT syndrome. Note the shortened QT interval (measured at 320 ms), indicating the characteristic feature of the syndrome. The tracing shows a typical rapid repolarization pattern associated with this condition.

Table 7. Diagnostic scoring system for short qt syndrome proposed by Gollob et al.

Electrocardiographic findings	Points
QTc^	
< 370 ms	1
< 350 ms	2
< 330 ms	3
Jpoint-Tpeak interval < 120 ms*	1
Clinical history#	**Points**
Sudden death†	2
Polymorphic ventricular tachycardia or ventricular fibrillation†	2
Unexplained syncope†	1
Atrial fibrillation	1
Family history#	**Points**
First- or second-degree relative with a high probability of SQTS	2
First- or second-degree relative with unexplained sudden death	1
Relative with sudden infant death	1
Genotype#‡	**Points**
Positive genotype	2
Variant of uncertain significance in genes associated with SQTS	1

^QTc calculated using Bazett's formula (QTc = QT/√RR).
*Measure in the precordial lead with the highest T wave amplitude.
#A minimum of 1 point must be obtained in the electrocardiographic section to earn additional points.
†Mutually exclusive.
‡Points can only be received once in this section.
≤ 2 points: low probability; 3 points: intermediate probability; ≥ 4 points: high probability.

Discussion

This comprehensive review presents a symptom-based framework designed to assist non-specialist physicians in managing pediatric arrhythmias, emphasizing the importance of tailored approaches that consider the unique physiological and genetic factors in children. Pediatric arrhythmias vary significantly, with many asymptomatic cases being benign. However, certain conditions, such as pre-excitation syndrome and LQTS, require vigilant monitoring due to the risk of severe complications[2,41,67].

Paroxysmal tachycardia, particularly SVT, is commonly encountered in pediatric patients. Initial management typically includes non-pharmacological interventions, with adenosine as the first-line pharmacological treatment[36]. In unstable patients, electrical cardioversion is recommended[22,30,37,54].

IAs, including LQTS, BrS, CPVT, and SQTS, present significant risks even in the absence of structural heart disease[4,59]. In these cases, genetic testing and family screening are crucial, with NGS enhancing the detection of pathogenic variants. However, many of these variants remain classified as VUSs, necessitating further research to clarify their clinical implications[71,73].

Pediatric arrhythmia management encompasses a range of strategies, including lifestyle modifications, pharmacological treatments, and interventional procedures such as catheter ablation and ICD placement. Beta-blockers play a central role in managing conditions, such as LQTS and CPVT[5,25,43,49,72,79], while ICDs, although lifesaving, present challenges in children, including device-related complications and the need for meticulous programming to minimize risks[5,19,74].

Since non-electrophysiology specialists are often the first to evaluate children presenting with arrhythmias and specific symptoms, this practical guide on the initial approach is highly valuable for ensuring appropriate treatment and timely, effective referral to specialized centers. Effective referral involves identifying cases at high risk for serious complications, including SCD, while managing benign cases–common in the pediatric population–with a conservative and vigilant approach, avoiding the use of antiarrhythmic medications that may be more harmful than beneficial.

Looking ahead, our findings highlight several areas in need of further research and improvement in clinical practice. There is a pressing need for more extensive pediatric-specific studies to develop evidence-based guidelines tailored specifically to children. In addition, continued advancements in genetic research are essential to clarify the clinical relevance of VUSs and to develop novel therapeutic interventions for managing IAs. By addressing these gaps, we can improve the care and outcomes for children affected by arrhythmias.

Limitations

Despite the comprehensive nature of this review, several limitations must be acknowledged. First, the reliance on existing literature may introduce bias, as studies with positive outcomes are more likely to be published. Second, the heterogeneity in study designs, patient populations, and diagnostic criteria across the included studies may limit the generalizability of our findings. In addition, the brief period of included studies (2019-2024) may exclude relevant research published outside this period. Finally, while this review aims to provide practical guidelines for non-specialist physicians, the rapidly evolving field of pediatric cardiology necessitates ongoing updates to ensure recommendations remain present and evidence-based.

Conclusion

This review underscores the complexity of pediatric arrhythmias and the importance of a symptom-based approach in their management. By synthesizing the present evidence and providing practical guidelines, we aim to equip non-specialist physicians with the tools necessary to effectively diagnose and treat pediatric arrhythmias, improving patient outcomes and reducing the incidence of SCD in this vulnerable population.

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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 study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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

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REVIEW ARTICLE

Cost-effectiveness of silver diamine fluoride for the prevention and control of early childhood caries: a scoping review

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Abstract

Early childhood caries (ECC) is the presence of one or more decayed, missing, or filled teeth in children up to 71 months of age. Among the recommendations proposed by the World Health Organization to counteract this condition is the application of silver diamine fluoride (SDF). The aim of this research was to analyze the available information on the cost-effectiveness of SDF as a public health intervention in the prevention and control of ECC. This scoping review included articles published in English between 2008 and 2023 about the cost-effectiveness of SDF for pre-schoolers. Scientific journal databases (PubMed, Free Medical Journal, Science Direct, Springer Link, and Google Scholar) were searched using the following keywords: ECCs, effectiveness, cost, SDF, economic evaluation, caries, pre-school, infant, and minimal invasive treatment. The information extracted included author, year, objective, population, design, perspective of the analysis, options to be compared, time horizon, discount rate, costs, and effectiveness. We identified a total of 526 articles. Of these, 514 were excluded due to lack of relevance to the study objective, and 5 were duplicates. The final sample comprised 7 articles. The reported costs of SDF treatments from the perspective of healthcare practitioners ranged from $0.7 to $1,456, with an incremental cost-effectiveness ratio ranging from –$7.73 to –$518.50. SDF is a cost-effective treatment for public health interventions to prevent and control ECC in pre-schoolers.

Keywords: *Caries. Pre-school children. Diamine silver fluoride. Cost. Effectiveness.*

Costo-efectividad del fluoruro diamino de plata para la prevención y control de la caries de inicio temprano: revisión sistemática exploratoria

Resumen

La caries de inicio temprano (CIT) es la presencia de uno o más dientes cariados, perdidos u obturados en niños hasta 71 meses de edad. Entre las recomendaciones que propone la Organización Mundial de la Salud, para contrarrestar esta condición, se encuentra la aplicación del fluoruro diamino de plata (FDP). El objetivo de esta investigación es analizar la información disponible sobre el costo-efectividad del FDP como intervención de salud pública en la prevención y control de la CIT. En la revisión sistemática exploratoria se incluyeron artículos publicados en inglés, entre 2008 y 2023, que abordaron el tema de costo-efectividad del FDP en preescolares. Se utilizaron los buscadores PubMed, Free Medical Journal, Science Direct, Springer Link y Google Scholar con las siguientes palabras clave: early childhood caries, effectiveness, cost,

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silver diamine fluoride, economic evaluation, caries, pre-school, infant y minimal invasive treatment. La información extraída incluyó: autor, año, objetivo, población, diseño, perspectiva del análisis, opciones a comparar, horizonte temporal, tasa de descuento, costos y efectividad. Se identificaron 526 artículos. Se excluyeron 514 por no relacionarse con el objeto de estudio y 5 por estar duplicados. La muestra final fue de 7 artículos. Los costos reportados de las intervenciones con FDP, desde la perspectiva del proveedor de salud, fluctúan entre $0.7 y $1456 dólares y una razón de costo efectividad incremental que va desde –$7.73 a los –$518.50 dólares. El FDP es un tratamiento costo-efectivo que puede utilizarse para intervenciones de salud pública para prevenir y controlar la CIT en preescolares.

Palabras clave: *Caries. Preescolares. Fluoruro diamino de plata. Costo. Efectividad.*

Introduction

Early childhood caries (ECC) is a multifactorial disease that affects approximately 70% of pre-school children seeking dental care in Mexico[1]. Etiopathogenesis of ECC involves the interaction of community, family, and host-specific factors[2]. Low socioeconomic status[3], social disadvantages[4], mother's educational level and emotional state[5-7], oral hygiene[8], transmission of *Streptococcus mutans*[9], and cariogenic diet[10] are some of the factors that contribute to this disease. When caries reaches advanced stages, it can be limiting and affect the child's growth and development[11].

In 2019, the World Health Organization (WHO) published the implementation manual: "Ending Childhood Dental Caries," which outlines action plans aimed at preventing and controlling ECC[12]. One proposed alternative is silver diamine fluoride (SDF), a high-concentration fluoride solution composed of silver, ammonium, and fluoride, which acts as an antimicrobial, cariostatic, and remineralizing agent[13].

ECC is a significant public health problem that requires resources for designing effective prevention and control programs. However, in the health sector, needs are infinite while resources are increasingly limited. Mexico's health investment of approximately 3% of its gross domestic product falls short of the 6% recommended by the WHO[14].

Economic evaluations are key decision-making tools that allow for the assessment of programs in terms of costs and consequences, with the aim of promoting more efficient use of resources in a scarcity environment[15].

The objective of this research is to analyze the available information on the cost-effectiveness of SDF as a public health intervention in the prevention and control of ECC.

Method

A scoping systematic review was conducted, following Arksey and O'Malley's methodology[16].

All articles published in indexed journals in English were selected, regardless of publication year. The review included all cohort studies and clinical trials reporting the cost and effectiveness of SDF in pre-schoolers. Furthermore, included were economic evaluations using any cost-effectiveness model and any treatment alternative in the control group for ECC prevention. Cost minimization or cost-utility economic evaluations focused on other pathologies or age groups were excluded.

The following search engines were used: Scielo, PubMed, Free Medical Journal, Science Direct, Springer Link, and Google Scholar. The information collection was conducted by three researchers working independently. The search was carried out from May 1 to May 26, 2024. The keywords used were: ECCs, effectiveness, cost, SDF, economic evaluation, caries, pre-school, infant, minimal invasive treatment.

The sample, phenomenon of interest, design, evaluation, research acronym was used to create the search strategy[17]. S: study population (preschoolers); PI: cost-effectiveness of SDF in the prevention and control of ECCs; D: all original publications with quantitative methodology addressing the phenomenon of interest were considered; E: the search strategy was not limited to the evaluation (E) of the publication, as a limited number of articles was found; R: all studies related to the topic of interest were selected.

The titles and abstracts from the initial search were evaluated by an independent researcher. Duplicate articles and those unrelated to the study objective were excluded. A list containing the author, title, and publication link was created in Microsoft Excel for data extraction.

Thorough evaluation and data extraction of the filtered articles was conducted by four researchers working collaboratively. The extracted data included: author, study publication year, study objective, study population, design, analysis perspective, options to compare, time horizon, discount rate, costs, and effectiveness evaluation.

The quality of selected articles was individually evaluated using M. Drummond's criteria[18] for conducting economic evaluation studies; observational studies were evaluated using the strengthening of the reporting of observational studies in epidemiology guidelines[19] and clinical trials using the CONSORT guidelines[20]. In addition, the grading of recommendations, assessment, development, and evaluation (GRADE) methodology was applied to evaluate the quality of scientific evidence[21] (Table 1).

Results

During the literature search, 526 articles were identified. 519 were eliminated (5 due to duplication and 514 due to lack of relevance to the study objective) (Fig. 1). The final sample consisted of 7 articles: 3 clinical trials and 4 cohort studies. The clinical trials obtained a high-quality level according to the GRADE methodology. Regarding the cohort studies, 3 obtained a low-quality level and one moderate (Table 1).

Xiao compared the cost-effectiveness of: (1) Pit and fissure sealant; (2) atraumatic restorative treatment (ART) technique; (3) Sodium fluoride; and (4) SDF. Over an 18-month time horizon, the most economical preventive treatments per tooth were sodium fluoride at US$0.3 and pit and fissure sealant at US$0.3. No statistically significant differences were found in the effectiveness of the treatments ($p \geq 0.05$)[22].

Hansen estimated the impact of adopting silver nitrate and fluoride varnish treatment on dental care costs. They identified a total cost of US$1456 in the group treated with silver nitrate + fluoride varnish and US$945 in the conventionally treated group, over a 28-month time horizon ($p \leq 0.0001$). The most expensive treatment with the highest number of appointments was silver nitrate + fluoride varnish[23].

Two years later, Hansen evaluated the impact of SDF considering coverage and reimbursement policies in two study groups: (1) incorporation of SDF in Medicaid and (2) use of SDF by expanded practice dental hygienists. Greater savings were found when SDF was applied by dental hygienists (–US$201/1000 patients/quarter). However, the application of SDF through Medicaid showed a higher utilization rate[24].

Davis compared the cost-benefit of children treated and not treated with SDF. In the SDF-treated group, an average of US$ 619.72 ± 563.51 was spent, and without SDF US$ 958.04 ± 824.65 ($p \leq 0.001$). The average treatment effect on the treated was –515.30 (cost-benefit). The savings obtained after the SDF application were significant[25].

Nguyen estimated the cost-effectiveness of: (1) Treatment under general anesthesia; and (2) Conventional treatment without general anesthesia (through a decision tree model where the base scenario was the application of SDF in standard care without general anesthesia and the alternative scenario was the application of SDF without standard care and without general anesthesia). In the base scenario, the average savings were $171.01 AUD/child/mean effectiveness 0.298 of general anesthesia avoided per year, and in the alternative scenario, the average savings were $518.50 AUD/child/mean effectiveness 0.300 of general anesthesia avoided per year[26].

Kodali analyzed the cost-effectiveness of: (1) prophylaxis + 38% SDF and (2) prophylaxis + glass ionomer restoration + 5% fluoride varnish. The most economical intervention was SDF with a cost of 67.30 Indian rupees to convert a tooth from active to inactive caries. The incremental cost-effectiveness ratio was –89.9 (for each tooth treated with SDF, there was a saving of 89.9 Indian rupees)[27].

Ali compared the clinical performance and cost-effectiveness of: (1) modified ART technique with SDF (silver-modified atraumatic restorative treatment [SMART]) and (2) conventional ART technique. The SMART technique showed greater savings (60.5 ± 3.5 Egyptian pounds per tooth compared to the ART technique 67.4 ± 4.1 $p \leq 0.001$) with shorter treatment time[28].

Discussion

SDF is a cost-effective public health intervention for ECC control. Three clinical trials and 4 cohort studies were included. All studies used the healthcare provider perspective. The time horizon periods ranged from 6 months to 4 years. The treatment options against which SDF was compared were resin pit and fissure sealants, ART technique, 5% sodium fluoride, glass ionomer, conventional treatment, and conventional treatment under general anesthesia. Only Kodali's study used a discount rate of 3%[27]. Different currencies were used to report costs: US dollars, Australian dollars, Indian rupees, and Egyptian pounds. The range of intervention costs with SDF was from $0.7/tooth to $1456 total cost. The effectiveness measures reported were incremental cost-effectiveness ratio, cost-benefit, average cases of general anesthesia avoided per year, mean survival time, and mean treatment time.

Table 1. Characteristics of incluided studies

Authors	Year of publication	Study objective	Study population	Study design	Analysis perspective	Comparison options	Time horizon	Discount rate	Costs	Effectiveness	Evaluation guideline	Quality of evidence GRADE
Xiao et al.	2008	Investigate the cost-effectiveness of four methods in caries prevention of pits and fissures in permanent teeth	161 Children from first to third grade in Shenzhen, China	Clinical Trial	Health Provider	FS: pit and fissure sealant resin ART: technique TRA NaF: sodium fluoride every 6 months SFD: annual application of silver diamine fluoride	18 months	N/R	FS: US $0.3 ART: US $1.0 NaF US $0.3 SFD: US $0.7 Cost per tooth treated	FS: 97.3% ART: 97.2% NaF: 96.4% SFD: 98.7% (Chi-square test, P≥0.05)	CONSORT	High
Hansen et al.	2017	Estimate the impact of adopting treatment with silver nitrate/ fluoride varnish on dental care costs and resource utilization	18,110 children 4612 Children treated with silver nitrate/ fluoride varnish 13498 Children with conventional treatment.	Retrospective cohort	Health provider	SN/FV Group of silver nitrate+fluoride varnish C: group with conventional treatment	28 months	N/R	SN/FV: $1455.9 ± 1125.1 dollars C: $944.7 ± 1192.4 dollars (p ≤ 0.0001)	In the 28-month term, the number of dental consultations was higher, by 21%, in the Silver nitrate group compared to conventional treatment	STROBE	Low
Hansen et al.	2019	Evaluate the impact of silver diamine fluoride considering coverage and reimbursement policies	117,599 pediatric patients from Oregon	Retrospective cohort analysis	Health provider	Medicaid=Inclusion of SDF in Medicaid EPDHS: use of SDF by expanded-function dental hygienists	4 years	N/R	Costs of care Medicaid= –$7.73/1,000 patients/quarter EPDHS: –$201/1,000 patients/quarter	Utilization rate Medicaid: 84 more SDF treatments/1,000 patients per quarter EPOHS: –91.7 SDF treatments/1,000 patients per quarter	STROBE	Moderate

(Continues)

Table 1. Characteristics of incluided studies *(continued)*

Authors	Year of publication	Objective of study	Study population	Study design	Analysis perspective	Comparison options	Time horizon	Discount rate	Costs	Effectiveness	Evaluation guideline	Quality of evidence GRADE
Davis et al.	2020	To compare dental care visits, procedures, and expenses between children with newly diagnosed early childhood caries who received and did not receive SDF.	354 children under 6 years of age 104 with silver diamine fluoride 250 without silver diamine fluoride	Retrospective cohort study	Healthcare provider perspective	SDF = treatment with silver diamine fluoride Without SDF: conventional treatment	2 years	N/R	General treatment expenses excluding subjects requiring general anesthesia SDF: $USD 619.72 ± 563.5 without SDF: $USD 958.04 ± 824.6 p = ≤ 0.001	Average treatment effect on the treated (ATET): 515.30 (cost-benefit)	STROBE	Low
Nguyen et al.	2022	To develop a cost-effectiveness model for a silver diamine fluoride intervention protocol compared to general anesthesia in Victorian children aged 2-10 years	102 Children aged 2-10 years 85 with silver diamine fluoride 5 lost to follow-up 12 general anesthesia	Cohort study	Healthcare provider perspective	GA: treatment under general anesthesia. C: conventional treatment without general anesthesia. Base scenario: Children who received SDF in standard care without general anesthesia. Alternative scenario: SDF without standard care and without general anesthesia	1 year	N/R	GA: $1793.23 Australian dollars C: $409.90 Australian dollars SDF: $190.81 Australian dollars in the first session $131.24 Australian dollars in second session	Children SDF in standard care without general anesthesia: Average savings of $171.01 AUD per child/mean effectiveness 0.298 of general anesthesia avoided per year. Children SDF without standard care without general anesthesia = average savings of $518.50 AUD per child/mean effectiveness 0.300 of general anesthesia avoided per year	STROBE	Low

(Continues)

Table 1. Characteristics of incluided studies *(continued)*

Authors	Year of publication	Objective of study	Study population	Study design	Analysis perspective	Comparison options	Time horizon	Discount rate	Costs	Effectiveness	Evaluation guideline	Quality of evidence GRADE
Kodali et al.	2022	To analyze the cost-effectiveness of silver diamine fluoride compared to glass ionomer followed by 5% fluoride varnish application	187 children aged 1-5 years Group A: 91 children Group B: 96 children	Randomized clinical trial	Healthcare provider	Group A: Prophylaxis + 38% SDF Group B: Prophylaxis+glass ionomer restoration + 5% sodium fluoride varnish application	6 months	3%	Global costs: Group A: $20,583 Group B: $34,369 (with discount rate). Group A: 67.30 Indian rupees to convert one active carious tooth to inactive Group B: 225.5 Indian rupees to convert one active carious tooth to inactive	Group A: 144 teeth with active caries after intervention Group B: 66 teeth with active caries after intervention. Incremental cost-effectiveness ratio was 89.9 (Per tooth inactivated with SDF)	CONSORT	High
Aly et al.	2023	To compare the clinical performance and cost-effectiveness of SMART technique versus conventional atraumatic Restorative Treatment (ART) in primary molars after 12 months of follow-up	55 children aged 5-9 years SMART: 29 children (50 molars) ART: 26 children (49 molars)	Clinical trial	Healthcare provider	SMART: modified ART with silver ART: conventional ART	12 months	N/R	SMART: 60.5 ± 3.5 Egyptian pounds per tooth ART: 67.4 ± 4.1 Egyptian pounds per tooth $p \leq 0.001$	Clinical performance (mean survival time) SMART: 11.8 months ART: 11.6 months ($p = 0.41$). Mean treatment time SMART: 7.8 min ART: 15 min ($p \leq 0.001$)	CONSORT	High

ART: atraumatic restorative treatment; GRADE: grading of recommendations, assessment, development, and evaluation; SDF: silver diamine fluoride; SMART: silver modified atraumatic restorative treatment, STROBE: strengthening the reporting of observational studies in epidemiology.

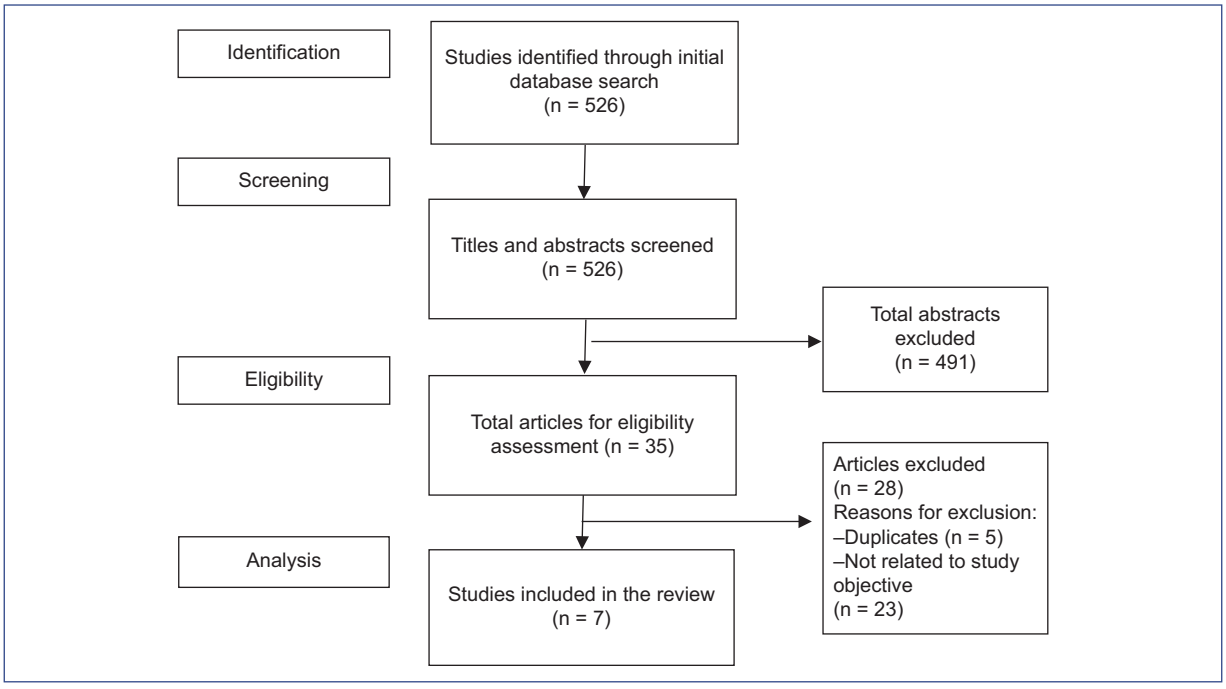

Figure 1. Flow diagram of articles selected for the scoping systematic review.

When comparing SDF with pit and fissure sealant and sodium fluoride, a lower cost was identified in these treatment alternatives (US $0.3) compared to SDF (US $0.7). There were no significant differences when comparing the effectiveness between SDF (98.7%) versus sealant (97.3%) and sodium fluoride (96.4%). The most expensive treatment alternative was the ART technique[22].

Silver nitrate is an inorganic salt with the chemical formula $AgNO_3$. This component, similar to SDF, has bactericidal and antimicrobial properties[29,30]. In the field of Dentistry, its use has been incorporated in the treatment of dental caries[31].

When comparing costs between silver nitrate application and conventional restorative treatment, there is a higher cost of care in the $AgNO_3$ group (US$1456 versus US$945). The increase in care costs is likely due to a higher number of consultations in the silver nitrate-treated group compared to conventional treatment[23].

Medicaid is a national program that, through the State, provides free or low-cost medical care to people of all ages with limited income and resources. Medicaid program names vary by State. Oregon's program is the Oregon Health Plan (OHP).

The OHP provides medical care coverage for residents who meet eligibility criteria. Coverage includes doctor visits, hospital care, mental health services, dental care, and additional benefits for children and pregnant women[32]. Among the dental services offered by the OHP program is antimicrobial treatment for caries arrest with the application of 38% SDF[33].

Hansen evaluated the impact of SDF considering coverage and reimbursement policies. When incorporating the SDF application into Oregon's Medicaid program, a savings of US$7.73/1000 patients/quarter was obtained, and coverage of 84 more SDF treatments/1000 patients/quarter. The savings were greater when SDF was applied outside the program through expanded practice dental hygienists (US$201/1000 patients/quarter). However, coverage was lower (–91.7 SDF treatments/1000 inhabitants/quarter), meaning that despite having lower savings in SDF application through the Medicaid program, there is a higher demand for this treatment[24].

On the other hand, Davis compared the average direct care expenses between children treated with SDF and those treated with conventional treatment. Savings of slightly more than US$300 were reported in children treated with SDF compared to conventional treatment (619.72 ± 563.51 versus 958.04 ± 824.65 $p \leq 0.001$)[25]. This study coincides with the results reported by Nguyen, where greater average savings

were observed using SDF, in addition to greater effectiveness in general anesthesia avoided/year[26].

Glass ionomer is versatile cement that chemically adheres to dental tissues (enamel and dentin) and releases fluoride. It has been used as a restorative material, liner, pit and fissure sealant, in the ART technique, and as an adhesive agent in Orthodontics[34].

SDF along with dental prophylaxis proved to have a lower cost compared to prophylaxis with glass ionomer restoration and 5% sodium fluoride application ($67.30 versus $225.5 Indian rupees, respectively). There was a saving of 89.9 Indian rupees for each tooth with caries that was inactivated with SDF[27].

As previously mentioned, glass ionomer is used as a restorative material in the ART technique. This is a dental procedure that involves the removal of softened tissue through the use of manual instruments[35]. Some studies have implemented the application of SDF as an adjunctive material to the ART technique to ensure dental caries arrest before cavity filling[36].

Aly compared the clinical performance and cost-effectiveness of the modified ART technique with SDF and the conventional ART technique. The ART technique modified with SDF proved to be more economical compared to the conventional one by almost 7 Egyptian pounds, and it also achieved a shorter working time for treatment application[28].

Among the strengths of this scoping systematic review are: Information was collected about SDF (a public health intervention proposed by the WHO for the prevention and control of ECC); the direct costs and effectiveness of SDF after its application as a public health measure were disclosed from the healthcare provider perspective. In addition, each article was evaluated with the appropriate checklist according to its design and the GRADE methodology to assess the quality of evidence.

Its main limitation is the small number of published articles on the subject. In addition, when collecting information about SDF intervention costs from international sources, the monetary units are expressed in dollars or currencies other than Mexican pesos, so costs would need to be converted to our national currency.

Conclusion

There are a very small number of articles published in indexed journals that evaluate the cost-effectiveness of SDF used for ECC control and prevention. The quality of the clinical trials included in this review, considering the GRADE system, was high. Regarding the observational studies, they had moderate-to-low quality. Taking into consideration the results of the research included in this review, SDF is cost-effective compared to conventional treatment and treatment under general anesthesia.

Recommendations

It is recommended to conduct more studies evaluating the cost and effectiveness of health interventions to improve decision-making and, thus, optimize the use of resources while maximizing benefits.

Considering the results of the research included in this review, the incorporation of SDF into programs and public policies aimed at the prevention and control of ECC at the population level is recommended.

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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 study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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

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RESEARCH ARTICLE

Hodgkin and non-Hodgkin lymphomas in pediatric-age patients of Northeast Mexico: 18-year outcomes and survival rates at an academic center

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Abstract

Background: *Hodgkin lymphoma (HL) and non-HL (NHL) are the third and fourth most common malignancies during childhood, with limited information available from Latin America.* **Method:** *We retrospectively studied patients with HL and NHL from a single academic center in Northeast Mexico between 2002 and 2020. Data included treatment regimens, staging, and survival outcomes. Survival was determined by Kaplan–Meier analysis, and features of lymphomas were compared using the X^2 test.* **Results:** *The study included 75 patients, 36 (48%) with HL and 39 (52%) with NHL. Males predominated (70%); the median age was 9 years. Stages III and IV were detected in 59% and median follow-up reached 50 months. Relapse occurred in 16 (21%) patients, 9 (12%) in the HL group and 7 (9%) in the NHL group. Thirteen (17.3%) patients underwent transplantation, 12 (85%) in the HL group; 11 are alive. Most deaths, 10/11 (91%), occurred in NHL patients. Five-year overall survival rates were 96% (95% confidence interval [CI] 95.6-97) for HL and 75% (95% CI 74.9-76.3) for NHL (p = 0.004). Five-year disease-free survival was 70% for HL (95% CI 69-72.5) and 69% (95% CI 67.7-71) for NHL (p = 0.672).* **Conclusion:** *Pediatric-age HL and NHL had similar frequency in the study population; most patients presented with advanced disease at diagnosis. A high success rate was documented for HL, while NHL outcomes were suboptimal.*

Keywords: *Pediatric lymphomas. Non-Hodgkin lymphoma. Hodgkin lymphoma. Transplantation in pediatric lymphomas. Survival in pediatric lymphomas.*

Linfomas Hodgkin y no Hodgkin en pacientes en edad pediátrica del noreste de México: resultados y tasas de supervivencia a 18 años en un centro académico

Resumen

Introducción: *Los linfomas Hodgkin (LH) y no Hodgkin (LNH) son la tercera y cuarta neoplasia maligna durante la infancia, con escasa información sobre sus características y evolución en Latinoamérica.* **Método:** *Se incluyeron pacientes ≤ 18 años con LH y LNH de un centro académico en el noreste de México entre 2002 y 2020. Los datos analizados incluyeron modalidades de tratamiento, estadificación y supervivencia. La supervivencia se determinó por análisis de Kaplan–Meier y las características de los linfomas se compararon mediante X^2.* **Resultados:** *Se incluyeron 75 pacientes, 36 (48%) con HL y*

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39 (52%) con LNH. Predominaron los varones (70%); la edad media fue de 9 años. Se detectaron estadios III y IV en el 59%, la mediana de seguimiento alcanzó los 50 meses. La recaída se produjo en 16 (21%) pacientes, 9 (12%) HL y 7 (9%) LNH. Trece (17.3%) pacientes fueron sometidos a trasplante, 12 (85%) en el grupo HL, 11 vivos actualmente. La mayoría de las muertes, 10/11 (91%), ocurrieron en pacientes con LNH. La sobrevida general (SG) a cinco años fue 96 % para LH y 75 % para LNH, (p = 0,004). La sobrevida libre de eventos (SLE) fue del 70 % para HL (IC del 95 %: 69-72,5) y del 69 % (IC del 95 %: 67,7-71) para LNH (p = 0,672). **Conclusión:** *Los LH y LNH en edad pediátrica tuvieron una frecuencia similar en la población del estudio. Se documentó una alta tasa de curación para LH, mientras que para LNH los resultados fueron subóptimos.*

Palabras clave: *Linfomas pediátricos. Linfoma de Hodgkin. Linfoma no Hodgkin. Trasplante en linfomas pediátricos. Supervivencia en linfomas de la infancia.*

Introduction

In patients of pediatric age, lymphoma is the third most frequent neoplasia, with a prevalence of 15%[1]. In 2021, the incidence in this age group was approximately 25/million, with 2,000 new cases diagnosed yearly[2]. Lymphoma makes up 12% (ages < 15 years) to 19% (ages 15-19) of childhood cancers in the United States[1]. The incidence of Hodgkin lymphoma (HL) and non-HL (NHL) varies according to gender, age, geographic location, and socioeconomic conditions[3]. HL is the third most common malignancy in this age group, and eight percent of all cancers at this age correspond to HL, with a higher incidence in adolescents.

Non-HL in children accounts for 7% of children and teens diagnosed annually in the United States. As in HL, the NHL incidence has increased, with a higher number seen in white children compared to other ethnic groups and a male predominance 2-3 times greater than in girls[2]. Between 1975 and 2010, the 5-year survival rate for pediatric NHL in the United States increased from 45% to 87% in children < 15 years and from 48% to 82% in adolescents aged 15-19[4].

In addition to classical chemotherapy, monoclonal antibodies, such as rituximab, have contributed significantly to increasing response rates in B-cell lymphomas[5].

Limitations for improvement in lymphoma outcomes in low- and middle-income countries and consequent betterment needs have been identified, including those on standards for diagnosis and classification, treatment affordability, long-term sustainability of cooperative programs, and development of clinical research projects, among others[6].

We report and compare the distribution of lymphomas by type, main diagnostic features, treatment modalities, and survival in an open-population pediatric Hispanic cohort diagnosed in a public hospital in Northeast Mexico over 18 years.

Method

A longitudinal and retrospective analysis from 2002 to 2020 in pediatric patients 18 years of age and younger diagnosed with any lymphoma at the Hematology Department of the Dr. Jose Eleuterio Gonzalez University Hospital and School of Medicine of the *Universidad Autónoma de Nuevo León* in Monterrey, Mexico, was performed. The hospital is an academic reference center for low-income, uninsured open population from the country's Northeast region. Electronic databases and clinical files were scrutinized, and age, sex, initial complete blood count, treatment regimen, Ann Arbor stage, date of birth, date of diagnosis, date to relapse, last visit/death, cause of death, transplantation, and survival data were accrued. Advanced disease was defined as a bulky disease or an Ann Arbor stage III-IV; no radiotherapy was used as part of the treatment. Due to the retrospective design of the study, informed consent was not required.

Statistical analysis

Data were analyzed using Statistical Packages for the Social Sciences Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). Overall survival (OS) was calculated from the date of diagnosis until the date of death or the past follow-up. Disease-free survival (DFS) was calculated from the date of diagnosis until relapse, death, or last visit. OS and DFS were calculated using the Kaplan-Meier method; the groups were compared using the log-rank test with a 95% confidence interval (CI). Categorical variables were displayed as absolute numbers and percentages. Comparisons were made with the Pearson X^2 test. Quantitative variables were analyzed with descriptive statistics, including median and ranges. A $p < 0.05$ was considered statistically significant.

Table 1. Principal characteristics of 75 pediatric lymphoma patients diagnosed in a single academic center in Northeast Mexico

Variable	All patients, n = 75 (%)	HL, n = 36 (48%) (%)	NHL, n = 39 (52%) (%)	p
Age, years median (range)	9 (2-18)	11 (3-17)	9 (2-18)	0.796
Follow-up, months, median (range)	50 (0.2-163)	62 (1-153)	38 (0.2-163)	0.361
Gender				0.465
Male	53 (70)	24 (67)	29 (74)	
Female	22 (30)	12 (33)	10 (26)	
Stage				0.003
I	12 (16)	8 (22)	4 (10)	
II	13 (17)	8 (22)	5 (13)	
III	23 (31)	8 (22)	15 (38)	
IV	21 (28)	9 (25)	12 (31)	
Missing	6 (8)	3 (8)	3 (8)	
Clinical finding				
Adenopathy	61 (81)	35 (97)	26 (67)	0.002
Mediastinal mass	12 (16)	6 (17)	6 (15)	0.880
Cough or dyspnea	8 (11)	4 (11)	4 (10)	0.905
Hepatomegaly	17 (23)	10 (28)	7 (18)	0.310
Splenomegaly	11 (15)	5 (14)	6 (15)	0.855
HSCT	14 (19)	12 (33)	2 (5)	0.004
Autologous	11 (15)	11 (31)	0	
Allogeneic	3 (4)	1 (3)	2 (5)	
Relapse	16 (21)	9 (25)	7 (18)	0.456
Progression	10 (13)	1 (3)	9 (23)	0.012
Death	11 (15)	1 (3)	10 (26)	0.005
TRM	1	0	1 (2.5)	0.333
5-year OS	85	96	75	0.004
5-year DFS	70	70	69	0.672

*DFS: disease-free survival; OS: overall survival; TRM: transplant related mortality.

Results

Data from 75 pediatric patients aged 2-18 years with histologically and immunohistochemically confirmed lymphoma from a single tertiary care hospital in Northeast Mexico over 18 years were analyzed. General demographic data, clinical stages, B symptoms, physical findings, and histopathologic diagnosis are displayed in tables 1 and 2. Of the total, 36 patients (48%) were diagnosed with HL and 39 (52%) with NHL. Male gender predominated (n = 52, 70%) with a median age at diagnosis of 9 years. Advanced stages (III and IV) were diagnosed in 47% and 69% of the patients, respectively. The median follow-up was 50 months (range: 2-163). A total of 16 (23%) patients experienced relapse, 9/36 (25%) in the HL group versus 7/39 (18%) in the NHL group, p = 0.467. Fourteen (18.7%) patients underwent transplantation, with HL patients receiving a higher proportion, 85.7% (12/14). Eleven transplants (78.6%) were autologous, all in the HL group, while 3 were allogeneic, 1 in the HL and 2 in the NHL group, respectively. Most deaths occurred in the NHL group, 10 (26%), compared to 1 (3%) in the HL group (p = 0.005). All patients with HL were treated with ABVD, while different protocols were used over time for NHL patients, as described in table 2. The 5-year OS was 96% (95% CI 95.6-97) in patients with HL and 75% (95% CI 74.9-76.3) in patients with NHL (p = 0.004), (Fig. 1), while the 5-year DFS was 70% (95% CI 69-72.5) in HL and 69% (95% CI 67.7-71) in NHL (p = 0.672), (Fig. 2).

HL

The median age at HL diagnosis was 11 years (range: 3-17). According to histopathological classification, nodular sclerosis was the most frequent subtype, with 25/36 (69%) cases reported. According to the Ann Arbor classification, the most frequent stage in the entire study group was IV, with 9 (25%) cases, and B symptoms were present in 15 (42%) patients at diagnosis. Lymphadenopathy was the main clinical sign in 35/36 (97%) patients, with a mediastinal mass observed

Table 2. Salient findings and treatment schemes administered to 75 pediatric lymphoma patients diagnosed at a single academic center in Northeast Mexico

Variable	n (%)
Hodgkin lymphoma	n = 36
Histological subtype	
Mixed cellularity	4 (11)
Nodular sclerosis	25 (69)
Lymphocyte depletion	0
Lymphocyte predominance	5 (14)
Missing	2 (6)
Treatment	
ABVD	36 (100)
Non-Hodgkin lymphoma	n = 39
Histological subtype	
Lymphoblastic lymphoma	23 (59)
Burkitt lymphoma	8 (20.5)
Anaplastic large cell lymphoma	4 (10.3)
Large cell lymphoma	2 (5)
Primary CNS lymphoma	1 (2.6)
Hydroa Vacciniforme	1 (2.6)
Treatment	
BFM	13 (33)
COG5971	10 (26)
Hyper-CVAD	7 (18)
LMB-89	6 (15)
CHOP	2 (5)
De Angelis	1 (2.5)

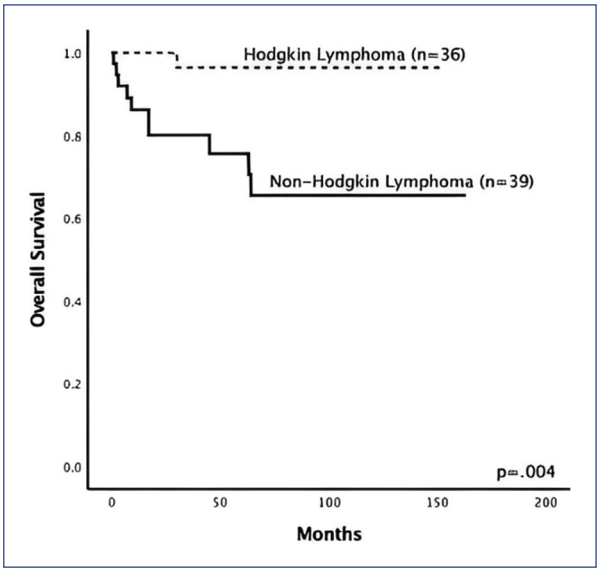

Figure 1. Overall survival for children with Hodgkin lymphoma (n = 36) and non-Hodgkin lymphoma (n = 39) treated at a reference center in Northeast Mexico from 2002 to 2020.

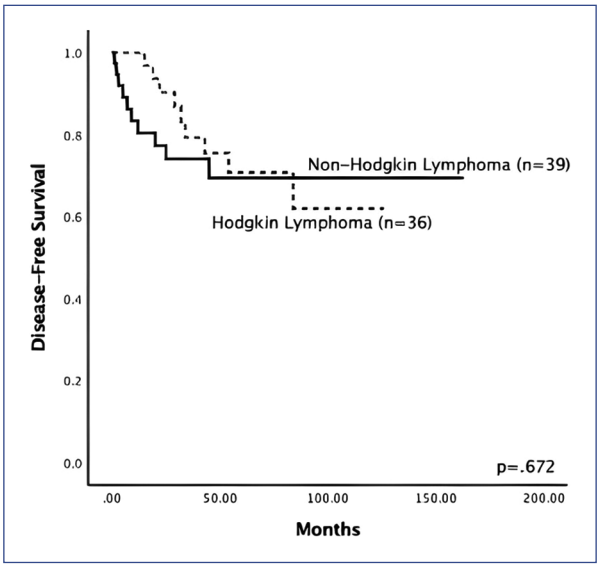

Figure 2. Disease-free survival for children with Hodgkin lymphoma (36) and non-Hodgkin lymphoma (39) treated at a reference center in Northeast Mexico from 2002 to 2020.

in 6 (17%) cases. Relapse developed in 9 (25%) patients. The median time from diagnosis to relapse was 32 months (range: 15-84), with 50% occurring in groups II and III/IV. Among relapsed patients, 4 (44.4%) experienced a second relapse. Autologous transplantation was performed in 11/36 (30.5%), and allogeneic transplantation was performed in 1 HL patient. One patient in this group died due to disease progression. He experienced a relapse 15 months after diagnosis and received additional chemotherapy. Subsequently, the patient was consolidated with an autologous transplant, experienced a second relapse 7 months later, and died 1 year post-transplant due to disease progression.

NHL

The median age for NHL at presentation was 9 years (range: 2-18). In this group, the anatomopathological diagnosis was compatible with lymphoblastic lymphoma in 23/39 cases (59%), followed by Burkitt lymphoma (BL) in 8 (21%) patients. Staging was classified according to the Murphy Staging System, with 27 patients (69%) in stage III/IV. The most frequently reported clinical manifestation was lymphadenopathy in 67% of patients. Visceromegaly was detected in 33% of patients during the initial evaluation, and 15% had a mediastinal mass. Eight patients (21%) experienced a relapse, with 50% occurring in the bone marrow, two patients in the central nervous system, and one patient in the testicle. The median time from diagnosis to relapse was 20 months

Table 3. Characteristics of 13 pediatric patients diagnosed with lymphoma and undergoing hematopoietic stem cell transplantation in a single academic center in Northeast Mexico

Patient	Age	Sex	Variety of lymphoma	DFS (months)	OS (months)	Second transplant	Status
1	15	F	HL	32	32	No	Alive
2	15	M	HL	19	91	No	Alive
3	6	M	HL	54	148	No	Alive
4	8	F	HL	22	153	No	Alive
5	13	M	HL	15	30	No	Dead
6	16	M	HL	43	73	No	Alive
7	17	M	HL	34	108	No	Alive
8	7	M	HL	90	90	No	Alive
9	14	M	HL	62	62	Yes	Alive
10	5	F	HL	79	79	No	Alive
11	10	F	HL	51	51	No	Alive
12	6	M	NHL	25	152	No	Alive
13	7	M	NHL	34	63	No	Dead

DFS: disease-free survival; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; OS: overall survival.

(range: 5-61). Two of these eight patients are currently alive following an allogeneic transplant.

In this group, 10/39 (25.6%) patients died: nine (90%) due to disease progression. Among these patients, seven were diagnosed with lymphoblastic lymphoma, one with BL, and one with refractory *hydroa vacciniforme*. One patient suffered a treatment-related death while in complete response.

Hodgkin and NHL differences

When comparing data between the two lymphoma types, no difference in median age or follow-up was found, whereas males predominated 2:1 in HL and 3:1 in NHL groups; advanced stages were more frequent in the NHL group (p = 0.003, table 1). Except for adenopathy (p = 0.002), no differences between HL and NHL for physical findings, including mediastinal mass, hepatomegaly, splenomegaly, cough, or dyspnea were found (Table 1).

Histological subtype diagnoses for both lymphomas and their treatment modalities are displayed in table 2.

Hematopoietic stem cell transplantation

Thirteen (17.3%) children received an autologous hematopoietic stem cell transplant; 11 (84.6%) were diagnosed with HL and 2 (15.4%) with NHL; one HL patient received two transplants after the first procedure resulted in graft failure and is currently alive. The median age for the transplant group was 10 years (range: 5-17), with a median DFS of 34 months (range: 15-90) and median OS of 79 months (range: 30-152). Two patients in the transplant group died, one of each lymphoma type; the longest post-transplant survival reported was 152 months (Table 3).

Discussion

HL ranks as the third, and NHL as the fourth most common childhood malignancy, with survival rates exceeding 90% in high-income countries[7]. Nevertheless, challenges persist in low-income populations, characterized by delayed diagnosis, restricted treatment access, limited therapy options, and elevated treatment-associated mortality[8]. Late-stage diagnoses remain prevalent, resulting in heightened tumor burdens and complications. Emerging therapeutic modalities, including immunotherapy and targeted treatments, are promising options but face considerable accessibility barriers in disadvantaged populations like the one in this report. The results of this study underscore the need for early diagnosis and referral, delivery of risk-adapted treatment, and targeted research endeavors to

improve outcomes for pediatric lymphoma patients, especially NHL, in high-risk groups.

Progress in the prognosis of this group of childhood cancers is principally due to the administration of intensive chemotherapy regimens, with toxicity-related deaths at 2% or lower; hence, 90% of children with HL and NHL are cured with first-line therapy[9,10]. Our HL pediatric group reached this standard, while those with NHL lagged considerably. In this respect, the administration of intensified chemotherapy schemes requires hospitalization, specialized nurse personnel, and advanced nutrition support, which is lacking in most public institutions of low-income populations, like ours.

In comparison with industrialized nations, the landscape in resource-limited areas of the world is less optimistic due to delayed diagnosis, lack of access to appropriate treatment and support, high rates of treatment-related mortality at 9%, treatment abandonment of 15%, and relapse associated with less intensive chemotherapy[8]. We documented only one patient with treatment-related mortality in complete response, accounting for 2.5% of the NHL group, while none occurred in the HL group.

Different authors describe diagnostic delay as contributing to all-cause treatment failure[11]. Lack of resources in the health system in our country may prevent the opportune detection and treatment of hematologic diseases; also, socioeconomic limitations in the general population can lead to delayed diagnosis and treatment, and be major contributors to childhood cancer death rates, including lymphoma[12]. Patients with a late diagnosis have a higher tumor burden and a higher risk for malnutrition, tumor lysis syndrome, comorbid infections, and early treatment-related death, with the associated higher costs of treatment for the main disease and its complications[13]. Diagnosis in advanced stages is the most frequent presentation in low to middle-income countries in > 70% of the cases, as observed in multiple studies[11-14]. This finding is related to greater difficulty in effective treatment due to more tumor burden, worse clinical condition at presentation, and more complications, such as tumor lysis syndrome, organic dysfunction, and infections[15].

In our cohort, almost 60% of patients were diagnosed with advanced stages at presentation, and stages III and IV were reported in around 70% of patients in the NHL group. Within this group, visceromegaly was present in a third of cases and a mediastinal mass in 15%. In contrast, advanced-stage HL was found in 47% of patients at diagnosis, and the main clinical manifestations were lymphadenopathy in 97% and B symptoms in 42%.

It is reported that 33% of childhood NHLs correspond to lymphoblastic lymphomas (LL), 40% BL, 20-30% diffuse large B-cell lymphoma (DLBCL), and 10-20% anaplastic large cell lymphoma[16,17]. The distribution of the different varieties in our patients differed considerably, with a predominance of LL of 59%, almost twice that reported; the second most frequent entity was BL, with 21%, considerably < 37% in Brazil[16]. Furthermore, it has been described that the most common type of HL in children under 10 years of age in developing countries is mixed cellularity, often associated with Epstein-Barr virus infection; remarkably, in our study group, the most frequent subtype was nodular sclerosis, being 69%, close to 76% reported in Brazil[18].

Our overall results for the NHL are inferior to the reported outcomes in high-income countries. However, compared to other low-to-middle-income countries, our results are equal or superior; in those populations, cure rates are below 50% for NHL and around 90% for HL[11,15]. In one study, the same treatment regimen for NHL was used in 6 different countries of Central America, reporting challenges like those mentioned previously. With a cohort of 405 patients, the 3-year OS was 70%, while in our group, it was 80%, and DFS was comparable at 66% versus 68%, using treatment protocols without dose reductions[14]. In a single-center study from Northern Brazil, results, such as ours were reported, with 5-year OS and DFS rates of 70% and 68%, respectively[17]. Interestingly, our single-center report included 39 children, compared with 76 contributed from Guatemala and 70 from Nicaragua in the Association of Pediatric Hematology Oncology of Central America (AHOPCA) report[14].

In a previous study, the AHOPCA group implemented a uniform protocol for the treatment of HL in four of its member institutions from January 1999 to December 2004. A total of 216 newly diagnosed HL patients were included, staged according to the Ann Arbor classification, and divided into favorable (stages I, IIA, and IIIA) and unfavorable (stages IIB, IIIB, and IV) groups. Subjects in the favorable group received six cycles of 28-day chemotherapy (COPP/COPP ABV), while subjects in the unfavorable cohort received eight cycles of 28-day chemotherapy with COPP/ABV. Event-free survival (EFS) at 5 and 10 years was 71% and 68%, comparable to 70% in our cohort[19]. A recent report from Greece included 93 children with HL over 25 years; the most common subtype was nodular sclerosis in 50.5%, while in our patients it accounted for 69%; B symptoms were present in 16.1% versus 42% in our patients, corresponding to more advanced states at presentation.

The OS and EFS were 95.7% and 83.9%, in comparison to 96% and 75% in our study, with our lower EFS explained by a relapse rate of 25%, compared to 7.5% in that study[20].

It is estimated that 90% of pediatric lymphomas worldwide occur in low-to-middle-income countries; hence, even modest improvements in EFS and OS could significantly reduce the burden of pediatric NHL[21].

Although new first-line treatments offer promising results, these options represent a challenge for low-middle-income countries due to the lack of access and high cost.

In this respect, rituximab was not part of the routine treatment regimen during the study period in our center; this biological agent is currently incorporated for treating Burkitt and DLBCL s in this age group.

It is important to note that there is an ongoing international collaboration to improve lymphoma outcomes, like the one fostered by the Pediatric Cancer Data Commons for developing the HL data collaboration (NODAL) to advance pediatric HL research[22].

Earlier diagnosis, referral to specialized centers, contemporary therapeutic approaches including biological agents, and incorporation of radiotherapy to the treatment protocols, as well as advanced imaging follow-up methods, are required in disadvantaged populations to close the gap with developed nations.

Survivors of pediatric lymphoma are at risk for second primary malignancies, with 40-year cumulative incidence rates up to 22.2% for HL and 12.6% for NHL in a recent report[23]; thus, long-term follow-up of these patients is critical to assure the best quality of life.

Conclusion

Comparable frequencies for HL and NHL were documented in our cohort of open-population pediatric-age patients in Northeast Mexico; survival rates for HL were similar to those in high-income countries, while for NHL lagged considerably.

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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 study does not involve patient personal data nor requires ethical approval. The Sex and Gender Equity in Research guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that artificial intelligence was used in the writing of this manuscript (SCISPACE, in introduction, data search in discussion).

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RESEARCH ARTICLE

Effectiveness and safety of topical sirolimus in children with angiofibromas and tuberous sclerosis complex

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Abstract

Background: *Tuberous sclerosis complex (TSC) is an autosomal dominant disease that can affect any organ with hamartomas. It is characterized by early-onset seizures and is associated with intellectual disability. The main dermatological findings include hypopigmented macules, shagreen patches, and angiofibromas, which appear in 81-96% of patients.* **Method:** *We conducted a quasi-experimental, before-and-after, open-label study in 10 patients with TSC and facial angiofibromas, aged 8-17 years, who were treated at the dermatology service of the Instituto Nacional de Pediatría in 2019 and 2020. All patients agreed to participate in the study and signed both consent and assent forms. All patients received treatment with 1% topical sirolimus for 6 months on the right side of the face, followed by 6 months on the left side of the face to assess recurrence. Each patient served as their own control. Measurements of baseline lesions were taken and followed monthly for 6 months. The changes in lesion size, measured in millimeters at each time point, were compared using repeated measures analysis of variance.* **Results:** *All children showed a decrease in the size and number of angiofibromas, as well as reduced erythema, from the 3rd month of treatment. Few recurrences were observed beginning at 4 months after discontinuation of the medication.* **Conclusion:** *Topical sirolimus is effective and safe for treating patients with angiofibromas and TSC.*

Keywords: *Tuberous sclerosis. Angiofibromas. Sirolimus. Children.*

Efectividad y seguridad del sirolimus tópico en niños con angiofibromas y complejo de esclerosis tuberosa

Resumen

Introducción: *El complejo esclerosis tuberosa (CET) es una enfermedad autosómica dominante y puede dañar cualquier órgano con hamartomas. Se caracteriza por inicio temprano de crisis convulsivas y se asocia con discapacidad intelectual. Los principales hallazgos dermatológicos incluyen las manchas hipopigmentadas lanceoladas, placas de Shagreen, y los angiofibromas, que aparecen del 81 al 96% de los pacientes.* **Método:** *Realizamos un estudio cuasi experimental, de antes y después, de etiqueta abierta, en 10 pacientes con CET y angiofibromas, en cara, de 8-17 años, que fueron atendidos en el servicio de Dermatología del Instituto Nacional de Pediatría, durante 2019 y 2020. Los pacientes aceptaron participar en el estudio y firmaron carta de consentimiento y asentimiento informado. Todos ellos recibieron tratamiento con sirolimus tópico al 1%, 6 meses en el lado derecho de la cara, y 6 meses en el lado izquierdo de la cara; para valorar recidivas, se tomó*

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como control al mismo paciente. Se realizaron mediciones de las lesiones basales y cada mes durante 6 meses. El cambio en el tamaño de las lesiones (en mm) en cada medición, se comparó mediante ANOVA de mediciones repetidas. **Resultados:** *Todos los pacientes presentaron disminución del tamaño, número de angiofibromas y eritema a partir del tercer mes de tratamiento, y se presentaron pocas recidivas a partir del cuarto mes de suspender el medicamento.* **Conclusiones:** *El sirolimus tópico es eficaz y seguro para tratar a los pacientes con angiofibromas y CET.*

Palabras clave: *Esclerosis tuberosa. Angiofibromas. Sirolimus. Niños.*

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant systemic disease that can affect any human organ with lesions known as hamartomas. It is caused by pathogenic variants in the tumor suppressor genes TSC1 and TSC2, which encode hamartin and tuberin, respectively. These genes are located on chromosomes 9q34 and 16p13.3, respectively. The hamartin-tuberin complex downregulates mTORC1[1].

The presence of angiofibromas in tuberous sclerosis can have significant repercussions for patients, with both physical and psychological implications. Angiofibromas are commonly found in school-aged patients with TSC. Although they rarely pose a life-threatening risk, they often become a source of stigma for these patients, affecting their self-esteem, social interaction, and consequently, their quality of life. Due to their potential to become disfiguring, various therapeutic options have been considered, including radiosurgery, cryosurgery, electrofulguration, CO_2 laser, and chemical peels, most of which are painful. Angiofibromas present as multiple erythematous or skin-colored papules in centrofacial areas, primarily on the nose and surrounding regions[1].

The accidental observation of facial angiofibroma regression in a patient with TSC who received oral sirolimus after a renal transplant has led to the development and increasing use of this drug through topical application. Sirolimus is a macrolide consisting of a ring with lactonic and lactam-like groups derived from the fermentation products of *Streptomyces hygroscopicus*. The disappearance of angiofibromas has been observed with its use[2].

The concentrations of topical sirolimus, the vehicle used, and the dosage vary among different studies. The use of topical sirolimus has been reported in active ingredient concentrations ranging from 0.003% to 1%, with the most common concentrations being 0.1% and 0.2%[3,4].

At the *Instituto Nacional de Pediatría*, 105 patients were registered from 2005 to 2017, all of whom were evaluated in the dermatology service outpatient clinic.

There is no consensus on management, with most treatments being painful, and multiple sessions are often required to achieve satisfactory results. Topical sirolimus represents a therapeutic option to achieve a sustained response in preventing the appearance of new angiofibromas.

The objective of this study was to analyze the effectiveness and safety of topical sirolimus in the treatment of children with angiofibromas and TSC. The study was approved by the Institutional Project Review Committees of the *Instituto Nacional de Pediatría* in Mexico City, with registration number 2019/003.

Method

After obtaining approval from the Research Ethics Committee, Biosafety Committee, and Research Committee of the *Instituto Nacional de Pediatría*, parents of the patients completed the informed consent form, and children provided assent letters (for children aged 6-18 years). Ten patients diagnosed with TSC were recruited. Patients with potential pregnancy, autoimmune conditions, or those taking oral sirolimus were excluded.

A quasi-experimental, open-label before-and-after study was conducted. The study included patients with angiofibromas and TSC treated at the dermatology service of the *Instituto Nacional de Pediatría* from 2019 to 2020, aged 8-17 years, who agreed to participate and signed both informed consent and assent letters.

Patients who met the selection criteria underwent baseline photography, lesion counting, documentation of lesion locations, and measurement of the largest lesions' diameters. Subsequently, they received the compounded sirolimus preparation with instructions to apply it once daily on the right side of the face for 6 months, followed by discontinuation on that side and initiation on the left side for another 6 months. Patients attended monthly follow-up appointments for photography and evaluation of lesion number and size. In addition, lesion resolution and sirolimus-related adverse events were assessed. After the initial 6-month treatment period, lesion recurrence was also evaluated.

Sirolimus solution (1 mg/1 mL) and CeraVe moisturizing lotion were used. The 1% sirolimus compounded

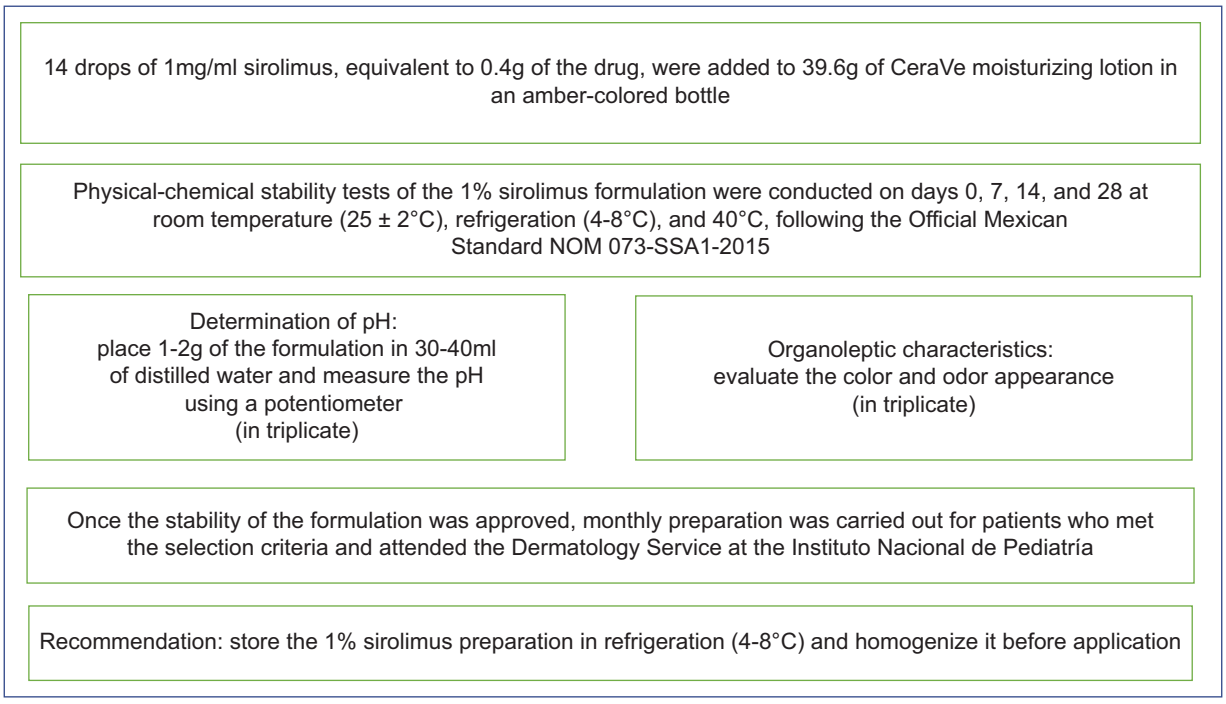

Figure 1. Preparation of the 1% sirolimus formulation.

formulation was prepared by incorporating 0.1 g of sirolimus into 19.9 g of CeraVe moisturizing lotion, which was then provided to patients. They transported it under refrigeration, and follow-up appointments were scheduled monthly. Details of the sirolimus preparation are recorded in figure 1.

Data analysis

The changes in the number and size of angiofibromas over the 6-month treatment period were analyzed using repeated measures analysis of variance, as were the recurrences after treatment discontinuation.

Results

Ten patients were included, with a median age of 15.5 years (range: 8-17 years). Six patients (60%) were male. All patients had numerous lesions of varying sizes. Table 1 shows the evolution of the lesions, demonstrating a decrease in both number and size from the 3rd month onward. Regarding recurrences, evaluation of the right side of the face 6 months after treatment discontinuation revealed new lesions appearing from the 4th-month post-treatment.

There was a positive correlation between age and the number of lesions, with older patients having more lesions ($r = 0.466$, $p = 0.038$). A positive correlation was also found between average lesion size and number of lesions, with larger lesions associated with greater lesion numbers ($r = 0.401$, $p = 0.08$). Conversely, a negative correlation was found regarding the percentage of resolved lesions, with older patients showing a lower percentage of resolved lesions ($r = -0.501$, $p = 0.024$).

The percentage of resolved lesions showed negative correlations with both the number of lesions ($r = -0.857$, $p < 0.001$) and lesion size ($r = -0.67$, $p = 0.001$). These findings suggest that early treatment initiation may be beneficial.

Regarding safety, two patients experienced local irritation during sun exposure, which resolved with sunscreen application, and treatment discontinuation was not required.

Discussion

TSC is a genetic, autosomal dominant disorder characterized by the formation of benign tumors in multiple systemic organs[4]. Facial angiofibromas are present as red or pink centrofacial papules, particularly in the nasofacial fold, cheeks, and chin. They develop in early childhood (6-8 years) and are present in over 80% of individuals with TSC (Figs. 2-5). These tumors, which contain vascular and connective tissue elements,

Table 1. Evolution of facial angiofibromas

Evaluated features	n	Month of treatment						p*
		1	2	3	4	5	6	
Number of lesions	20	113	113	94	74	47	53	< 0.001
Average size (mm)	20	39	39	34	30	24	20	< 0.001
Disappeared lesions	20	0	0	18	37	48	59	< 0.001
Recurrences Average number of lesions	10	0	0	0	0.3	2.7	6.5	< 0.001

*Repeated measures analysis of variance. Within-subjects effects.

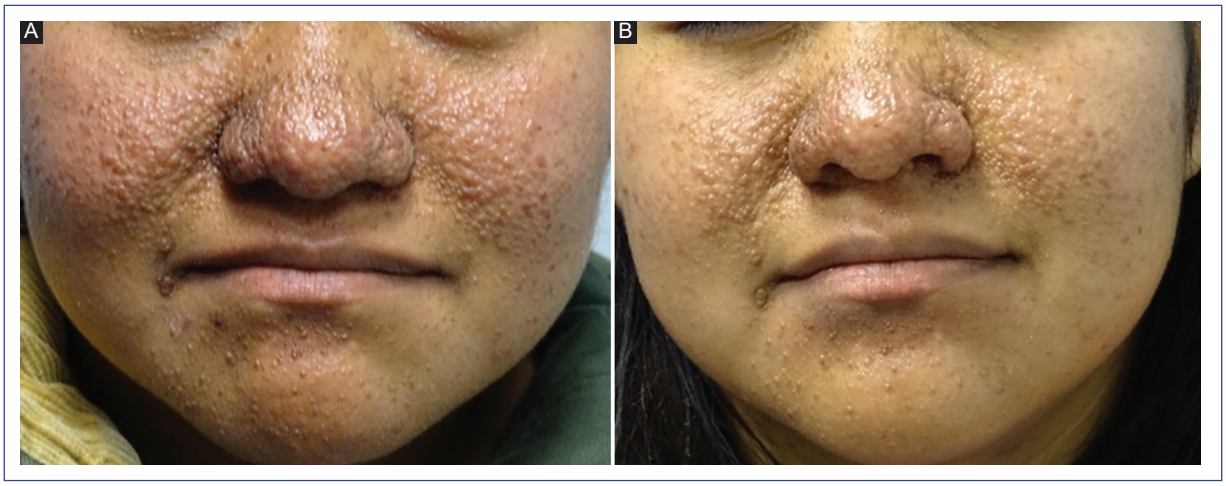

Figure 2. A and **B:** a 15-year-old adolescent with tuberous sclerosis and angiofibromas shows decreased lesion size and disappearance of small angiofibromas after 12 months of treatment with 1% sirolimus lotion. Note the absence of erythema.

constitute major criteria for TSC and commonly affect school-age children and adolescents, significantly impacting their self-esteem[4].

An ideal treatment for TSC has not yet been established; however, various procedures such as radiosurgery, cryosurgery, electrofulguration, CO_2 laser, and chemical peels are available. These treatments are often painful, invasive, and expensive[1,4].

The literature reports promising outcomes with topical sirolimus, which has been compounded at concentrations ranging from 0.001% to 1%. However, traditional preparation processes involve crushing and sieving sirolimus tablets and incorporating them into a vehicle (such as cold cream, polyvinylidene fluoride [PVDF] in ointment, gel, or petroleum jelly), resulting in poor cosmetic outcomes. Direct application of sirolimus solution (1 mg/mL) on angiofibromas resulted in intense irritation, necessitating a reduction in application frequency from twice daily to once daily. However, a compounded formula with sirolimus solution (1 mg/mL) mixed with emollients has been reported to be better tolerated by patients in previous studies[4,5].

Consequently, we used sirolimus oral solution (1 mg/mL) mixed with a moisturizing lotion, which significantly improved the organoleptic properties and cost of the formula. This formulation was prepared by the pharmacology department, and physicochemical stability tests were conducted on the 1% sirolimus formulation. The preparation requires refrigerated storage and has an optimal duration of 1 month.

In general, our patients showed improvement starting from the 3rd month of using 1% sirolimus in CeraVe moisturizing lotion, and this improvement persisted throughout both the initial 6-month application on the right cheek and the subsequent 6-month application on the left cheek. However, patients with large angiofibromas exhibited only

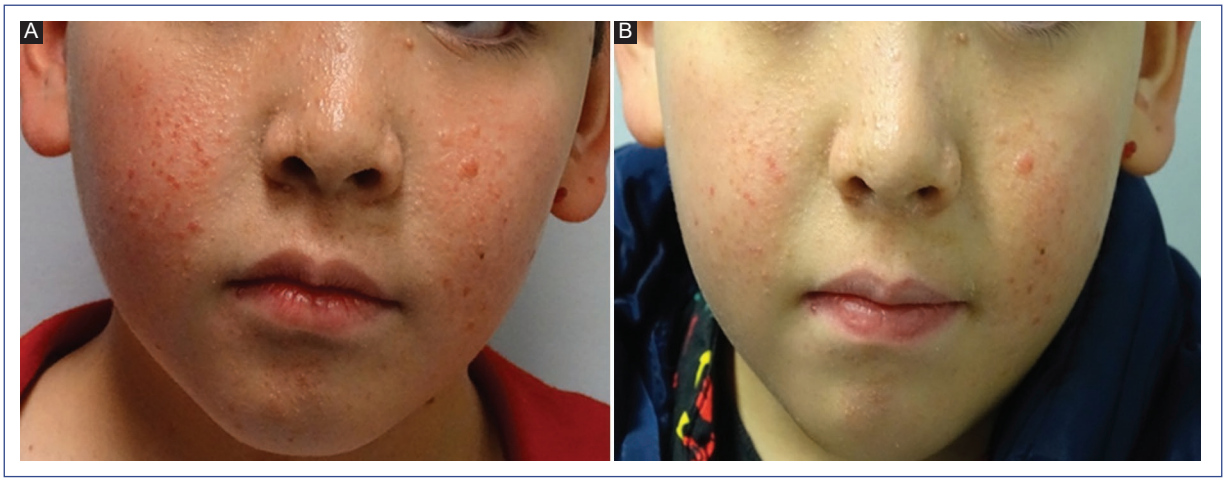

Figure 3. A and **B:** an 11-year-old boy with tuberous sclerosis and angiofibromas shows results after 1 year of treatment with topical sirolimus.

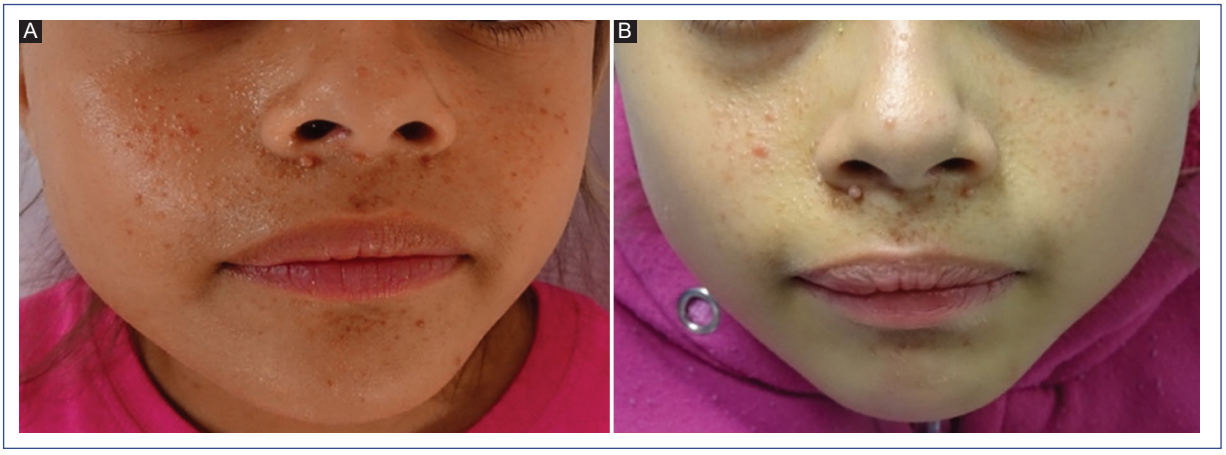

Figure 4. A and **B:** a 13-year-old girl with tuberous sclerosis and angiofibromas after 1 year of treatment with 1% sirolimus lotion.

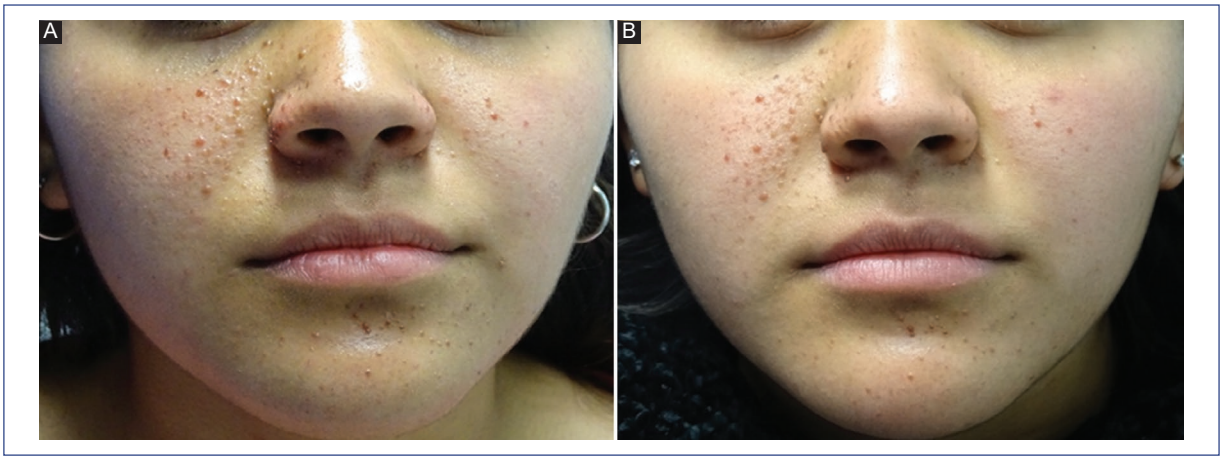

Figure 5. A and **B:** a 16-year-old adolescent, after 1 year of treatment with 1% sirolimus lotion. A decreased lesion size and disappearance of multiple angiofibromas can be observed.

a moderate response (40-80%). In addition, we found that children with smaller and fewer lesions showed a good response (80%) (Figs. 2-5). Therefore, while the efficacy and tolerability of 1% sirolimus in CeraVe moisturizing lotion have been demonstrated for small angiofibromas, this was not the case for larger lesions. This aligns with Foster's findings[5], which indicated a decrease in size and disappearance of smaller lesions but no significant change in larger lesions.

Multiple reports have demonstrated a good safety profile, with only six cases of local irritation reported: four related to the direct application of sirolimus oral solution (1 mg/mL) and two associated with the PVDF vehicle. In our study, we observed two patients with local irritation that resolved with sunscreen application. In studies monitoring systemic effects, no adverse effects have been reported, and sirolimus plasma levels have remained below detection limits, well below both therapeutic values and the toxicity range[2,5].

We consider 1% topical sirolimus to be a good treatment option for facial angiofibromas in children. While the ideal formulation has not been established, we found that 1% sirolimus in CeraVe lotion is highly effective in children, causing neither discomfort nor pain. Early initiation of treatment helps improve patients' self-esteem. However, in adolescents, ablative treatments with shaving and electrodesiccation can be used, followed by the application of 1% or 2% sirolimus. Long-term studies are needed to establish which treatment is most effective and have the lowest recurrence rate.

In our patients, the recurrence time after treatment cessation was 4 months. This information may guide treatment scheduling, allowing for planned treatment interruptions and resumption after this period.

It is important to emphasize that formulations, regardless of type, should be prepared by trained personnel under appropriate pharmacological laboratory conditions. Home preparation without proper controls should not be encouraged.

Conclusion

Topical sirolimus is an effective and safe treatment for facial angiofibromas in children with TSC, showing significant improvement, particularly in smaller lesions. The treatment has a good safety profile, with minimal side effects, mainly local irritation. While larger lesions showed a more moderate response, early treatment improved patients' self-esteem. Recurrence of lesions occurred about four months after discontinuation, suggesting the need for periodic treatment cycles. Further studies are needed to optimize dosage and treatment duration.

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Conflicts of interest

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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 study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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

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RESEARCH ARTICLE

Pediatric eosinophilic esophagitis: survey of gastroenterologists from Latin America and Spain

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Members of the Young LASPGHAN working group of the Latin American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (LASPGHAN).

Abstract

Background: *Eosinophilic esophagitis (EoE) is an immuno-allergic disease characterized by esophageal dysfunction and eosinophilic infiltration of the esophagus. Its prevalence has increased, making it the leading cause of dysphagia and food impaction in children and adolescents. Understanding the approach taken by pediatric gastroenterologists in different regions is crucial.* **Method:** *Multicenter and cross-sectional observational study, carried out through a virtual questionnaire during 2022, answered voluntarily and anonymously. Percentage descriptive statistics were performed.* **Results:** *118 responses were obtained. Approximately 3% of physicians diagnose up to two cases of eosinophilic esophagitis per year. About 55.9% performed 3-4 biopsies in the upper and lower thirds of the esophagus for diagnosis. Initial treatments in patients without stenosis: proton pump inhibitors (PPI) 33.9%, triple therapy (TT) (PPI + diet + topical corticosteroids [TCSs]) 26.27%, and combined (diet + PPI) 21%. Patients with stenosis: TT 52.58%, combined (TCSs + PPI) 13.4%. Initial dietary treatment: according to allergy tests 26.2%, empirical exclusion of 6-8 foods 25.4%, and 2-4 foods 23.7%. The first endoscopic control is performed at 8 and 12 weeks in 46.6% and 38%, respectively. 52% referred to an allergist and 47.4% to nutrition. About 48.3% do not monitor basal cortisol in corticosteroid treatment for more than 3 months.* **Conclusion:** *The diagnostic and therapeutic approach in EoE is heterogeneous. Dietary treatment shows the exclusion of a large number of foods and monitoring the prolonged use of corticosteroids is not a common practice.*

Keywords: *Eosinophilic esophagitis. Eosinophilia. Dysphagia in pediatrics. Esophageal dysfunction. Food impaction.*

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Esofagitis eosinofílica pediátrica: encuesta a gastroenterólogos de Latinoamérica y España

Resumen

Introducción: *La esofagitis eosinofílica (EEo) es una enfermedad inmuno-alérgica, con disfunción esofágica e infiltración eosinofílica del esófago. Su prevalencia ha aumentado, siendo la principal causa de disfagia e impactación alimentaria en niños y adolescentes. Resulta crucial conocer el abordaje por gastroenterólogos pediátricos en diferentes regiones.* **Método:** *Estudio observacional multicéntrico y transversal, mediante cuestionario virtual en 2022, respondido en forma voluntaria y anónima a gastroenterólogos pediatras de Latinoamérica y España. Se realizó estadística descriptiva porcentual.* **Resultados:** *Se obtuvieron 118 respuestas. El 53% diagnostica hasta dos pacientes por año, mientras que el. 55,9% realiza 3-4 biopsias en los tercios superior e inferior esofágico para diagnóstico. Tratamientos de inicio más utilizados en pacientes sin estenosis: Inhibidor de Bomba de Protones (IBP) 33,9%, triple terapia (IBP + dieta + corticoides tópicos) 26,27% y combinado (dieta + IBP) 21%. Pacientes con estenosis: triple terapia 52,58%, combinado (corticoides tópicos + IBP) 13,4%. En mantenimiento de pacientes sin estenosis: IBP + dieta 32,2%. Pacientes con estenosis: triple terapia 32,2%. Tratamiento dietético de inicio: según test de alergia 26,2%, empírico con exclusión de 6-8 alimentos 25,4% y 2-4 alimentos 23,7%. El primer control endoscópico se realiza a las 8 y 12 semanas en 46,6% y 38%, respectivamente; el 52% deriva a Alergista y el 47,4% a Nutrición. Además, el 48,3% no controla cortisol basal en tratamiento corticoideo prolongado.* **Conclusión:** *El abordaje en la EEo es heterogéneo. El tratamiento dietético muestra la exclusión de muchos alimentos y el monitoreo del uso prolongado de corticoides no es una práctica habitual.*

Palabras clave: *Esofagitis eosinofílica. Eosinofilia. Disfagia en pediatría. Disfunción esofágica. Impactación alimentaria.*

Introduction

Eosinophilic esophagitis (EoE) is an immuno-allergic disease with symptoms of esophageal dysfunction characterized by eosinophilic infiltration in the esophagus. Its prevalence has increased in recent years, now being the main cause of dysphagia and food impaction in children and adolescents[1]. Recent studies estimate a prevalence of 25/10,000 individuals in the United States and Europe[2]. Despite the existence of diagnostic and therapeutic guidelines, its management remains heterogeneous. The symptomatology is non-specific, varying according to age. In young children, it manifests as feeding difficulties, while in older children, dysphagia, retrosternal pain, and food impaction are the main symptoms. At present, a clinical-histological evaluation is necessary to confirm the diagnosis. There is a greater prevalence in males, with the ratio in both children and adults being approximately 3:1. The main objectives of treatment are the resolution of clinical symptoms, maintenance of histological remission, and prevention of long-term complications. Effective treatment has been shown to reverse subepithelial fibrosis and, therefore, can prevent complications such as remodeling and stenosis[3].

This work aims to understand the current diagnostic and therapeutic approach to pediatric EoE by healthcare professionals. For this purpose, the young researchers group of the Latin American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (LASPGHAN) conducted a survey directed at pediatric gastroenterologists from Latin America and Spain. Through this survey, the intent is to identify experience and adherence to international guidelines during daily practice.

Method

This is a descriptive, observational, and multicenter study in which pediatric gastroenterologists, both members and non-members of LASPGHAN from Latin America and Spain were invited to respond to an online survey between October and November 2022 that evaluates the management of patients with EoE in terms of diagnosis, treatment, and follow-up. Their responses were to be based on their experience in daily practice.

Participants were invited through an email link to access a Google Forms online questionnaire, available in Spanish and Portuguese, with single-choice questions, multiple-choice questions, and others with free text options. The survey was self-administered and anonymous.

Statistical analysis

The collected data were analyzed using descriptive statistics with Microsoft Excel and Google Forms. In this study, the STROBE-Checklist, specifically designed for cross-sectional studies, was applied.

Ethical considerations

This work complies with current bioethical research regulations. As this was a survey conducted among healthcare professionals without identifying them, it did not require review by the Ethics Committee.

The approach of this work does not involve the manipulation of sensitive data that could compromise the privacy or integrity of individuals.

Within the framework of this research, it is clarified that obtaining informed consent from participants was not necessary, given that the methodology used consisted of a voluntary self-administered survey. Participation in the survey was completely optional, and individuals freely decided to provide their responses without external pressure.

The nature of the self-administered survey ensures that participants have full control over the information they share, and no data are collected that would directly or indirectly identify the respondents or the patients they reference. The questionnaire has been designed so that the privacy and confidentiality of participants are protected at all times.

Likewise, it is guaranteed that the data collected is handled anonymously and in aggregate during analysis, preserving the confidentiality of participants, respecting the ethical principles of research, and aligning with relevant regulations regarding privacy and confidentiality.

Results

A total of 118 pediatric gastroenterologists responded to the survey, with the countries having the greatest participation being Argentina (20%), Brazil (20%), Mexico (13%), Venezuela (11%), Colombia (11%), and Spain (8%) (Fig. 1).

About 28.8% of respondents had more than 20 years in the specialty and 33% had < 5 years. Professionals with 6-10 years and 11-19 years of work in pediatric gastroenterology correspond to 23.7% and 14%, respectively.

More than half of the respondents work in both public and private settings (61% and 60%, respectively). About 40% also work in private practice, and 31% belong to teaching or university hospitals.

About 53% diagnose up to two patients/year with EoE. 31.3% diagnose 3-5 patients. Only 6.7% diagnose 6-10 and 8.5% diagnose more than 10 patients/year.

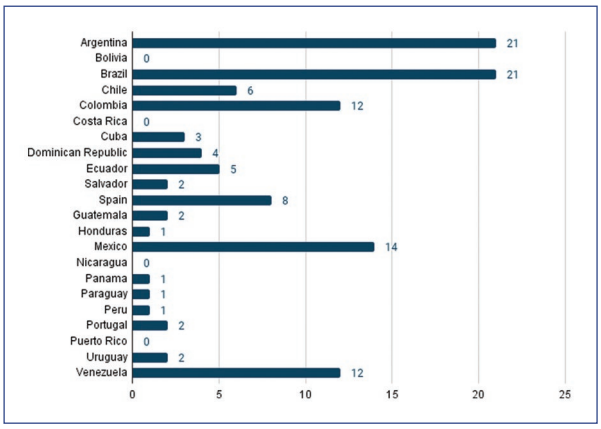

Figure 1. Distribution of participants by country (n). Number of professionals who participated in the survey, distributed by country of origin.

Diagnostic, therapeutic, and evolutionary management of patients with EoE

Diagnostic methodology and endoscopic findings

Respondents were asked about how many biopsies and from which portions of the esophagus they perform when EoE is suspected; 55.9% perform 3-4 biopsies in each of the upper and lower segments of the esophagus and 17% take 1-2 biopsies in each of these locations (Fig. 2A). 15.2% of respondents perform 3-4 biopsies randomly and a percentage < 1% (0.85%) perform them in a targeted manner to lesions or abnormalities found in the esophageal mucosa (Fig. 2B). About 8.4% of the participating professionals do not perform endoscopy in their daily practice and therefore refer their patients for this procedure.

The most frequently observed endoscopic findings are longitudinal furrows (67%) and exudates (64%), followed by concentric rings (34%), normal mucosa (32%), and friability/crepe paper mucosa (22%). Esophageal stenosis was reported in 7.6% (Fig. 3).

The endoscopic reference score for EoE (EREFS) score is a scoring system used to evaluate the severity of EoE based on the presence and severity of five endoscopic characteristics of EoE: edema, concentric rings, exudates, furrows, and stenosis[1]. About 36.4% of specialists use it during the diagnostic procedure, 34.7% report not using it, and 18.6% are unaware of its existence. The phenotypic characteristics of the disease, based on endoscopic and histopathological findings, are useful for the therapeutic approach. The most frequently observed disease phenotype in this survey is the inflammatory type (79.6%).

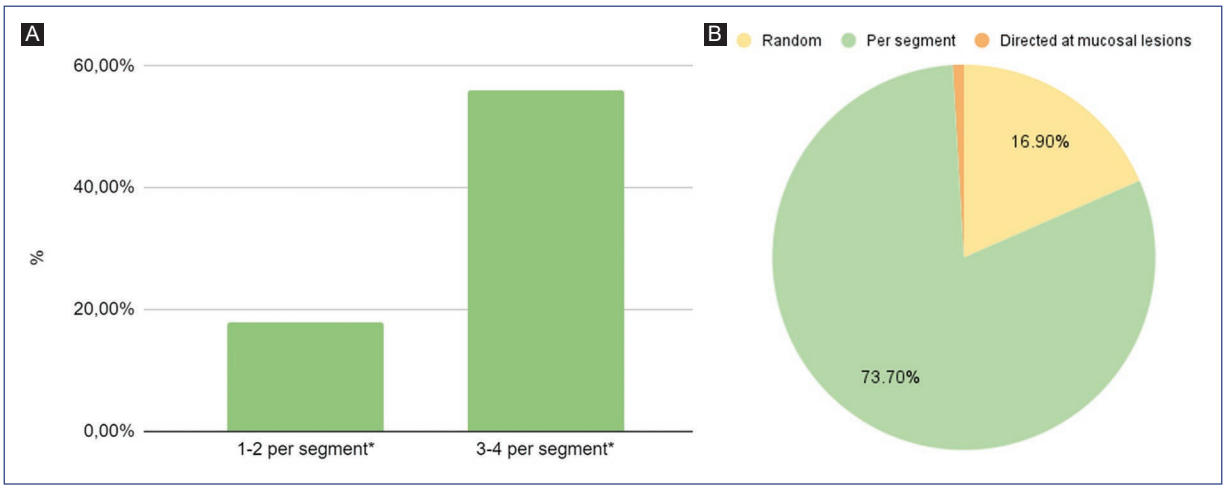

Figure 2. A: number of biopsies performed per esophageal segment for diagnosis of eosinophilic esophagitis. **B:** approaches to esophageal biopsy sampling for the diagnosis of eosinophilic esophagitis.
*Upper and lower segments of the esophagus.

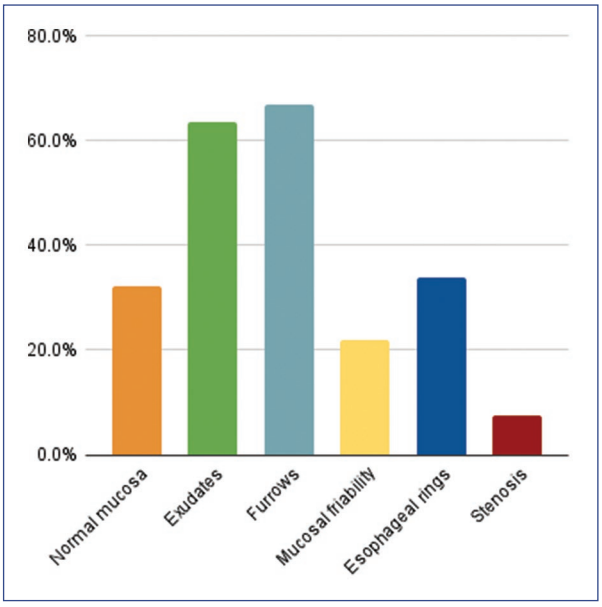

Figure 3. Endoscopic findings of the esophageal mucosa in diagnostic endoscopy.

Therapeutic management

The survey inquired about the most commonly used therapeutic strategies at disease diagnosis or during acute flares, and in the maintenance phase, both in patients with inflammatory and stenosing involvement.

The most used first-line treatments in patients with inflammatory involvement are: proton pump inhibitor (PPIs) (33.9%), followed by triple therapy (TT) (PPI + exclusion diet [ED] + topical corticosteroid [TCS]) (26.2%) and combination therapy (ED + PPI) (21%) (Fig. 4). On the other hand, the approach for those with stenosing involvement is: TT (52.5%), combination treatment (TCS + PPI) (13.4%), and topical glucocorticoids (12.37%). 9% use oral corticosteroids and 3% use intravenous steroids.

For maintenance treatment of patients with inflammatory phenotype, the most commonly used strategies are PPI associated with ED (32.2%), PPI (19.4%), TCS (12.7%), and ED (10%) (Fig. 4). In patients with esophageal stenosis: TT (32.2%), followed to a lesser extent by TCS in association with PPI, oral corticosteroids associated with PPI or diet, and TCS (16% each).

Of the available TCS, 51% of professionals report using budesonide in home preparation, 38.9% use Fluticasone aerosol (swallowed), 16% use commercial budesonide preparation, and 2.5% use oral dispersible budesonide.

Regarding ED, 26% of respondents indicate a diet directed by allergy testing; 25.4% empirically exclude 6-8 foods, 23.7% exclude 2-4 foods, and 10% exclude only 1 food. The remaining 14.4% adapt the ED according to the patient's clinical history.

Extensively hydrolyzed formulas or elemental formulas as first-line treatment in children under 12 months are used by 52.5% of professionals and in children under 24 months by 23.7%. 21% of gastroenterologists use them in patients with multiple food allergies, 15% in children with severe nutritional compromise at any age, and 6.7% in cases of stenosing phenotype. About 3% of professionals do not have access to this resource and 5.9% report not using them.

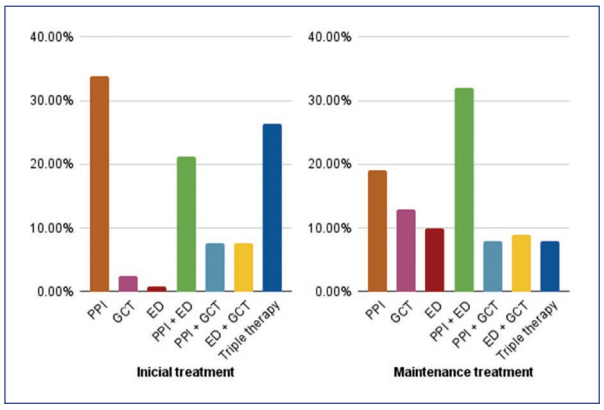

Figure 4. Treatment in non-stricturing eosinophilic esophagitis. Therapeutic approach at the beginning (left) and maintenance (right). DE: elimination diet; GCT: topical steroids; PPI: proton pump inhibitor; Triple therapy: PPI + GCT + ED

At the time of the survey, 3.3% of respondents have patients with EoE under treatment with biological agents.

Follow-up of patients with EoE

Post-treatment endoscopic evaluation

The majority of respondents (84.6%) perform the first upper gastrointestinal endoscopy (UGE) follow-up between 8 and 12 weeks after initiating treatment (46.6% and 38%, respectively). 9% of professionals wait more than 12 weeks to request it, and 3.4% do not perform the first endoscopic follow-up if the patient is asymptomatic after establishing treatment.

Regarding the endoscopic schedule for the follow-up of asymptomatic patients with EoE, 35.5% perform control UGE every 6-12 months and 32.2% every 12-24 months; 26.2% of professionals report indicating control endoscopy only if the patient presents symptoms during their evolution, and approximately 5% perform it only in case of therapeutic modifications

Since the stenotic phenotype is not predominant in pediatrics, esophageal dilation is not a routine procedure performed by all pediatric endoscopists. In our survey, only 27.2% of professionals have experience with this therapeutic approach.

Multidisciplinary approach

It was recorded that 52% always request an evaluation of these patients by a pediatric allergist. 27.2% make this referral only if the patient has an allergic history, 12.7% only if they prescribe an ED, and 14% of professionals do not refer their patients to be evaluated by this specialty.

About 47.4% of professionals report always referring their patients with EoE to a pediatric nutritionist. 28.8% only in case of nutritional compromise, 17.5% in case of prescribing targeted diet therapy, 8.2% when prescribing a 4-food ED, and 5% if it is a 6-food ED. 11.3% of respondents do not request an evaluation of the patient by a pediatric nutritionist.

Respondents were asked if they consulted with pediatric endocrinology for patients on corticosteroid treatment. About 16.9% responded that they always make the referral. 60.7% do so only when adverse effects of corticosteroids occur, and 22.8% never indicate evaluation by this specialty.

Prolonged use of corticosteroids

EoE is a pathology that may require the use of steroids for a prolonged period (< 3 months) in many patients.

The most observed adverse effect from the use of TCSs was oropharyngeal candidiasis (38.8%). About 22.8% report having had patients with esophageal candidiasis, 6.7% growth delay, 5% osteopenia or altered basal cortisol, and 4.2% asthenia. About 41.5% have not observed adverse effects from their use.

Despite the prolonged prescription of TCSs, 48.3% do not request basal cortisol measurement. About 22.8% of professionals perform this laboratory test only if the patient presents adverse effects from steroids, and 22% report always requesting a basal cortisol measurement.

Discussion

EoE has been a focus of research since the early nineties when it was recognized as an independent clinical entity. At present, we have guidelines and consensus that guide the medical practice of specialists. It is a disease of immuno-allergic character whose incidence and prevalence are increasing in the pediatric population.

In a study conducted by Shah et al. using the criterion of 15 eosinophils per high-power field for diagnosis, a significant increase in diagnostic sensitivity was demonstrated when increasing the number of esophageal mucosal biopsies obtained, going from 73% with a single sample to 100% with six[4]. Today, it is recognized

that eosinophilic infiltration in the esophagus can be irregular, making it necessary to obtain biopsies from proximal and distal segments, at least six in total, to achieve an accurate diagnosis. In our survey, most professionals perform between three and four biopsies per esophageal segment, complying with international standards.

The endoscopic approach is the first diagnostic test when this pathology is suspected, presenting characteristic but not pathognomonic findings.

The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Eosinophilic Gastrointestinal Disorders Working Group reports in their multinational longitudinal registry that among 582 patients, whitish exudates and longitudinal furrows were the most frequently reported characteristics. They also observed an endoscopically normal esophagus in 17% of patients, without reporting stenosis[5]. Similarly, our survey respondents mention exudates and longitudinal furrows as the most frequently observed findings in their practice. Likewise, endoscopists do not usually find stenotic behavior, with the inflammatory phenotype being the most frequent. As we have advanced in our knowledge of this pathology over the years, we currently approach esophageal involvement using an endoscopic score. It is interesting to highlight that in the 2014 ESPGHAN guideline, this type of macroscopic assessment was carried out subjectively by the specialist[6]. However, we now have a score that allows us to standardize and classify these types of lesions more precisely. The EREFS score was proposed as a tool to classify and rate the presence and severity of the five main endoscopic characteristics of EoE[7]. In the present survey, almost 19% of professionals are unfamiliar with this score, and more than a third do not use it in their daily practice. Recent studies on the concordance with histological data have obtained contradictory results. Some authors indicate that endoscopists should not base the diagnosis of EoE, nor make presumptions about the activity or remission of this disease based exclusively on endoscopic findings[8]. On the other hand, Wechsler et al. report in their prospective work a sensitivity and specificity of 89.6% and 87.9%, respectively with the use of this score at the time of diagnostic suspicion[7]. We understand that it should be reported at the time of the endoscopic procedure as it is a tool that helps us identify with some precision those patients with EoE. Similarly, we emphasize the importance of taking esophageal biopsies in all patients with suspected diagnosis, as it is reported that up to 30% of patients may present with normal-appearing mucosa[9].

In relation to treatment objectives, these include the resolution of symptoms and remission of histological activity to avoid fibrostenotic complications. In the 2017 recommendation guideline, PPIs are proposed as effective treatment for symptomatic improvement and endoscopic remission in slightly more than half of patients[8]. Our survey shows that this therapeutic approach is used in non-stenotic EoE as first-line treatment by the majority of respondents, a third of whom use it as monotherapy. For the fibrostenotic phenotype, PPIs are indicated by more than half of professionals, mainly associated with diet and corticosteroids. Systemic steroids are not currently recommended in the management of patients with EoE[8,10]. About 3% of respondents have indicated them.

EDs are effective in achieving clinical-histological results in pediatric patients with EoE[10]. The elimination of six foods results in a higher rate of histological remission when compared to the exclusion of 2-4, but is associated with lower compliance and a greater number of endoscopies. At present, less restrictive empirical diets are the ones of choice, recommending the elimination of 2 foods and increasing the level of restriction to 4 in those patients who do not respond to treatment[9]. Among the respondents, the number of excluded foods was highly variable in relation to what is reported in the literature. Less than a quarter of the surveyed gastroenterologists restrict between 2 and 4 foods. The empirical exclusion of a single food is the approach least practiced by professionals. This discrepancy between international guidelines and common practice somehow reflects the difficulty we have in implementing an empirical therapy of one, two, or four foods. It seems that a more cautious and restrictive strategy is safer for us, despite the nutritional disorders that this entails.

According to the ESPGHAN guideline for the management of EoE in pediatric patients, the failure of allergy test-directed dietary therapy to induce remission has been attributed to the inability of these tests to accurately detect causal food antigens[6,11]. In the present survey, however, we observe a high percentage of professionals who rely on these tools to guide dietary treatment.

The British Society for Pediatric Gastroenterology, Hepatology and Nutrition guideline for diagnosis and treatment of EoE states that exclusive elemental formulas have a limited role in the treatment of EoE since, despite their high efficacy, they have very low compliance rates and suggests reserving this tool for patients refractory to other treatments[10]. In this survey,

elemental formulas are used in infants under 1 year of age by half of the respondents. Other reported indications were multiple food allergies, severe nutritional compromise, and stenotic phenotype.

Successful results depend on treatment adherence, which in turn is determined by palatability, cost, third-party coverage, and the effect of treatment on quality of life[11,12]. Henderson et al. reported a satisfactory clinical response and disease remission (defined as a decrease in eosinophil count < 15 eosinophils/high-powered field) in 96% of patients on an elemental diet, 81% of patients with classic six-food elimination diet (SFED), 80% of patients with modified SFED, and 65% of patients with directed diet[13].

In EoE, the different strategies aimed at inducing and maintaining remission are best achieved through a multidisciplinary team. From our survey, we observe that practically half always use this methodology. A smaller percentage reserves this approach for those with some history of atopy or particular dietary treatment.

When reviewing dietary treatment, we observe that many gastroenterologists exclude a large number of foods. Almost 50% decide to initiate this approach by removing at least two or more foods, without opting for a step-by-step ED. This suggests that in practice, we tend to follow a "top-down" treatment approach rather than a "step-up" one. While we could affirm that more than 75% of respondents observe good adherence to the diet, the dietary therapeutic strategies we use highlight the fundamental role of the nutritionist when approaching the patient and their family. This survey reveals that nearly a third of professionals only refer to nutrition specialists when faced with evident nutritional compromise. Similarly, an even smaller percentage refers patients in cases of more restrictive diet therapies. This indicates that a significant portion of professionals only consider nutritional support in situations of high dietary complexity, and not as a routine practice for this pathology.

Regarding the pharmacological approach, monitoring the prolonged use of corticosteroids is not a common practice. Hsu E. and colleagues, in their work on the impact of adrenal insufficiency in pediatric patients under corticosteroid treatment, report that 5 out of 106 patients presented it when morning basal cortisol was measured[14]. Although the article presents a low percentage, it is important to recognize it and make a timely consultation with the specialist, as cortisol monitoring might be advisable for children with EoE who receive high doses of topical steroids for long periods or if they concomitantly receive corticosteroids through other routes (oral, inhaled, or nasal)[8].

Conclusion

This study offers a global view of the management of EoE in Latin America and Spain. However, the heterogeneity in the participation of each country limits the ability to draw conclusions at the local level regarding the management of this pathology in each of them.

The diagnosis of EoE is challenging due to the diversity of its symptoms. Despite the challenges it presents in its practical management, the majority of the surveyed specialists follow the diagnostic guidelines proposed in the latest international guides; however, a not insignificant percentage continues to perform biopsies randomly, which implies a reduction in this yield. While endoscopic control at the beginning of treatment tends to be performed in a timely manner, it becomes very arbitrary at the time of maintenance.

There are discrepancies when it comes to the therapeutic approach. We observe that combination therapy is frequently used both at the initiation and in the follow-up of these patients. It seems difficult to homogeneously follow the guidelines in daily practice. We must be careful when indicating diet therapy in these patients, taking into account that the exclusion of multiple foods from the beginning of treatment can imply a nutritional risk, in addition to difficulties in the social sphere and in relation to the acquisition of skills associated with feeding. Likewise, a more limited exclusion of foods from the beginning would imply a reduction in the number of endoscopic controls.

Finally, we believe that interdisciplinary work is another fundamental pillar to optimize the follow-up and treatment of these patients, facilitating adherence and minimizing long-term adverse effects.

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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 study does not involve patient personal

data nor requires ethical approval. The SAGER guidelines do not apply.

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

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RESEARCH ARTICLE

Results of a concurrent training protocol in muscle function and quality of life in the pediatric population with type 1 diabetes: a pilot study in public health

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Abstract

Background: *Type 1 diabetes mellitus (T1DM) prevalence has increased in prevalence worldwide. T1DM is characterized by negative changes in glycemic control (e.g., increased risk of hypoglycemia) and moreover negatively impacts the quality of life and muscle function of the pediatric population with the disease.* **Method:** *seven participants of the Hospital Dr. Exequiel González Cortés (age 11 [10-13] years, 4 male and 3 female) participated in a 12-week, twice-weekly concurrent training program plus continuous glucose monitoring (CGM). The participants underwent the following assessments: anthropometric measurements (weight, height, and BMI), glycemic control (Glycated hemoglobin [HbA1c], hypoglycemic events diaries, time in range, and glycemic diaries), muscle function (standing broad jump, prone plank, 10 maximum repetitions [10RM] squat, and chest press), quality of life (Kidscreen-27 questionnaire), and aerobic capacity (20 m shuttle run test). Statistical analysis used the Shapiro–Wilk test (normality), one-way Analysis of variance (differences between months), and paired t-test (pre-post differences).* **Results:** *The HbA1c increased ($p = 0.047$). Muscle function improved in standing broad jump ($p = 0.03$), prone plank ($p = 0.01$), 10RM squat ($p = 0.03$), and 10RM chest press ($p = 0.01$). Quality of life increased in physical function ($p = 0.03$) and total score ($p = 0.01$). The running distance in the 20 m shuttle run test increased ($p = 0.01$).* **Conclusion:** *The concurrent training program plus CGM is effective in improving quality of life, muscle function, and running capacity in the pediatric population with T1DM.*

Keywords: *Concurrent exercise. Concurrent training. Continuous glucose monitoring. Type 1 diabetes. Quality of life. Public health.*

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Resultados de un protocolo de entrenamiento concurrente en hipoglicemias, función muscular y calidad de vida en población pediátrica con diabetes tipo I: un estudio piloto en salud pública

Resumen

Introducción: *La diabetes tipo 1 (DM1) ha incrementado su prevalencia a nivel mundial. La DM1 se caracteriza por generar cambios negativos en el control glicémico (por ejemplo, mayor riesgo de hipoglicemias), además de impactar negativamente la calidad de vida y función muscular de la población pediátrica con la patología.* **Método:** *siete participantes del Hospital Dr. Exequiel González Cortés (edad 11 [10-13] años, 4 masculino y 3 femenino) participaron de un programa de entrenamiento concurrente de 12 semanas, 2 veces por semana con MCG. Se realizaron medidas antropométricas (peso, talla e IMC), control glicémico (Hb1Ac, hipoglicemias diarias, tiempo en rango y glicemias diarias), función muscular (salto largo a pies juntos, plancha prona, 10RM de sentadilla y 10RM de press de banca), calidad de vida (cuestionario Kidscreen-27) y capacidad aeróbica (shuttle 20m run test). El análisis estadístico utilizó la prueba de Shapiro–Wilk (normalidad), ANOVA de 1 vía (diferencia entre meses) y t test pareado (cambios pre – post).* **Resultados:** *La Hb1Ac se incrementó (p = 0.04), mejoró la función muscular en salto largo a pies juntos (p = 0.03), plancha prona (p = 0.01), 10RM de sentadilla (p = 0.03) y press de banca (p = 0.01). Mejoró la calidad de vida en función física (p = 0.03) y puntaje total (p = 0.01). Mejoraron los metros recorridos en el shuttle 20m run test (p = 0.01).* **Conclusión:** *Un protocolo de entrenamiento concurrente junto con MCG mejoró la calidad de vida, función muscular y capacidad de correr en NNA con DM1.*

Palabras claves: *Ejercicio concurrente. Entrenamiento concurrente. Monitoreo continuo de glucosa. Diabetes mellitus tipo 1. Calidad de vida. Salud pública.*

Introduction

Type 1 diabetes mellitus (T1DM) is characterized by the destruction of pancreatic Beta cells, normally due to an autoimmune process resulting in a loss of endogenous insulin production[1]. Worldwide, at least 108,300 children < 15 years old were diagnosed with T1DM in 2021[2]. In Chile, the incidence has almost tripled from 2006 to 2021 (8.0-23.1/100,000 inhabitants, respectively)[3]. The fluctuating levels of blood glucose related to T1DM increase the risk of ketoacidosis and hypoglycemic events, among other complications[4]. Moreover, the life expectancy of this population could be reduced by 15-20 years, while the risk of death could be increased 3-4 times compared to peers without T1DM[4]. Therefore, glycemic control becomes fundamental in the population with T1DM. In addition, the pediatric population with T1DM presents lower levels of muscle function[5] and quality of life[6] than their peers without T1DM. Importantly, physical exercise has evidenced a positive role in glycemic control (e.g., hypoglycemic events)[7,8], muscle function[9], and quality of life[7,8] in the pediatric population with T1DM. Unfortunately, the pediatric population with T1DM presents lower levels of physical activity[10]. The above is associated principally with fear of hypoglycemic events during exercise[11]. An alternative to decrease the hypoglycemic events is continuous glucose monitoring (CGM)[12]. Thus, the combination of physical exercise and CGM could be relevant in T1DM control and reducing its negative consequences. Therefore, the aim of this pilot study was to describe the results of a pilot program conducted in a public health hospital facility to analyze the effect of concurrent exercise plus CGM on weekly hypoglycemic events, muscle function, aerobic capacity, and quality of life of the pediatric population with T1DM attended in a public health system.

Method

Participants

The inclusion criteria were a pediatric population between 7 and 14 years old diagnosed with T1DM and managed by the endocrinology specialist team of the HEGC. To be considered in the analysis, the participants had to attend at least 75% of the training sessions. The exclusion criteria were moderate-to-severe cognitive deficiency, traumatological condition that would prevent performing the exercise, and cardiorespiratory disease that contraindicated performing the exercise. The study followed the national and international ethics declarations and was approved by the scientific ethics committee of the *Servicio de Salud Metropolitano Sur*, Santiago, Chile (code: 04-19012022).

Study design

The participants underwent measurements over three consecutive days:

Table 1. Concurrent training program

Aerobic training planning						
Weeks	**1-2**	**3-4**	**5-6**	**7-8**	**9-10**	**11-12**
Working time (min)	25	25	25	25	25	25
Maximal aerobic velocity (%)	50	55	60	65	70	75
Strength training planning						
Weeks	**1-2**	**3-4**	**5-6**	**7-8**	**9-10**	**11-12**
Standing broad jump (set × repetitions)	2 × 10	3 × 8	3 × 10	3 × 12		
Push-up (set × repetitions)	2 × 10	3 × 8	3 × 10	3 × 12		
Prone plank (set × repetitions) [s])	2 × 30	2 × 45	2 × 60			
Squat (set × intensity [RM]))	3 × 10 at 30%	3 × 10 at 40%	3 × 10 at 50%	3 × 8 at 60%	3 × 8 at 70%	
Chest press (set × intensity [RM])	3 × 10 at 30%	3 × 10 at 40%	3 × 10 at 50%	3 × 8 at 60%	3 × 8 at 70%	

RM: repetition maximum.

Day 1: pre-participative evaluation[13], capacitation, installation of CGM, and anthropometric measurements (body weight, height, and body mass index [BMI]), Clark test (hypoglycemic events auto-recognition).
Day 2: glycated hemoglobin (HbA1c) after 8-12 h of fasting in the HEGC dependences.
Day 3: quality of life questionnaire, muscle function (standing broad jump, push-up, prone plank, squat, and chest press 10 maximum repetitions [10RM]), and aerobic capacity (20 m shuttle run test).

Training protocol

Before, during, and after the concurrent training protocol, we implemented a rigorous security protocol related to hypoglycemic or hyperglycemic events in the pediatric population with T1DM following the guidelines of Moser et al. 2020[14]. The concurrent training protocol was developed and executed by a multidisciplinary team of experts in training[15,16]. The participants completed a concurrent training protocol throughout 12 weeks, 2 times/week. The endurance training protocol consisted of 25 min of endurance training at 50% of the aerobic maximum velocity (AMV), which was estimated following the proposal of García et al.[17]. The AMV increased by 5% every 2 weeks until it reached 75%. The strength training protocol consisted of different exercises for the upper extremities (push-ups and chest press), lower extremities (long jump and squats), and trunk (prone plank)[15,16]. The details of concurrent training protocol intensity and volume are presented in table 1.

Measurements

CGM

The Medtronic® CGM dispositive was used. The reports submitted 1 week before the start of the training protocol and throughout the 12-week period were analyzed. The weekly hypoglycemic (54-70 mg/dL [< 54 was considered a hypoglycemic event]), percentage of time in range (70-180 mg/dL), and mean weekly glycemic concentration (mg/dL) were used.

Anthropometrics

Body weight and height were measured using a lever scale and stadiometer SECA®. Then, the BMI was calculated. BMI and height z-scores were calculated using height and BMI plus biological sex and age.

Glycemic control

Blood venous samples were collected after 8-12 h of fasting. The HbA1c was used to analyze glycemic control.

Quality of life

Measured through the Kidscreen-27 questionnaire[18]. The five items (physical well-being, psychological well-being, autonomy and relationship with the environment, friends and social support, and school environment) plus the total score were used.

Clarke test

Questionnaire to assess the sensitivity and perception of hypoglycemic events in the pediatric population with T1DM.

Standing broad jump

The participant stood behind the jump line with feet shoulder-width apart. From that position, they jumped as far as possible, landing with both feet simultaneously[19]. Three attempts were made, and the best score in centimeters (cm) was considered.

Push-up test

The participants positioned themselves on a mat, supported their feet and hands at shoulder width, and performed maximum repetitions of trunk lifts with a 90° arm flexion[20]. The maximum number of repetitions (reps) was considered.

Prone plank

Only the forearms and toes were allowed to be in contact with the mat, maintaining the isometric position for as long as possible[21]. The total time recorded in seconds (s) was used.

10RM squat and chest press

The subject performed a bench press and a squat press with a weight in kilograms (kg) that allowed them to perform up to 10 repetitions. The indirect RM was then calculated using the formula proposed by Martínez-Cava et al.[22]. The estimated 1RM was used.

20 m shuttle run test

It involved running 20 m back and forth at an incremental speed starting at 8.5 km/h, which increased by 0.5 km/h/min. Maximum oxygen consumption (VO_2 max) in ml/kg/min was estimated using the formula by Leger et al.[23], and the distance covered in meters (m) was recorded.

Statistical analysis

Due to the small sample size, all statistical analyses were conducted using non-parametric tests. A Wilcoxon test was applied to evaluate changes in the dependent variables after the concurrent training protocol. Changes in the variables measured by the CGM were compared using a Friedman test at 4, 8, and 12 weeks of intervention. When significant differences were identified with the Friedman test, a *post hoc* Dunn test was performed. Statistical significance was set at $p \leq 0.05$. Data are presented as the median with interquartile range (IQR). Statistical analyses were conducted using PRISM 9.0 (GraphPad, California, 2019).

Results

The participants (n = 7, 11 [10-13] years, 4 males and 3 females) were recruited from the Pediatric Endocrinology Unit to the Physical Activity and Sports Medicine Unit of the *Hospital Dr. Exequiel González Cortés* (HEGC). The participants had a period of 12 (8-28.5) months from the first T1DM diagnosis to the start of protocol training. Baseline insulin treatment before protocol training consisted of insulin glargine (Lantus, Sanofi, Paris, France), n = 3, at a dose of 11 (10-31) UI and insulin degludec (Tresiba, Novo Nordisk, Bagsværd, Denmark), n = 4, at a dose of 16 (5.7-31.5) UI. Of the 8 participants who started, one withdrew from the training protocol due to personal problems. The baseline characteristics of the participants are shown in table 2.

Time slots associated with hypoglycemic events

The hypoglycemic events were divided into time slots (00:01-06:00, 06:01-12:00, 12:01-18:00, and 18:01-00:00) and counted. The hypoglycemic episodes from 00:01 to 06:00 were 19.1% of the events, from 06:01 to 12:00 were 25.7% of the events, from 12:01 to 18:00 were 33.8% of the events and from 18:01 to 00:00 were 21.3% of the events. The time slot from 06:01 to 12:00 was divided into 06:01-09:00 or pre-training and 09:01-12:00 or immediately post-training, considering that the training sessions took place at 09:00. Thus, of the 25.7% of hypoglycemic episodes that occurred in this time slot, 65.7% occurred in the pre-training time slot and 34.2% in the post-training time slot. Therefore, the number of hypoglycemic episodes directly related to exercise was 8.7%. The hypoglycemic episodes that occurred during the training protocol were treated with 30g of fast-assimilating carbohydrate.

Table 2. Dependent variables before and after 12 weeks of the concurrent training protocol in the pediatric population with T1DM

Variable	Before intervention (median plus IQR)	After intervention (median plus IQR)	p
Anthropometric			
Weight (kg)	47.7 (38.5-67.2)	47.4 (39.4-70.6)	0.50
Height (cm)	143.0 (138.7-168.0)	146.0 (140.75-170.0)	0.03
Height-z (SD)	–0,5 (–0.9-2.3)	–0.7 (–0.8-2.3)	0.23
BMI (kg/m^2)	20.8 (19.7-24.8)	20.9 (19.2-25.7)	0.93
BMI-z (SD)	0.9 (0.7-2.3)	0.82 (0.4-2.4)	0.20
Glycemic control			
Hb1AC (%)	6.9 (5.8-7.6)	6.7 (6.3-9.0)	0.04
Muscle function			
Standing broad jump (cm)	129.0 (103.5-152.0)	129.0 (107.5-180.0)	0.03
Push-up test (rep)	4.0 (0.5-29.0)	10.0 (5.0-39.0)	0.06
Prone plank (s)	43.5 (26.0-99.2)	81.5 (79.9-139.3)	0.01
10RM squat (kg)	31.3 (25.9-44.7)	36.0 (30.6-51.7)	0.03
10RM chest press (kg)	17.9 (17.0-41.9)	25.1 (22.6-48.5)	0.01
Quality of life			
Physical well-being (points)	88.8 (86.1-100)	100 (100-100)	0.03
Psychological well-being (points)	96.4 (92.8-100)	96.4 (96.4-100)	0.12
Autonomy and relationship with the environment (points)	85.7 (83.9-92.8)	89.2 (85.7-92.8)	0.50
Friends and social support (points)	87.5 (87.5-100)	93.7 (87.5-100)	0.50
School environment (points)	93.7 (84.3-100)	93.7 (87-5-100)	0.50
Total score (points)	90.4 (88.7-97.4)	94.1 (93.1-97.8)	0.01
Aerobic capacity			
VO_2 max (mL/kg^{-1}/min^{-1})	41.5 (39.6-46.3)	41.5 (39.6-46.3)	0.50
Distance running in shuttle 20 m run test (m)	200.0 (180.0-760.0)	280.0 (240.0-960.0)	0.01

BMI: body mass index; BMI-z: body mass index by z-score; Hb1AC: glycated hemoglobin; Height-z: height by z-score; RM: repetition maximum; rep: repetitions; VO_2 max: maximal oxygen consumption; IQR: interquartile range.

CGM

One week before the start of the training protocol, a median plus IQR of 0.30 (0.0-0.50) hypoglycemic episodes/week was recorded. A median plus IQR of 0.30 (0.19-0.40) hypoglycemic episodes/week was recorded during the 1st month of intervention, 0.20 (0.10-0.58) episodes/week during the 2nd month, and 0.15 (0.08-0.55) episodes/week during the 3rd month. One week prior to the start of the training protocol, the median plus IQR of the weekly glucose concentration was 149.00 (133.00-213.00) mg/dL. The median plus IQR of weekly glucose concentration was 158.25 (133.00-214.75) mg/dl during the 1st month of intervention, 160.75 (139.38-226.00) mg/dL during the 2nd month, and 153.00 (137.75-208.08) mg/dL during the 3rd month. One week before the start of the training protocol, the median plus IQR time in range was 80.00 (65.00-94.00)%. The median plus IQR time in range was 70.00 (51.63-93.75)% during the 1st month of intervention, 66.00 (52.63-94.00)% during the 2nd month and 66.50 (52.00-94.00)% during the 3rd month. No significant differences were found between the baseline and concurrent protocol training scores for the three variables.

Anthropometrics

Significant differences were evidenced in the pre-to-post-intervention for height, increasing from 143.0 (138.7-168.0) to 146.0 (140.75-170.0) cm ($p = 0.03$). No significant differences were observed for height z-score ($p = 0.23$), weight ($p = 0.64$), BMI ($p = 0.82$) and BMI z-score ($p = 0.20$).

Glycemic control

Significant differences were observed in the pre-to-post-intervention for HbA1c, increasing from 6.9 (5.8-7.6)% to 6.7 (6.3-9.0)% ($p = 0.046$).

Quality of life

Significant differences were observed in the pre-to-post-intervention in the physical well-being

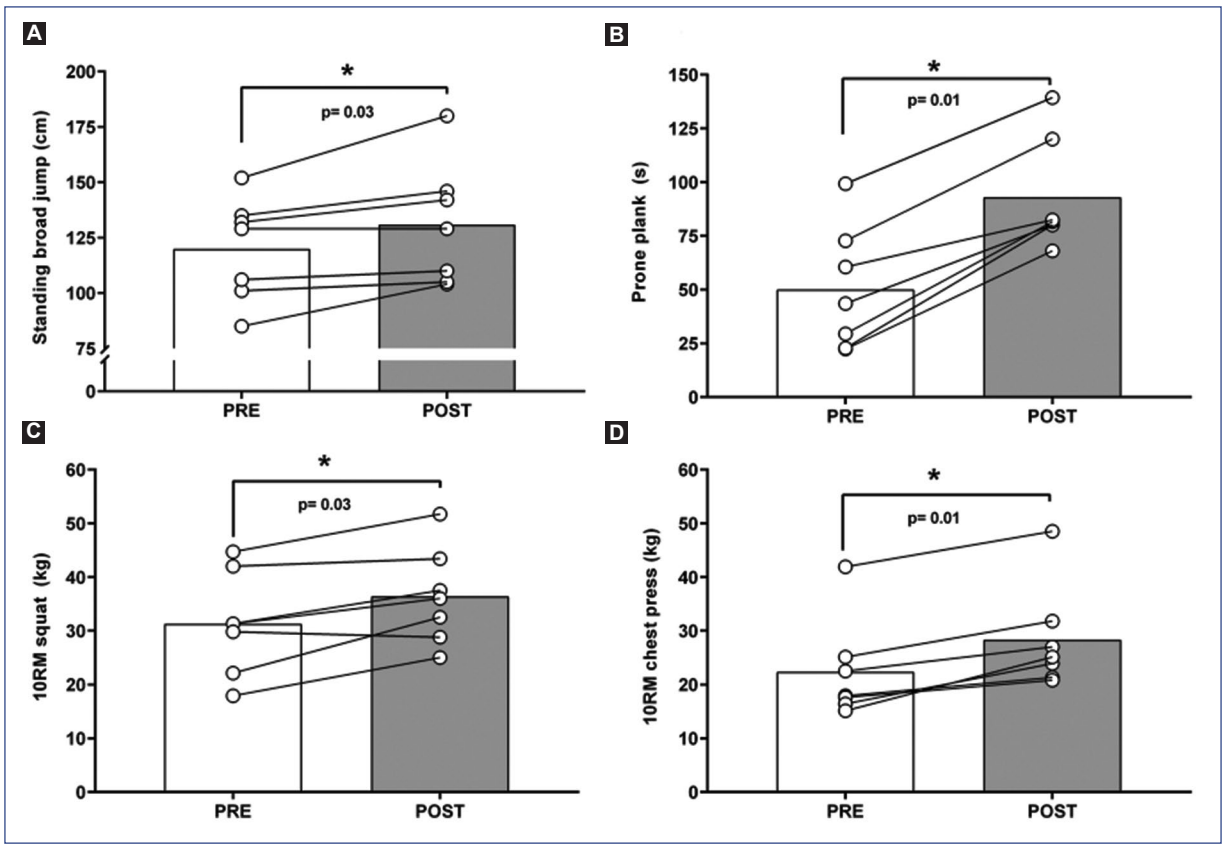

Figure 1. Changes in the standing broad jump **A**: prone plank **B**: 10RM squat and **C**: 10RM chest press **D**: of the participants plus their means ± standard deviation before (pre) and after (post) of a concurrent training protocol of 12 weeks. *Significant difference between the pre- and post-measurements

domain, increasing from 88.8 (86.1-100) to 100 (100-100) points (p = 0.03) and the total score from 90.4 (88.7-97.4) to 94.1 (93.1-97.8) points (p = 0.001). No significant differences were observed for the rest of the Kidscreen-27 domains (Table 2).

Muscle function

Significant differences were observed in the pre-to-post-intervention in the standing broad jump, increasing from 29.0 (103.5-152.0) to 129.0 (107.5-180.0) cm (p = 0.03) figure 1A. Similarly, the prone plank increased from 43.5 (26.0-99.2) to 81.5 (79.9-139.3) s (p = 0.01) figure 1B, the 10RM squat increased from 31.3 (25.9-44.7) to 36.0 (30.6-51.7) kg (p = 0.03) figure 1C, and the 10RM chest press increased from 17.9 (17.0-41.9) to 25.1 (22.6-48.5) kg (p = 0.01) figure 1D. No significant differences were observed for the push-up test (p = 0.06).

Aerobic capacity

Posterior to the intervention, the distance covered in the 20m shuttle run test increased from 200.0 (180.0-760.0) to 280.0 (240.0-960.0) m (p = 0.01). No significant differences were observed in the VO_2 max (p = 0.17).

Discussion

Following the concurrent training protocol, the HbA1c, muscle function, quality of life, and aerobic capacity increased significantly in the pediatric population with T1DM. Throughout the intervention, no changes were evidenced in the weekly hypoglycemic episodes, weekly glycemic concentration, and time in range.

Throughout the three intervention months, the pediatric population with T1DM showed no changes in the weekly hypoglycemic episodes, and the mean of hypoglycemic episodes per day was 1.6-1.8. Similarly, Laffel et al.[24] showed 1.4-1.5 daily hypoglycemic episodes.

Therefore, our results could support that physical exercise programs in T1DM patients are safe and could be used as a strategy to include physical activity and sports habits throughout the 1st year of the appearance of the disease. Despite the lack of results related to weekly glycemic concentration and time in range, our results are below those reported in the literature[24]. Laffel et al.[24] reported weekly glycemic concentrations and time in the range between 199-209 mg/dL and 37-43%, respectively. In our study, we reported weekly glycemic concentration and time in the range between 163-168 mg/dL and 44-66%, respectively, which could demonstrate better glycemic control in our study population. It is important to mention that the results of Laffel et al.[24] incorporated only CGM without any exercise intervention. To the best of our knowledge, there is no evidence of the effects of concurrent protocol training plus CGM on the variables mentioned above in the pediatric population with T1DM.

At the end of the concurrent training protocol, the HbA1c decreased from 6.9 (5.8-7.6)% to 6.7 (6.3-9.0)%. Our results differ from those reported in the literature[25,26], which showed that following diverse training protocols, the HbA1c decreases in the pediatric population with T1DM. We hypothesized that the increase in HbA1c was due to the planning of our concurrent training protocol. Thus, the meta-analysis of Garcia-Hermoso et al.[25] reported that concurrent training was superior to endurance training alone, but concurrent training should have a duration of ≥ 24 weeks and be of high intensity (aerobic phase), characteristics that contrast with our protocol of 12 weeks and moderate intensity (aerobic phase). Therefore, in the future, the aerobic phase should include high-intensity components such as high-intensity interval training (HIIT). Importantly, the fear of exercise-associated hypoglycemic events is greater in the pediatric population who has completed exercise programs compared to their peers who have not completed exercise programs[27]. One strategy to reduce this fear of exercise-associated hypoglycemia is to consume carbohydrates[28]. Therefore, we hypothesized that this strategy could have increased HbA1c levels even though participants were under nutritional control. Thus, in a larger trial, we need to consider nutritional education sessions related to carbohydrate overconsumption before the start of the training protocol to avoid this HbA1c increase.

The muscle function improved after the concurrent training protocol, showing an improvement in the standing broad jump ($p = 0.03$), prone plank ($p = 0.01$), 10RM squat ($p = 0.03$), and 10RM chest press ($p = 0.01$). Our results are in line with those reported by other authors[9,26], in which other concurrent training protocols improved the muscle function of the pediatric population with T1DM. Specifically, D'hooge et al.[9] showed that after a concurrent training protocol of 20 weeks, 2 times/week, the strength of the upper and lower extremities (1RM) increased by 72.2% and 23.1%, respectively. The reported improvements in muscle function were relevant, considering the detrimental effects of T1DM on muscle function and mass[5,29]. Thus, Maratova et al.[5] after a 9-year follow-up, found that the pediatric population with T1DM showed a decrease in muscle function and mass even following the pharmacological treatment for the disease. Similarly, Tan et al.[29] compared muscle function and architecture between pediatric populations with and without T1DM, and showed that the pediatric population with T1DM presented lower muscle function expressed by 40.5% and 31.5% lower torque of the knee flexors and extensors and architectonic changes, such as 12.8% lower thickness of the rectus femoris. Therefore, the addition of a concurrent training protocol could maintain and prolong ideal values for muscle function and mass in the pediatric population with T1DM.

The quality of life improved after the concurrent training protocol in the physical function domain ($p = 0.03$) and the total score ($p = 0.01$) of the Kidscreen-27 questionnaire. Our results are relevant considering the lower quality of life of the pediatric population with T1DM compared with healthy peers[6]. The systematic review of Absil et al.[26] showed that in only 1 of 7 studies, the quality of life improved after different training protocols in the pediatric population with T1DM. Therefore, our results are novel compared with the available evidence[30]. The quality of life of this population is reduced due to the fear of hypoglycemic episodes[30]. Thus, when the parents are in the highest quartile of fear of hypoglycemic episodes, the pediatric population with T1DM showed a 20% lower quality of life compared to those in the lowest quartile of fear of hypoglycemic episodes[30]. Interestingly, the use of CGM devices evidenced a decrease in the fear of hypoglycemic episodes among parents of the pediatric population with T1DM[31]. Therefore, we hypothesized that the use of CGM, the lower hypoglycemic episodes reported (fewer than 2 daily), and the improvement in muscle function could contribute to the increases in the quality of life in the pediatric population with T1DM.

The concurrent training protocol showed an increase in the distance covered in the 20m shuttle run test ($p = 0.01$) without change in the VO_2 max estimated by the

same test. We hypothesized that the improvement in the distance covered in the 20m shuttle run test (26.9%) is related to a neuromuscular improvement in response to the resistance training phase of the concurrent training protocol[32]. Thus, the improvement in intra and intermuscular coordination would be responsible for a better running capacity. Alternatively, we believe that no changes in VO_2 max could be a result of the aerobic phase intensity proposed in the concurrent training protocol not being high enough to generate central and peripheral adaptations. Moreover, the estimation equation used[23] could underestimate the changes due to considering only the age and level reached in the test. Similarly, other concurrent training protocols[9] have also not produced improvements in VO_2 max. However, when HIIT protocols are compared with moderate-intensity continuous training (MICT) in the pediatric population with T1DM[33], the HIIT protocols produce significant improvements (6.1%) versus no changes (3.1%) in the MICT protocol for VO_2 max[33]. Therefore, if we aim to improve the VO_2 max of the pediatric population with T1DM, the recommendation should be centered on ensuring that the aerobic phase of the concurrent training protocol is based on the HIIT protocol.

The main strength of this study is providing safe planning of concurrent training protocol with positive results in glycemic control, muscle function, and quality of life, which could guide clinical practice in public health. In contrast, the study design (pilot study) presents certain limitations, such as the small number of participants and the absence of a control group. Therefore, this represents one of the first steps in exercise treatment for the pediatric population with T1DM in public health, and more studies are needed in this area.

Conclusion

A 12-week concurrent training protocol with CGM is safe regarding the risk of hypoglycemic episodes and effective in improving muscle function, running capacity, and quality of life of the pediatric population with T1DM.

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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 study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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

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