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INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO. DENOMINAÇÃO DO MEDICAMENTO: Dioralyte, pó para solução oral. **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA: Substâncias activas** g/saqueta: Glicose 3,56; Cloreto de sódio 0,47; Cloreto de potássio 0,30; Citrato dissódico 0,53. **INDICAÇÕES TERAPÊUTICAS:** Correcção da perda de líquidos e electrólitos nos lactentes, crianças e adultos. Tratamento da diarreia aquosa de várias etiologias, incluindo as gastrenterites, em todos os grupos etários. **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Cada saqueta deve ser sempre dissolvida em 200 ml de água. O volume de Dioralyte reconstituído a tomar deve ser decidido pelo médico assistente, tendo em consideração o peso do doente e o estado e gravidade da situação. Um princípio básico no tratamento da diarreia é a substituição da perda de líquidos e a manutenção de uma ingestão de líquidos suficiente para repor a sua perda nas fezes. A ingestão diária deve ser baseada num volume de 150 ml/Kg de peso nos lactentes e 20–40 ml/Kg de peso nos adultos e crianças. Uma aproximação razoável é a seguinte: -lactentes – 1 a 1,5 vezes o volume alimentar habitual; - crianças – 1 saqueta após cada dejecção diarreica; - adultos – 1 ou 2 saquetas após cada dejecção diarreica. Inicialmente, podem ser necessárias maiores quantidades de Dioralyte para assegurar uma reposição precoce do equilíbrio hidro-electrolítico. Nos estadios iniciais do tratamento da diarreia, todos os alimentos, incluindo o leite de vaca e o leite artificial, devem ser interrompidos. Não se deve no entanto interromper o aleitamento materno. Nas crianças amamentadas sugere-se que se dê à criança o mesmo volume de Dioralyte do que o da alimentação normal, seguindo-se o aleitamento. Pode ser necessário, durante este período, a expressão do leite residual da mama. Após 24-48 horas, quando os sintomas desaparecerem, a dieta normal deve ser retomada gradualmente para evitar o agravamento da situação. O regime sugerido para o tratamento da diarreia infantil grave baseado no peso corporal em Kg é apresentado no quadro anterior. Quando a diarreia é acompanhada de vómitos, sugere-se ingestão frequente de pequenas quantidades de Dioralyte. No entanto, é importante que seja tomado o volume total necessário de Dioralyte. Quando o funcionamento dos rins é normal torna-se difícil superhidratar por via oral e quando existem dúvidas acerca da dosagem correcta, mais vale tomar a mais do que a menos. **CONTRA-INDICAÇÕES:** Não se conhecem contra-indicações ao Dioralyte. No entanto, existem algumas situações em que o tratamento com Dioralyte é inapropriado, tais como por exemplo, situações de oclusão intestinal requerendo intervenção cirúrgica, ou em caso de vómitos persistentes e desidratação grave ou diarreia infantil grave em que será necessária uma terapêutica por via intravenosa. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:** O Dioralyte só deve ser reconstituído com água. Cada saqueta deve ser sempre reconstituída em 200 ml de água. Uma solução mais fraca do que a recomendada não contém a concentração óptima de glicose e electrólitos e uma solução mais forte do que a recomendada pode provocar desequilíbrio electrolítico. Se a diarreia não melhorar rapidamente, os doentes deverão ser reavaliados. Nos idosos, a administração de soluções contendo glucose e electrólitos deve ser cuidadosa em caso de alterações renais ou hepáticas graves ou em outras situações em que o balanço electrolítico normal se encontre alterado. Nos lactentes, deve interromper-se durante 24 horas a alimentação com leite de vaca ou leite artificial, que deverão ser reintroduzidos gradualmente quando a diarreia tiver diminuído. Não se deve interromper o aleitamento materno. **EFEITOS INDESEJÁVEIS:** Podem ocorrer náuseas ou vómitos após a administração da solução, em particular quando esta é ingerida com demasiada rapidez. Estão também descritos casos isolados de desconforto abdominal e de obstipação.Data da revisão do texto: Janeiro de 2004.**TITULAR DA AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO: KORANGI - Produtos Farmacêuticos, Lda. Medicamento não sujeito a receita médica. Para mais informações contactar o Titular da Autorização de Introdução no Mercado**

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ACKNOWLEDGMENT TO REVIEWERS

The editorial board of the Portuguese Journal of Pediatrics would like to thank all the reviewers who collaborated in the editorial process of the manuscripts submitted in 2025, being fully aware that the work of scientific review by peers is the highest expression of scientific citizenship.

Therefore, on behalf of all the readers, authors, and editors of the Portuguese Journal of Pediatrics, thank you!

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EDITORIAL

Peer review: the unseen foundation of scientific quality

Revisão por pares: a base invisível da qualidade científica

David Lito[1]* *and Inês Azevedo*[2]

[1]*Hospital Beatriz Ângelo, Loures;* [2]*Faculdade de Medicina, Universidade do Porto, Porto. Portugal*

Since its foundation in 1938, the Portuguese Journal of Pediatrics (PJP) has predominantly relied on voluntary academic contributions. With the exception of the Executive Editor-in-Chief and the Editorial Assistant, members of the editorial board and reviewers serve without financial compensation. Their work reflects professional responsibility and commitment to advancing pediatric science.

The PJP employs a double-blind editorial review system, whereby author and reviewer identities remain concealed to each other. This approach aims to promote impartiality and reduce bias. As specified in the journal's editorial policies and reviewer instructions, reviewers are expected to provide constructive and confidential evaluations, disclose conflicts of interest and adhere to the established ethical standards.

The review process requires a detailed assessment of the scientific content, including the evaluation of study design, methodology, statistical analysis, interpretation of the results, and consistency between the objectives and the conclusions. The process is iterative: authors respond to reviewer comments, and revised manuscripts may undergo further independent critical appraisal to confirm that concerns have been appropriately addressed.

Recent data indicate that the editorial review system is under increasing pressure. In 2020, the global scientific output reached approximately 2.9 million published articles,[1] and reviewers collectively devoted over 130 million hours to manuscript review that year, which is estimated to be worth 1.5 billion USD in uncompensated labor in the United States.[2] However, recruitment efficiency has declined. In 2013, editors required 1.9 invitations to secure one completed evaluation. This figure increased to between 2.4 and 2.7 by 2017, and is projected to reach 3.6 by 2025.[3]

The COVID-19 pandemic further reduced reviewer availability. Acceptance rates declined from approximately 35%-40% pre-pandemic to 9% in 2021-2022.[4] Reviewer workload has become increasingly concentrated, with an estimated 20% of researchers conducting up to 90% of reviews in the biomedical sciences.[5] Survey data from medical journals similarly report increased reviewer burden and recruitment challenges.[6]

In Portugal, Villanueva et al. described the editorial process in Acta Médica Portuguesa, highlighting the importance of independent expert evaluation.[7]

Last year, 95 manuscripts were submitted to the PJP, 48 of which were ultimately published. An average of 3.7 reviewers were invited to assess each accepted manuscript, and approximately 45% completed their assessments.

To improve efficiency, the PJP has implemented artificial intelligence-assisted screening tools.

The integrity and credibility of scientific publishing depend on rigorous independent reviews. Expert evaluation remains "the cornerstone of scientific publishing.[8]" Strengthening and valuing this process is therefore essential.

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The Editorial Board thanks all reviewers for their commitment. The Portuguese Journal of Pediatrics remains firmly committed to recognizing and supporting reviewers whose expertise is fundamental to its scientific rigor.

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ORIGINAL ARTICLE

The Portuguese Pediatric Oncology Centre in support of pediatric cancer patients from Portuguese-speaking African countries: the experience of a decade of a cooperation agreement

Cátia Martins, Sónia Silva, Filipa Curinha, Mónica Jerónimo, and Manuel João Brito*

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Abstract

Introduction and Objectives: Pediatric cancer is a leading cause of non-traumatic death in children over the age of one in high-income countries. However, low- and middle-income countries (LMICs) experience higher incidence and mortality rates due to late diagnoses, treatment abandonment, and inadequate healthcare systems. This study characterizes pediatric cancer patients from Portuguese-speaking African countries (PALOP) treated at a Portuguese Pediatric Oncology Centre (POC) under health cooperation agreements. **Methods:** Retrospective descriptive study of patients referred to a POC between January 2013 and December 2022. Since 2015, the POC has collaborated with the only National Reference Centre for Onco-Ophthalmology. **Results:** A total of 43 patients were referred, 65% of whom were male, with a median age of 3.2 years. Most patients came from Guinea-Bissau (34.9%), Cape Verde (32.6%), and Angola (23.3%), with 72.1% evacuated under cooperation agreements. Only 30.2% had initiated treatment in their home country. The median time from symptom onset to the POC consultation was 166 days. Solid tumors were most prevalent (76.7%), especially retinoblastoma (48.8%) and rhabdomyosarcoma (15%). Leukemia accounted for 45.5% of non-retinoblastoma cases. Metastatic disease significantly increased mortality risk ($p < 0.001$). Recurrence occurred in 23.3%, and 32.6% of patients died. Currently, 58.0% are out of treatment. **Discussion:** The high prevalence of retinoblastoma reflects the collaboration between the POC and the only National Reference Centre for Onco-Ophthalmology. The overall survival rate of 67.4% was higher than typically observed in LMICs, partly due to the high number of children with retinoblastoma. However, this improved survival rate, emphasizes the need for improved diagnostic and treatment strategies, as well as strengthened international collaboration to enhance pediatric cancer care in resource-limited settings.

Keywords: Neoplasms. Child. Developed countries. Less-developed countries.

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Centro Português de Oncologia Pediátrica no apoio a doentes pediátricos oncológicos provenientes de países africanos de língua oficial portuguesa: uma década de um acordo de cooperação

Resumo

Introdução e Objetivos: A doença oncológica pediátrica é uma das principais causas de morte não traumática em crianças mais de um ano, em países de elevado rendimento. Nos países de baixo e médio rendimento (PBMR), a incidência e mortalidade são superiores pelo diagnóstico tardio, abandono de tratamento e sistemas de saúde insuficientes. Este estudo caracteriza os doentes oncológicos pediátricos provenientes de Países Africanos de Língua Oficial Portuguesa (PALOP) tratados num Centro de Oncologia Pediátrica (COP) português. **Métodos:** Estudo retrospetivo descritivo de doentes de PALOP tratados num COP, entre janeiro/2013 e dezembro/2022. Desde 2015, o COP colabora com o único Centro de Referência Nacional de Onco-Oftalmologia. **Resultados:** Foram incluídos 43 doentes, 65% do sexo masculino, com idade mediana de 3,2 anos. A maioria proveio da Guiné-Bissau (34,9%), Cabo Verde (32,6%) e Angola (23,3%); 72,1% foram evacuados ao abrigo de acordos de cooperação. Apenas 30,2% iniciaram tratamento no seu país e decorreu uma mediana de 166 dias desde o início de sintomas até à observação no COP. Os tumores sólidos predominaram (76,7%), sobretudo o retinoblastoma (48,8%) e o rabdomiossarcoma (15%). Excluindo os retinoblastomas, as leucemias representaram 45,5% dos casos. A presença de doença metastática à admissão do COP aumentou o risco de mortalidade ($p < 0,001$). A recidiva da doença ocorreu em 23,3% e 32,6% dos doentes faleceram. **Discussão:** A elevada prevalência de retinoblastomas reflete a colaboração do COP com o único Centro de Referência Nacional de Onco-Oftalmologia. A sobrevida global (67,4%) foi superior à observada em PBMR, em parte justificada pelo elevado número de crianças com retinoblastoma. Contudo, esta sobrevida superior destaca a necessidade de melhorar o diagnóstico e tratamento, e reforçar colaborações internacionais para facilitar os cuidados oncológicos em ambientes com recursos limitados.

Palavras-chave: Criança. Cancro. Países em desenvolvimento. Países desenvolvidos.

Keypoints

What is known

- Pediatric cancer, although rare, is a leading cause of non-traumatic death in children over one year of age in high-income countries (HICs).
- In HICs, the five-year survival rate for children with cancer has increased in recent years to approximately 80%, in stark contrast to the 20% survival rate in low- and middle-income countries (LMICs).
- In LMICs, higher incidence and mortality rates are prevalent due to late diagnoses, treatment abandonment, and inadequate healthcare systems.

What is added

- The prevalence of solid tumors, even when excluding retinoblastoma cases, was higher than that of leukemias among patients referred from Portuguese-speaking African Countries.
- Only 30.2% of patients had begun antineoplastic therapy in their home country, even though it takes a median of 166 days from symptom onset to their first observation at a Portuguese Pediatric Oncology Centre.
- Despite delays in diagnosis and treatment, the overall survival rate was 67.4%, partly due to the high incidence of retinoblastoma, a tumor with a generally good prognosis. When excluding these cases, the survival rate drops to 54.5%, which remains higher than the typical survival rates observed in LMICs.

Introduction

Oncological disease is rare in the pediatric age, but in high-income countries (HIC) in particular, it is the leading cause of non-traumatic death in children over one year of age.[1,2] It is estimated that one in every 260 children and adolescents will be diagnosed with cancer before the age of 20,[2] with approximately 280,000 diagnoses and 110,000 cancer-related deaths reported worldwide in 2020.[3] Current figures may be higher, as pediatric cancer is underdiagnosed in many regions.[1]

In the United States of America (USA), according to Cancer Statistics 2023,[2] leukemia is the most common pediatric malignancy (28%), followed by central nervous system (CNS) tumors (26% of which, nearly one third, are benign or low-grade malignancies). Among adolescents, CNS tumors are most frequent (21%), followed by lymphomas (19%). Advances in diagnostics and treatment over recent decades have markedly improved

survival outcomes. Between 1970 and 2020, mortality from childhood and adolescent cancers in the USA declined by 70% and 64%, respectively, largely due to enhanced treatment protocols and improved management of side effects. The five-year survival rate increased from 58% in the mid-1970s to 85% between 2012 and 2018, and from 68% to 86% in adolescents.[2] Similar trends have been observed in Europe, mainly HICs, where survival reached approximately 80% by 2007.[4] In Portugal, considered a HIC, 387 new pediatric neoplasms were diagnosed in 2020, according to the National Oncological Registry of All Tumors in the Portuguese Resident Population, accounting for 0.73% of all cancer cases, with mortality rates ranging from 1.2 and 4.6 deaths per 100,000 person-years.[5] In contrast, low-and middle-income countries (LMICs) face considerable challenges. Epidemiological data remains limited, but a higher incidence of childhood cancer has been observed, likely driven by genetic predispositions, exposure to infectious diseases, and environmental factors.[6] This incidence is expected to increase by 30% by the end of the decade.[7-9] Low health literacy and limited access to care often lead to delayed or missed diagnoses, worsening prognosis and lowering survival rates.[1] It is estimated that nearly 90% of children with cancer reside in LMICs,[10,11] where the cure rate is around 20%, significantly lower than the 80% observed in HICs.[12] Late presentation, treatment abandonment, coexisting conditions (such as malnutrition and infections), insufficient palliative care, and ineffective healthcare systems represent major limitations to pediatric oncological care in LMICs.[13] Africa is particularly affected, accounting for over 20% of global pediatric cancer cases,[14] with incidence projected to increase by 70% between 2012 and 2030.[15] Despite this growing burden, fewer than half of Sub-Saharan African countries have an established policy or strategic plan for cancer control.[15] Addressing these disparities will require investment in healthcare infrastructure, the implementation of national cancer control plans, and strengthened international collaboration.[11]

Between 1977 and 1992, Portugal established health cooperation agreements with Portuguese-speaking African countries (PALOP), namely Angola, Mozambique, Cape Verde, Guinea-Bissau, and São Tomé and Príncipe, which remain active.[16] These agreements regulate the evacuation of patients from PALOP to Portuguese public hospitals in cases where the former do not have adequate resources to treat certain diseases.[17] This study aims to characterize the population of children and adolescents with cancer from PALOP who were treated at a Pediatric Oncology Centre (POC) in Portugal.

Methods

This was a retrospective, descriptive, single-center study based on the clinical records of children and adolescents from PALOP, observed at the Hospital Pediátrico of the Unidade Local de Saúde de Coimbra (ULS Coimbra) with a diagnosis of oncological disease, from 1 January 2013 to 31 December 2022.

The POC at ULS Coimbra is one of four pediatric oncology centers in Portugal. It treats all children and adolescents diagnosed with cancer up to the age of 17 years and 364 days, primarily serving the central region of Portugal. Notably, since 2015, it has collaborated with the only National Reference Centre in Onco-Ophthalmology, receiving and managing all Portuguese and PALOP children diagnosed with retinoblastoma.

All patients under 18 years of age with oncological disease, born in one of the PALOP, were included in the study. Data was obtained according to the General Data Protection Regulation. The study was conducted in accordance with ethical and legal principles, following the recommendations of the World Medical Association's revised Declaration of Helsinki (2013), the International Committee of Medical Journal Editors, and the Committee on Publication Ethics.

Demographic and clinical characteristics were analyzed, including sex, age, country of origin, diagnosis, and duration of symptoms until the first medical assessment and from this until the first consultation at the POC – ULS Coimbra. Staging, treatment carried out in the country of origin, the number of hospitalizations per year and their duration, disease progression, recurrence, and follow-up were also evaluated.

This was a convenience sample, so the sample size was defined by the total number of children and adolescents diagnosed with cancer during the study period.

Statistical analysis was conducted using the IBM Statistical Package for the Social Sciences (SPSS®), version 27. The mean, standard deviation, median, and interquartile range (IQR) were calculated for the continuous variables, while relative and absolute frequencies were determined for nominal variables. The normality of the distributions was assessed using the Kolmogorov-Smirnov test. Survival analysis was performed based on Kaplan-Meier curves. Chi-square and Kruskal-Wallis tests were used to determine associations and differences between variables, respectively. The significance level (α) was set at 0.05.

Table 1. Demographic and clinical characteristics of the sample

Variable	Total (n = 43)	Country of origin				
		Guinea-Bissau (n = 15)	Cape Verde (n = 14)	Angola (n = 10)	Mozambique (n = 2)	São Tomé e Príncipe (n = 2)
Male sex, n (%)	28 (65.1)	12 (80)	10 (71.4)	4 (40)	1 (50)	1 (50)
Age in years, median (IQR)	3.2 (5.3)	4.3 (9.3)	2.4 (7.1)	2.3 (2.7)	1.7 (1.4)	6.9 (2.2)
Solid tumors, n (%)	33 (76.7)	10 (66.7)	11 (78.6)	9 (90)	1 (50)	2 (100)
Solid tumors with metastatic disease, n (%)	8 (24.2)	4 (40.0)	3 (27.3)	1 (11.1)	0 (0)	0 (0)
Start of treatment in country of origin, n (%)	13 (30.2)	4 (26.7)	4 (28.6)	2 (20)	2 (100)	1 (50)
Days elapsed from the onset of symptoms to the first medical observation, median (IQR)	92 (212)	101 (325)	70.5 (182)	153 (207)	56.5 (5.5)	265.5 (120.5)
Days elapsed from the first observation to the consultation at the POC, median (IQR)	74 (112)	85 (185)	68 (89)	74 (197)	131.5 (110.5)	36 (13)

IQR: interquartile range; POC: pediatric oncology center.

Results

Between 1 January 2013 and 31 December 2022, 43 pediatric patients from PALOP with a diagnosis of oncological disease were treated at the POC of ULS Coimbra. Of these, 65.1% (n = 28) were male and had a median age of 3.2 years (IQR 5.3 years). In this sample, 34.9% (n = 15) came from Guinea-Bissau, 32.6% (n = 14) from Cape Verde, 23.3% (n = 10) from Angola, 4.7% (n = 2) from Mozambique and 4.7% (n = 2) from São Tomé and Príncipe. The sample characterization is presented in table 1.

Out of the patients referred to the POC, 72.1% (n = 31) were evacuated under the cooperation agreements between the Portuguese government and the PALOP. A statistically significant difference ($p < 0.001$) was identified between the patients' origin and referral through the evacuation process. A total of 93.3% (n = 14) were evacuated from Guinea-Bissau, 20% (n = 2) from Angola, 85.7% (n = 12) from Cape Verde, 100% (n = 2) from Mozambique, and 100% (n = 2) from São Tomé and Príncipe.

From the onset of symptoms to the first medical assessment in the country of residence, an average of 158.5 days elapsed, with a median of 92.0 days (IQR 212 days). From the first assessment in the country of origin to the first consultation at the POC of ULS Coimbra, the mean duration was 113.9 days, with a median of 74.0 days (IQR 112 days). There was no statistically significant relationship found between the country of origin and the time elapsed until the first medical observation or until the observation at the POC.

A median of 4.5 new patients (IQR 3.3) were observed annually. These patients required a median of 39 hospitalizations per year (IQR 31.5), with a median duration of four days (IQR 5.8).

Table 2 presents the diagnosis and clinical course according to the country of origin.

Regarding diagnosis, among patients with leukemia, 14.0% (n = 6) had acute lymphoblastic leukemia (7.0% B-cell and 7.0% T-cell), and 7.0% (n = 3) had myeloblastic leukemia (4.7% acute, 2.3% chronic).

At the initial observation at the POC, among the patients with solid tumors, 24.2% (n = 8) were at stage IV, and a statistically significant relationship was identified between the tumor type and the presence of metastasis ($p < 0.001$): three (37.5%) patients had a diagnosis of osteosarcoma, three (37.5%) of retinoblastoma, one (12.5%) of neuroblastoma, and one (12.5%) of rhabdomyosarcoma.

Concerning antineoplastic therapy, 30.2% (n = 13) had started treatment in their country of origin, among which 11.6% (n = 5) received chemotherapy, 9.3% (n = 4) corticosteroid therapy, 2.3% (n = 1) imatinib, 4.7% (n = 2) underwent enucleation, and 2.3% (n = 1) had started treatment that was not specified. No association was found between the start of therapy and the country of origin or the presence of metastasis. Palliative therapy was initiated upon arrival at the POC in 7.0% (n = 3) of patients.

During follow-up at the POC, disease recurrence was observed in 23.3% (n = 10), with a mean time to recurrence of 337.8 days and a median of 260 days (IQR 744). The event-free survival curve is presented in figure 1.

Table 2. Diagnosis and clinical course

Variables	Total (n = 43)	Country of origin				
		Guinea Bissau (n = 15)	Cape Verde (n = 14)	Angola (n = 10)	Mozambique (n = 2)	São Tomé e Príncipe (n = 2)
Solid tumors, n (%)	33 (76.7)	10 (66.7)	11 (78.6)	9 (90.0)	1 (50.0)	2 (100)
Glioma	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50.0)
Hepatoblastoma	1 (2.3)	0 (0)	0 (0)	0 (0)	1 (50.0)	0 (0)
Nephroblastoma	1 (2.3)	1 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)
Neuroblastoma	1 (2.3)	1 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)
Osteosarcoma	3 (7.0)	1 (6.7)	2 (14.3)	0 (0)	0 (0)	0 (0)
Rhabdomyosarcoma	5 (11.6)	1 (6.7)	3 (21.4)	1 (10.0)	0 (0)	0 (0)
Retinoblastoma	21 (48.8)	6 (40.0)	6 (42.3)	8 (80.0)	0 (0)	1 (50.0)
Leukemia, n (%)	10 (23.3)	5 (33.3)	3 (21.4)	1 (10.0)	1 (50.0)	0 (0)
ALL B/T	6 (14.0)	2 (13.3)	3 (21.4)	1 (10.0)	0 (0)	0 (0)
AML/CML	3 (7.0)	2 (13.3)	0 (0)	0 (0)	1 (50.0)	0 (0)
JMML	1 (2.3)	1 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)
Relapse, n (%)	10 (23.3)	4 (26.7)	4 (28.6)	2 (20.0)	0 (0)	0 (0)
Under surveillance, n (%)	25 (58.1)	6 (40)	9 (64.3)	7 (70)	2 (100)	1 (50)
Deaths, n (%)	14 (32.6)	6 (40)	4 (28.6)	3 (30)	0 (0)	1 (50)

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; JMML: juvenile myelomonocytic leukemia.

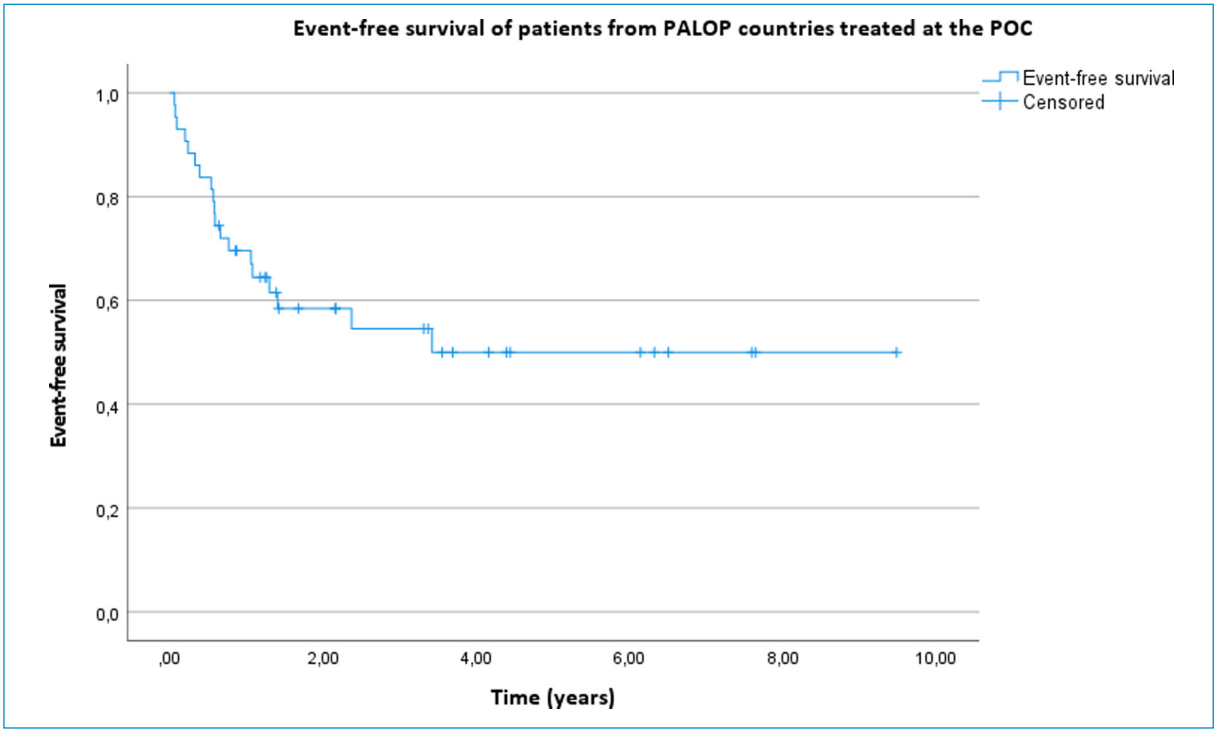

Figure 1. Event-free survival of patients from PALOP treated at the POC (Kaplan-Meier curve).

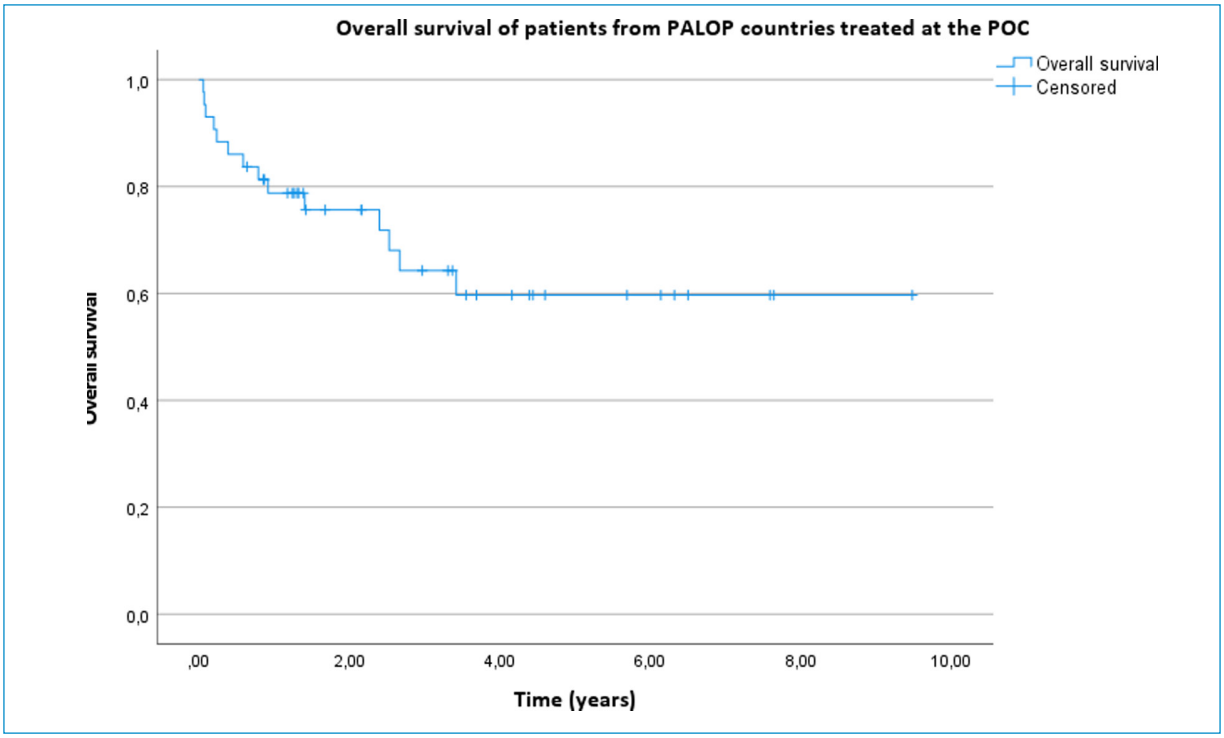

Figure 2. Overall survival of patients from PALOP treated at the POC (Kaplan-Meier curve).

Currently, 58.1% (n = 25) of patients have completed treatment: 46.5% (n = 20) are under surveillance at the POC and 11.6% (n = 5) are being followed up at another hospital or in their country of origin. Of the remaining patients, 9.3 % (n = 4) are undergoing treatment and 32.6% (n = 14) have died. The overall survival curve of the sample is presented in figure 2.

A statistically significant relationship was found between the presence of metastatic disease and mortality ($p < 0.001$): of the eight patients with metastasis, seven (87.5%) died. However, of the 14 patients who died, 10 (71.4%) had solid tumors (four with retinoblastoma, two with rhabdomyosarcoma, two with osteosarcoma, one with neuroblastoma, and one with glioma), of which seven (50.0%) had metastatic disease.

Excluding cases of retinoblastoma, out of a total of 22 patients, 54.5% (n = 12) had solid neoplasms and 45.5% (n = 10) had leukemia. Disease recurrence was observed in 18.2% (n = 4) of patients and 45.5% (n = 10) died.

Discussion

This is a heterogeneous sample in terms of the origin of the patients followed at the POC, with the countries of Guinea-Bissau, Angola, and Cape Verde representing 90% of the patients observed at the POC. The high number of patients from Guinea-Bissau can be justified by the voluntary cooperation between members of the POC and doctors from this country, enabling discussion and perhaps earlier referral for these patients. In Angola and Mozambique, there are Pediatric Oncology Services, and therefore greater diagnostic accuracy and treatment capacity, with less need for evacuation of this type of pathology to Portugal. Although a high number of patients came from Angola, this is justified by the significant percentage of patients (80%) who did not come through the evacuation process but rather by their own means or with the support of Angolan charity institutions.

The epidemiology of neoplastic diseases on the African continent differs significantly from that described in HICs.[18] In many centers, the lack of complementary diagnostic methods leads to underdiagnosis. However, some oncological diseases are more common on this continent, particularly those related to infections (Kaposi's sarcoma, Burkitt's lymphoma, Hodgkin's lymphoma, and hepatocellular carcinoma) and embryonal neoplasms (such as retinoblastoma and nephroblastoma).[18-20] According to Stefan DC et al.,[18] who evaluated the distribution of pediatric cancer in Africa, the most frequent pediatric tumors on this continent were lymphomas, nephroblastoma (which can have an incidence of over 20% in some countries), Kaposi's sarcoma, and retinoblastoma. According to the *Registo Oncológico Nacional de Todos os Tumores na*

População Residente em Portugal, in 2020,[5] the main diagnoses up to the age of 19 were CNS tumors at 15.7%, acute lymphoblastic leukemia at 11.6%, followed by non-Hodgkin's lymphomas at 9.6%, and bone tumors at 8.3%. In the sample presented, solid tumors were the most common, accounting for 76.7% of cases. Among these, the most common was retinoblastoma, identified in 48.8% of patients. As we mentioned before, this is one of the most common neoplasms in some African countries. It is simple to diagnose and, if diagnosed early, has a high cure rate.[18] In Portugal, in 2020, it represented about 0.8% of oncological diagnoses.[5] However, it is important to note that the POC of the ULS Coimbra collaborates with the only National Reference Centre for Onco-Ophthalmology. For this reason, all cases of retinoblastoma referred to Portugal are directed to this center, unlike other malignant tumors, which may explain the high prevalence of this pathology. In this case, high mortality was observed among retinoblastoma cases, with 19.0% of deaths (n = 4), which may be justified by delayed diagnosis and a high rate of metastasis (37.5%). Excluding retinoblastoma cases, leukemia was the most frequent diagnosis, observed in 45.5% of the remaining patients. This sample did not show a low incidence of this pathology in LMICs, which can probably be explained by the fact that this is a convenience sample and thus not representative of the PALOP population.[21] Regarding soft tissue sarcomas, these represent 4-8% of all pediatric neoplasms in Caucasian populations, and 4.9% in Portugal.[5] Of these, two-thirds to three-quarters are rhabdomyosarcomas. In the African continent, the incidence of this neoplasm is very variable and based on limited scientific data.[19] In this sample, it accounts for 11.6% of cancer cases, making it the third most common and significantly higher than reported in our country, probably due to greater accessibility in diagnosis. Bone tumors represent about 5% of all neoplasms in children. Their incidence in African countries is not clearly described, as histological confirmation is not always available. However, osteosarcoma appears to be the most common bone neoplasm.[19] In this study, it accounts for 7% of cancer cases, similar to the known incidence in Portugal.[5] They presented a poor prognosis, probably due to late referral: all three cases presented with metastatic disease and two eventually died. Regarding CNS tumors, these are the second most commonly described malignant disease in children in HICs, which seems to be related to the high availability of diagnostic methods. In the African continent and other LMICs, the lower incidence rates probably reflect the difficulty in accessing neuroradiology exams, with a consequent delay in diagnosis and underdiagnosis of this pathology.[18,21] The incorrect assumption of infectious differential diagnoses, such as cerebral malaria, tuberculous meningitis, and bacterial meningitis, also appears to contribute to this underdiagnosis.[18] In this study, only one CNS tumor case was identified, corresponding to 2.3% of the total, which is quite different from Portuguese records, where it is the most frequent oncological diagnosis in the pediatric age.[5] Regarding embryonal neoplasms, nephroblastoma is one of the most common solid tumors in Africa, with an incidence of over 20% in some countries, while in HICs it does not exceed 6-7%.[18] Contrary to expectations, only one case was identified in this sample. Neuroblastomas account for 6-10% of all childhood cancers. In Africa, the incidence is much lower, which probably reflects, once again, the lower accessibility of complementary diagnostic methods,[19] which is consistent with the results of this sample, with only one case identified.

This sample does not reflect the distribution of oncological disease in PALOP, as not all diagnosed cancer cases are referred to Portugal because there are Pediatric Oncology Services in two of these countries. It only evaluates the cases referred to the POC of the ULS Coimbra. There is underdiagnosis or death of some children who are referred or who do not get referred for evacuation. These factors create bias in the sample, which may explain the high number of leukemia cases in our study, which was not expected in a sample from an LMIC.

It is essential to understand the epidemiology of oncological disease in LMICs and to create effective policies for the early diagnosis and treatment of this pathology. Thus, it is crucial to create or update national cancer disease registries, which are still scarce.[15] The lack of resources available makes these countries dependent on international collaboration, so governments must implement and finance local cancer policies.[15] A significant improvement in the treatment outcomes of Francophone African children with oncological disease has been achieved through various forms of international collaboration with HICs, particularly with France.[20] Partner countries have contributed not only to the training of healthcare professionals skilled in oncological care, but also to the creation and development of infrastructure, complementary diagnostic methods, and treatment protocols for oncological disease adapted to LMICs. They have also provided a large percentage of the funds needed to achieve these goals.[20] Priority should be given to interventions that also improve general pediatric care, especially through the enhancement of supportive care and complementary diagnostic

methods. Thus, the existing local infrastructure should be the starting point for any initiative in cancer treatment.[22] International collaboration can also facilitate the evacuation of these patients for treatment after referral, as is the case with the established protocols with the Portuguese government. However, based on the results of this study, it can be seen that, although most patients arrive in Portugal through the evacuation process, it takes far too long than would be necessary in this context.

Despite the delay in diagnosis and the consequent presence of metastatic disease, the survival rate was 67.4%, significantly higher than the 20-40% observed in LMICs.[20] This rate can be partly justified by the high incidence of retinoblastomas, which have a good prognosis; excluding these cases, the survival rate drops to 54.5%.

The limitations of this study have been presented throughout the discussion, particularly the fact that it is based on a convenience sample that evaluates only the cases referred to the POC of ULS Coimbra. Finally, it should be noted that, despite reflecting 10 years of oncological disease evacuated from PALOP, the sample size is small, which limits the drawing of reliable conclusions.

Conclusion

The epidemiological analysis of oncological disease in this sample from African countries reveals significant disparities in incidence patterns and predominant neoplasms compared to those described in the LMICs. This study found a high prevalence of solid tumors in children and adolescents, especially retinoblastomas, which emerged as the most common neoplasm. Mortality was lower than observed in LMICs, probably due to the high number of children with retinoblastoma and the low number of children with metastatic disease.

The creation or updating of national oncological disease registries is essential for understanding the epidemiology and developing effective policies to combat pediatric cancer in LMICs. The lack of resources, coupled with limited access to adequate healthcare, leads to diagnostic delays and underdiagnosis of oncological disease, as well as the low survival rates seen in these populations. Thus, international collaboration plays a vital role in enhancing healthcare by providing training, developing infrastructure, and offering financial support. The mortality rate in these countries could be reduced by prioritizing access to appropriate diagnostic and treatment methods, as well as ensuring the rapid evacuation of these children. Furthermore, improving diagnosis, facilitating healthcare access, and increasing public awareness of these conditions are crucial to ensuring medical help is sought in time.

Author contributions

C. Martins: conception and design of the study, report, review, or another type of work; acquisition of data either from patients, research studies, or literature; drafting the article; final approval of the version to be published; agreement to be accountable for the accuracy or integrity of the work. S. Silva: analysis or interpretation of data from patients, research results, or literature search; critical review of the manuscript for important intellectual content; final approval of the version to be published; agreement to be accountable for the accuracy or integrity of the work. F. Curinha: analysis or interpretation of data from patients, research results, or literature search; drafting the article; final approval of the version to be published; agreement to be accountable for the accuracy or integrity of the work. M. Jerónimo: drafting the article; final approval of the version to be published; agreement to be accountable for the accuracy or integrity of the work. M.J. Brito: critical review of the manuscript for important intellectual content; final approval of the version to be published; agreement to be accountable for the accuracy or integrity of the work.

Previous presentations

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

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

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ORIGINAL ARTICLE

Home hospitalization as a safe and well-accepted new approach: a retrospective cross-sectional study at a level II hospital

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Abstract

Introduction and Objectives: Pediatric home hospitalization (PHH) is a promising alternative to conventional inpatient care for selected acute pediatric conditions. This study aims to describe our first year of experience and to evaluate the safety, efficacy, and quality of care provided by the Pediatric Home Hospitalization Unit (PHHU) in a level II hospital in Lisbon. **Methods:** A retrospective cross-sectional study was conducted, including all patients admitted to the PHHU between June 2023 and May 2024. Data was obtained from clinical records and from caregiver satisfaction surveys administered prior to admission and following discharge. Statistical analyses were performed using IBM SPSS Statistics software (version 29.0.0, IBM Corp., Armonk, NY, USA). **Results:** There was a total of 211 admissions (60.7% male; median age 4.1 years). Infectious diseases were the most common reason for admission (78.7%), particularly deep neck and skin/soft tissue infections, all treated at home with intravenous antibiotics (54.2% using continuous infusion systems). Other reasons included sickle cell disease crises (6.2%) and initial diabetes management (6.2%). The median length of stay was 2.5 days. Eleven patients required readmission to hospital. Caregiver feedback was highly positive: 87% found the workload to be the same or lower than expected; 81% reported less disruption to daily routines ($p < 0.05$); and 95% noted improvements in at least one domain of child well-being. While 77% anticipated an excellent experience, 92% reported it exceeded expectations ($p < 0.05$). Most (86.4%) preferred home care, and 97% would opt for PHH again. **Discussion:** PHH proved to be a safe, effective model with high caregiver satisfaction. These results support the potential for the broader adoption of PHH, enhancing pediatric care and family-centered outcomes.

Hospitalização domiciliária como uma abordagem nova, segura e bem aceite: um estudo retrospetivo transversal num hospital de nível II

Resumo

Introdução e Objetivos: A hospitalização domiciliária pediátrica (HDP) constitui uma alternativa promissora ao internamento convencional para determinadas patologias agudas em idade pediátrica. Este estudo tem como objetivo descrever a experiência do primeiro ano de funcionamento e avaliar a segurança, eficácia e qualidade dos cuidados prestados pela Unidade de Hospitalização Domiciliária Pediátrica (UHDP) de um hospital de nível II em Lisboa. **Métodos:** Estudo descritivo e retrospetivo, realizado com todos os doentes admitidos na UHDP entre junho de 2023 e maio de 2024. A recolha de dados baseou-se

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em registos clínicos e questionários de satisfação preenchidos pelos cuidadores antes da admissão e após a alta. A análise estatística foi realizada com recurso ao SPSS (versão 29.0.0, IBM Corp., Armonk, NY, USA). **Resultados:** Houve um total de 211 admissões (60.7% do sexo masculino; idade mediana de 4,1 anos). As patologias infeciosas foram as mais prevalentes (78.7%), destacando-se as cervicais profundas e cutâneas/tecidos moles, todas tratadas com antibioterapia endovenosa no domicílio (54.2% com sistemas de infusão contínua). Seguiram-se manifestações agudas de doença falciforme (6.2%) e diabetes inaugural (6.2%). A mediana de dias de internamento foi 2.5. Onze doentes necessitaram de reinternamento hospitalar. A satisfação dos cuidadores foi elevada: 87% consideraram a carga de trabalho igual ou inferior à expectável; 81% referiram menor impacto nas rotinas diárias ($p < 0.05$); e 95% notaram melhorias em pelo menos um domínio do bem-estar da criança. Embora 77% antecipassem uma experiência excelente, 92% referiram que esta foi superada ($p < 0.05$). A maioria (86.4%) preferiu o domicílio e 97% voltariam a recorrer à HDP. **Discussão:** A HDP demonstrou-se um modelo seguro e eficaz, com elevada aceitação pelos cuidadores. Estes resultados sustentam o seu potencial para uma implementação mais ampla, promovendo cuidados centrados na criança e na família.

Keywords: Home hospitalization. Pediatric. Therapeutic. Satisfaction. Caregivers.

Keypoints

What is known

- Home hospitalization is an outpatient care model where patients transition from traditional inpatient care to receiving the same treatment at home.
- In pediatric care, illness and hospitalization represent a crisis, mainly due to children's limited coping mechanisms for stress.
- Hospital admission should only occur when a child's condition cannot be managed at home or day hospitals (the Charter of the Rights of Children in Hospital).

What is added

- This is a pioneering project at the national level, with no published data available from Portugal to date. Our study reveals that the PHH model may provide high-quality healthcare, optimizing family and hospital resources, offering early hospital discharge, and minimizing the impact on family dynamics.
- The PHH model demonstrates its safety and effectiveness in managing different pathologies and treatments when inclusion criteria are met.
- PHH has shown great results that support its viability, supporting the potential for its national and global expansion.

Introduction

In healthcare, we face the challenge of ensuring quality and excellence in care while addressing the negative effects inherent to hospitalization. To meet this challenge, new care delivery models have emerged, often redefining the roles of hospitals and outpatient care. Home hospitalization is one such outpatient care model where patients transition from traditional inpatient care to receiving the same treatment at home.[1,2] Furthermore, studies reveal that this hospitalization model has proven to be effective, safe, and efficient, while also contributing to an improved quality of life for patients, their families, and caregivers.[3,4,5]

In pediatric care, illness and hospitalization represent a crisis, mainly due to children's limited coping mechanisms for stress. Additionally, removing a child from their familiar environment increases their vulnerability.[1,6] Therefore, as stated in the Charter of the Rights of Children in Hospital, hospital admission should only occur when a child's condition cannot be managed at home, in outpatient clinics, or day hospitals.[7] Keeping children in their family environment is often more beneficial than conventional hospitalization, whenever the clinical situation allows this to happen.[2] In line with the concept of humanization and aiming to improve the quality of care, new international pediatric hospitalization models have emerged based on the proven benefits seen in adult care, showing similarly positive results.[2-4,6] However, no national data has been published to date.

Pediatric home hospitalization (PHH) is therefore defined as an alternative care model for children with acute or exacerbated chronic conditions, ensuring the continuity of therapeutic interventions in the home setting, as long as the specific clinical, social, and geographic criteria are met.[1,2,8]

The aim of this study is to describe our experience and to evaluate the efficacy, safety, and perceived quality of care provided during the first year of Pediatric Home Hospitalization Unit (PHHU) activity.

Methods

We conducted a retrospective cross-sectional, descriptive, and quantitative study of the patients admitted to the PHHU from a level II hospital in Lisbon

during its first 12 months of activity (June 1, 2023 to May 31, 2024). We also analyze the children's and caregiver's experience on PHH.

Patients

Out of all the children referred to the PHHU, only those who met the inclusion criteria and none of the exclusion criteria (Supplementary Table 1). were admitted for continued care through home hospitalization.

When a potential candidate is identified in the pediatric ward, the attending physician meets with the PHHU team members to jointly review the inclusion and exclusion criteria. Once the criteria are met, the family is informed and given the option to proceed with home-based care. The caregiver and, when appropriate, the child/adolescent sign the informed consent, accepting PHH and participation in this study. The medical and nursing teams provide the necessary training to caregivers, ensuring they can correctly administer treatments at home and solve simple problems with the catheter and infusion system. Every case is assessed by the social worker to ensure the necessary social criteria are present for incorporation into the program.

The PHHU operates on-site from 8 a.m. to 11 p.m., with nighttime support provided by the lead pediatric ward nurse via telephone, who coordinates with the on-call internal pediatric physician if necessary, ensuring 24/7 coverage. Home visits are scheduled based on medication schedules and clinical monitoring needs: two to three visits each day by the nursing team, one of which includes a physician. On weekends and public holidays, only nursing visits are conducted, with cases discussed with the internal pediatric physician when necessary. A follow-up telephone call is conducted 24 to 72 hours after discharge to assess the child's clinical status, ensure treatment adherence, reinforce caregiver training, and clarify any remaining questions.

It should be noted that, to date, no children have been admitted to home hospitalization with continuous cardiorespiratory telemonitoring. Blood samples were collected at home, while other examinations and specialist consultations were conducted during hospital visits, after which patients returned home to continue hospitalization.

Data collection

Demographic data was collected, including patient age, sex, diagnosis, procedures/treatments, length of hospitalization, hospital visits (for examinations, treatments, or consultations with other specialties), hospital returns (defined as the need for a return to a conventional inpatient setting following a period of home hospitalization), and readmissions (defined as patients who were readmitted within a month after being discharged from the PHHU).

During the first year of PHHU activity, all admitted families received a pre-admission questionnaire addressing their reasons for accepting home hospitalization and their expectations regarding the process. A post-discharge questionnaire was also provided to evaluate their experience and satisfaction. Both questionnaires were answered by the caregivers.

Analysis

The data was reviewed retrospectively from an internal database. Relative and absolute frequencies were calculated for qualitative variables. Quantitative variables were analyzed using measures of central tendency and dispersion, including median, minimum, and maximum values. The responses from questionnaires were analyzed, and statistical evaluation was performed using SPSS (version 29.0.0, IBM Corp., Armonk, NY, USA), applying the Wilcoxon test. A p value of < 0.05 was considered statistically significant.

Results

Patients

During the study period, there was a total of 265 referrals to the PHHU, resulting in 211 admissions, corresponding to 196 patients, with a median age of 4.1 years (minimum of 12 days; maximum of 17.7 years). The distribution by sex and age group, and the reasons for non-admission to the PHHU, are presented in table 1.

Hospitalization

We observed a median hospitalization duration of 2.5 days (minimum of one day; maximum of 17 days), totaling 811 days of home hospitalization among the admitted patients. There were 1706 home visits.

Diagnoses

Among the admitted patients, infectious diseases were the most common diagnoses, particularly deep neck infections and skin and soft tissue infections. Among non-infectious conditions, acute manifestations of sickle cell disease and inaugural type 1 diabetes predominated. Table 2 details the distribution of

diagnoses at admission and the number of hospitalizations of patients with chronic conditions.

Treatments, complementary diagnostic means, visits to hospital, and hospital returns

The main treatments and care involved antibiotic therapy, analgesia, education (especially in type 1 diabetes – involving children, parents, grandparents, other family members, and even teachers), and motor rehabilitation. All the patients with an infectious pathology were treated with intravenous antibiotic therapy, 90 (54.2%) of whom were on ambulatory infusion systems. There were four patients with an epicutaneous catheter and one with a central venous catheter, and no catheter complications were recorded.

Some admitted patients required scheduled hospital visits for complementary diagnostic examinations or specialist consultations. Table 3 summarizes these episodes.

There were 11 (5.2%) hospital returns (i.e., transfers from home hospitalization to conventional hospitalization), all of which were admitted to the pediatric ward. None required intensive care or presented clinical deterioration (Table 3).

There were five readmissions after discharge from the PHHU: two infants with poor weight progression (previously admitted with a urinary tract infection); one with exacerbation of anemia and one with pneumonia (in two patients with sickle cell disease, previously admitted with a splenic sequestration); and one urinary tract infection (in a chronic patient with uropathy and multiple urinary tract infections).

Satisfaction

In total, 196 caregivers responded to the pre-admission questionnaire, and 184 to the post-discharge questionnaire.

Caregivers mainly agreed to being incorporated into the PHHU for health-related reasons and for the comfort of home. Table 4 shows the detailed distribution.

Most caregivers anticipated an equal or lower workload and less disruption of daily routines compared to hospital care, which was confirmed after discharge. Satisfaction exceeded expectations, with nearly all caregivers willing to repeat PHHU if needed (Table 5).

In terms of children's comfort, sleep, eating, play, and hygiene, 95% felt PHHU was better than the hospital in at least one domain, matching pre-admission expectations (Table 6).

Table 1. Characterization of patients admitted to the PHHU (sex and age) and reasons for the non-admission of patients

Admitted patients	
Sex	**n (%)**
Male	119 (60.7%)
Age group (distribution)	
0-3 years	76 (38.8%)
0-6 months	27 (13.8%)
6-12 months	6 (3.1%)
12-24 months	25 (12.8%)
2-3 years	18 (9.2%)
3-6 years	37 (18.9%)
6-9 years	33 (16.8%)
9-12 years	16 (8.2%)
12-15 years	21 (10.7%)
15-18 years	13 (6.6%)
Non-admitted patients (reasons)	
Reasons	**n (%)**
They do not meet the clinical criteria (clinical instability or comorbidities not manageable at home)	18 (33.3%)
Decline of the home hospitalization model	15 (27.8%)
They do not meet geographic criteria	5 (9.2%)
Lack of a caregiver capable of providing care	5 (9.2%)
Inadequate housing conditions	4 (7.4%)
Treatments unfeasible in the PHHU	4 (7.4%)
Lack of available slots	3 (5.7%)
Total	54

PHH: pediatric home hospitalization.

Discussion

The first home hospitalization unit in Portugal was established in 2015, focusing on adult care.[3] This model quickly confirmed the international data that was already known, demonstrating multiple advantages by providing a personalized approach tailored to the individual reality of each patient in their usual environment, proving to be a valid alternative to conventional hospital admission, leading to the rapid expansion of similar units across the country.[5]

PHH provides a personalized approach tailored to the individual realities of each child or adolescent within their family home environment. This hospitalization

Table 2. Diagnoses at admission to the PHHU and their division into infectious and non-infectious pathologies and the number of hospitalizations of chronic patients in the PHHU

Infectious pathologies	n (%)
Deep neck	41 (19.4%)
Skin and soft tissue	35 (16.6%)
Urinary tract	29 (13.7%)
Respiratory tract	28 (13.3%)
Gastrointestinal tract	14 (6.6%)
Occult bacteremia	9 (4.3%)
Bone and/or joint	7 (3.3%)
Central nervous system	3 (1.5)
Total	166 (78.7%)
Non-infectious pathologies	**n (%)**
Acute manifestations of sickle cell disease	13 (6.2%)
Type 1 diabetes	13 (6.2%)
Post-operative care	4 (1.9%)
Lower respiratory diseases	2 (0.9%)
Neurological diseases	2 (0.9%)
Constipation	2 (0.9%)
Nephrotic and nephritic syndromes	2 (0.9%)
Others	7 (3.4%)
Total	45 (21.3%)
Chronic disease	**Number of hospitalizations**
Sickle cell disease	35 (16.6%)
Type I diabetes	13 (6.2%)
Uropathy	7 (3.3%)
Neurological disease	2 (0.9%)
Inflammatory bowel disease	1 (0.5%)
Total	58 (27.5%)

Table 3. Characterization of hospitalizations in the PHHU: scheduled visits to the hospital and hospital returns

Scheduled visits to the hospital	Number of episodes
Assessment by subspecialty	16
Imaging tests	10
Motor rehabilitation	4
Total	30
Hospital returns	**Number of patients**
Clinical worsening	6 (2.8%)
Non-compliance with admission criteria	2 (0.9%)
Scheduled for surgery/invasive tests	2 (0.9%)
Caregiver decision	1 (0.6%)
Total	11 (5.2%)

Table 4. Responses to the question "Reasons for accepting incorporation into the PHHU"*

Reasons for accepting incorporation into the PHHU	n (%)
For my child's health	77 (40.5%)
For the comfort of being at home for my child and the rest of the family	58 (30.5%)
Because of the complexity it adds to our family dynamic to have my child hospitalized	24 (12.6%)
Because this was the advice of the medical team	20 (10.5%)
Because it makes it easier to balance family help with work	7 (3.7%)
Because of the financial burden of having my child hospitalized	4 (2.2%)

*Caregivers could select more than one option. There was a total of 190 responses.

model aims to ensure timely and safe care while maintaining continuity of treatment focused on the patient's needs, thereby promoting the patient's well-being and recovery.[9] In contrast with other studies, where most patients were children between the ages of three and six years,[2,10-12] our study found that a significant proportion of patients were between zero and three years old (38.8%). This demonstrates that this hospitalization model is suitable even for very young children, for whom continuing care in their family environment may be especially beneficial. By receiving care in their own environment, they experience reduced external stress and disruption.[6] Moreover, this model may help maintain daily family routines, namely the breastfeeding of younger siblings, which can otherwise be disrupted due to the hospitalization of the sick sibling.

The median length of hospital stay, at 2.5 days, aligns with the literature, which reports medians ranging from two to four days.[2,10-12]

The principal findings suggested that home care during the acute phase is particularly important for infectious pathologies,[2,8,13] as also observed in our unit, where these were the most common diagnoses at admission (78.7%).

Table 5. Evaluation of the caregiver's expectation (based on the response to the pre-admission questionnaire) versus their actual experience (based on the response to the post-discharge questionnaire)

Variables	Expectation	Actual experience	p
Workload	**n (%)**	**n (%)**	
More	23 (11.7%)	24 (13.0%)	0.932
Equal	108 (55.1%)	106 (57.6%)	
Less	53 (27.1%)	52 (28.3%)	
No response	12 (6.1%)	2 (1.1%)	
Affects daily routine			
More	19 (9.7%)	10 (5.4%)	0.007
Equal	38 (19.4%)	26 (14.1%)	
Less	130 (66.3%)	148 (80.5%)	
No response	9 (4.6%)	0	
Overall view of the PHHU			
1 = Poor	0	0	< 0.01
2 = Weak	0	0	
3 = Average	3 (1.5%)	0	
4 = Good	44 (22.4%)	14 (7.6%)	
5 = Excellent	144 (73.5%)	168 (91.3%)	
No response	5 (2.6%)	2 (1.1%)	
Overall, how will the child/adolescent feel at home?			
Better	160 (81.6%)	159 (86.4%)	0.466
Equal	28 (14.4%)	24 (13.1%)	
Worse	1 (0.5%)	0	
No response	7 (3.5%)	1 (0.5%)	

Most chronic diseases have episodes of exacerbation, and this hospitalization model has also proven to be effective in such cases.

Sickle cell disease is a chronic condition that can lead to multiple hospitalizations,[14,15] which may significantly impact patients' lives and family dynamics, and PHH may address their needs within their home environment. In type 1 diabetes, these benefits are even more pronounced, as PHH can play a crucial role in empowering caregivers to manage this chronic disease in their own environment while involving other adults responsible for the child's care.[10,11] As concerns uropathy, all seven admissions were due to urinary tract infections in the same child, reflecting a significant reduction in hospital readmissions for this chronic condition. This underscores the significant impact that home hospitalization can have on children with chronic diseases, their families, and their daily routines.

Regarding scheduled visits to the hospital, these are essential for providing the best continuation of care for our children and adolescents. Effective scheduling requires constant communication and discussion with other specialties, who are invited to provide input on decisions regarding the transfer to the PHHU and to maintain follow-up during hospitalization at home.

Our results suggest that home care can be seen as effective and secure, as shown in other studies.[2,8,13] There were 5.2% returns and 2.4% readmissions – similar to other studies, which report rates ranging from 3% to 13%.[2,7,16,17] In every case, readmission was due to clinical reasons that were different to the first

Table 6. Evaluation of the child/adolescent's expectation (based on the response to the pre-admission questionnaire) versus their actual experience (based on the response to the post-discharge questionnaire) from the caregiver's perspective

Variables	Expectation	Actual experience	p
Comfort	**n (%)**	**n (%)**	
Better	158 (80.6%)	157 (85.3%)	0.869
Equal	21 (10.7%)	19 (10.3%)	
Worse	2 (1.0%)	0	
No response	15 (7.7%)	8 (4.4%)	
Sleep	**n (%)**	**n (%)**	
Better	150 (76.5%)	156 (84.8%)	0.796
Equal	25 (12.8%)	16 (8.7%)	
Worse	1 (0.5%)	4 (2.1%)	
No response	20 (10.2%)	8 (4.4%)	
Food	**n (%)**	**n (%)**	
Better	131 (66.8%)	143 (77.7%)	0.145
Equal	47 (24.0%)	33 (17.9%)	
Worse	0	0	
No response	18 (9.2%)	8 (4.4%)	
Play	**n (%)**	**n (%)**	
Better	156 (79.6%)	156 (84.8%)	0.131
Equal	18 (9.2%)	13 (7.1%)	
Worse	1 (0.5%)	0	
No response	21 (10.7%)	15 (8.1%)	
Hygiene	**n (%)**	**n (%)**	
Better	122 (62.2%)	121 (65.8%)	0.799
Equal	51 (26.1%)	51 (27.7%)	
Worse	0	0	
No response	23 (11.7%)	12 (6.5%)	

hospitalization and did not reveal clinical worsening. More than half of the cases involved chronic patients.

In terms of caregivers' experiences, 80.4% of caregivers felt that this model disrupted their daily routine less than expected, compared to conventional hospitalization ($p = 0.007$). Our findings align with other studies, which report that the primary satisfaction factors were increased opportunities for children to continue their schoolwork and for parents to continue to work, and more time spent with family.[7,18] Although reported by only 13% in our study, it is important to note that there were caregivers describing a greater workload with home hospitalization. Even though we did not analyze this data, this is significant, as it may indicate signs of fear, fatigue, and anxiety related to caring for a sick child at home.[19] Thus, it is important to prepare and involve parents in the care process from the time of admission, to enhance their ability to provide care and recognize warning signs. Future studies could further explore the demographic and psychosocial characteristics of caregivers and develop more targeted support strategies.

Also, 86.4% of caregivers felt that they were better at home than in conventional hospitalization. Home

care facilitates a continuation of normal life for the children and their families, with psychosocial benefits.[20,21] Analyzing caregivers' perspectives on how children/adolescents experienced this hospitalization model, in areas such as comfort, sleep, eating, and hygiene, 95% felt PHHU was better than the hospital in at least one domain, with no cases where caregivers felt the experience was worse than anticipated. These results may be linked to the aforementioned benefits, including greater privacy and comfort, as well as improved sleep and appetite.[19-21]

Finally, the fact that 97% of respondents would opt for this model again, if needed and if the admission criteria were met, helps validate home hospitalization as a safe alternative to conventional inpatient care. With an adequate team and support for patients and their families, early hospital discharge can lead to better financial management for the hospital without compromising patient care.[13] This is also expected to contribute, on the one hand, to a decrease in nosocomial infections and, on the other, to a reduction in hospitalization-related costs.[5]

Future studies should explore the broader socioeconomic impact of PHH – not only on families and healthcare systems, but also on society at large. Particular attention should be given to how this model may contribute to reduced parental work absenteeism, as well as to the different experiences of caregivers across different family structures and cultural backgrounds. It would also be important to investigate healthcare professionals' perspectives regarding this model. The multidisciplinary team's views on operational challenges and benefits would be a valuable complement.

Looking ahead, there are many opportunities for progress. Since most admissions are related to infectious diseases, it may be beneficial to consider direct referrals and admissions from the Emergency Department or Short-stay Observation Units, ensuring proper clinical and social assessment. To enable this development, it is essential to consider the consistent diagnostic profiles admitted to the PHHU and to monitor their progression, in order to identify conditions that present linear clinical behavior and are eligible for home hospitalization from the outset. At the same time, the direct involvement of a social worker for admitted cases will be necessary. For all of this to be feasible, it is crucial that all physicians are familiar with the PHHU admission protocol.

Limitations

The main limitations of our study include: (1) it is a descriptive and retrospective study, therefore the outcomes of different pathologies in home hospitalization compared to conventional hospitalization were not analyzed. A prospective, comparative study would be essential to determine the superiority or equivalence of the PHHU in terms of clinical outcomes; (2) a notable aspect of the study was the participants' willingness to complete the surveys, as well as the different methods of survey administration. The initial questionnaire was completed in the hospital, whereas the second questionnaire was administered after the acute home-hospitalization period. The assurance that medical care would continue may have contributed to the higher response rate for the first survey. Additionally, the questionnaires were not translated into other languages, which may limit their completion and comprehension. In a multicultural society, this may limit the participation of non-Portuguese-speaking caregivers, thereby affecting the generalizability of the results.

Conclusion

While the benefits of home hospitalization in adults are well-established, pediatric experiences remain underexplored in international literature. With this hospitalization model, it was possible to provide high-quality healthcare, improve access to care, optimize family and hospital resources, minimize the impact on family dynamics, and involve caregivers in the child's care in a home environment, ensuring comfort, satisfaction, and greater humanization of care. In this study, the PHH model demonstrates its safety and effectiveness in managing different pathologies and treatments when inclusion criteria are met. The positive reception from caregivers further supports its viability, supporting the potential for its national and global expansion. This study highlights PHH's strong caregiver acceptance, with most willing to repeat it if needed. These findings also suggest the potential for broader implementation to enhance patient and family comfort and care during hospitalization, for example, with the expansion of admissions from the Pediatric Emergency Department, as the team's learning curve progresses.

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Author contributions

All the authors declare that they have made a substantial contribution to the manuscript, meeting the established requirements: significant and direct intellectual contribution to the design and development of the article; participation in data analysis and interpretation; involvement in manuscript writing, revision of versions, and critical review of content; approval of the final version; and agreement to be accountable for the accuracy and integrity of the entire paper.

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Conflicts of interest

All authors declare that they have no conflicts of interest related to this paper.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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

Supplementary data

Supplementary data are available at DOI: 10.24875/PJP.25000026. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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PORTUGUESE JOURNAL OF PEDIATRICS

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ORIGINAL ARTICLE

Assessment of compliance regarding the first dose of the MMR vaccine, after the 2012 update of the Portuguese National Vaccination Program: a cross-sectional study in a Portuguese central hospital

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Abstract

Introduction and Objectives: In 2012, the Portuguese National Vaccination Program (PNVP) brought the first dose of the measles, mumps and rubella (MMR) vaccine forward, from 15 to 12 months. The main objectives of this study were to assess compliance with this recommendation and to identify which factors may be associated with incorrect vaccination. **Methods:** An observational cross-sectional study was conducted through anonymous surveys, delivered by hand, to caregivers of children attending the Pediatric Emergency Department of a Lisbon Public Hospital (PERLPH) between January and March 2023. Sociodemographic characteristics, the timing of the first MMR dose, and reasons for delay/non-vaccination were analyzed. An information leaflet on the 2020 PNVP and false contraindications was provided. **Results:** A total of 203 caregivers participated. Out of the children, 40.4% were immigrants or had immigrant parents; 95.6% resided in the Lisbon district and were aged between 13 months and 11 years old. Although 93.1% had received the first MMR dose, 27.1% were vaccinated with an average delay of 2.24 months. A statistically significant link between the immigrant population and the delay with the first MMR dose was identified (p value = 0.012). **Discussion:** Vaccination coverage at 12 months of age with the first MMR dose, in the studied population, was below the recommended threshold. Immigrant status, municipality of residence, and contextual national and international factors may impact vaccination rates. These findings underscore the need for targeted information campaigns and strategies to promote timely vaccination, particularly among vulnerable populations.

Keywords: PNVP. MMR. Compliance. Delay.

Avaliação do cumprimento da primovacinação com a VASPR, após a atualização de 2012 do Programa Nacional de Vacinação: um estudo transversal num hospital central português

Resumo

Introdução e Objetivos: Em 2012, o Programa Nacional de Vacinação (PNV), da Vacina contra o Sarampo, Parotidite Epidémica e Rubéola (VASPR) adiantou a primeira dose dos 15 para os 12 meses de idade. Os principais objetivos deste estudo foram avaliar: o cumprimento da primovacinação com a VASPR, aos 12 meses de idade; quais os fatores relacionados com

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a sua vacinação incorreta. **Métodos:** Estudo observacional, transversal, realizado através da aplicação de um inquérito anónimo, entregue em mão, aos acompanhantes das crianças que se dirigiram ao Serviço de Urgência Pediátrica de um Hospital Público de Lisboa, entre janeiro e março de 2023. Analisaram-se os parâmetros sociodemográficos, realização da primeira dose da VASPR e razões do possível atraso/não realização. Entregou-se um folheto informativo com o esquema vacinal mais recente e falsas contraindicações das vacinas. **Resultados:** Participaram 203 acompanhantes, sendo 40,4% das crianças imigrantes ou com pais imigrantes; 95,6% residiam no distrito de Lisboa, com idade compreendida entre os 13 meses e os 11 anos. Embora 93,1% tenham feito a primeira dose da VASPR, 27,1% realizaram com um atraso médio de 2,24 meses. Verificou-se uma relação estatisticamente significativa entre a população imigrante e o atraso na primovacinação com a VASPR (*p value* = 0,012). **Discussão:** A cobertura vacinal com a primeira dose da VASPR aos 12 meses, na população estudada, encontra-se abaixo do limite recomendado. O concelho de residência, ser integrante da população imigrante e os contextos nacionais e internacionais, podem influenciar a cobertura vacinal. Assim, é importante a implementação de campanhas de informação e estratégias para promover a vacinação atempada, principalmente em populações vulneráveis.

Palavras-chave: PNV. VASPR. Cumprimento. Atraso.

Keypoints

What is known

- A vaccination coverage against measles of at least 95% is required to meet the herd immunity threshold to achieve and sustain measles elimination.
- Socioeconomic factors, health or military crises, and disinformation campaigns can affect vaccination coverage rates in a population.
- Portugal has an MMR vaccination rate above 95%.

What is added

- The immigrant population is unequally covered compared to the non-immigrant population in terms of vaccination with the first dose of the MMR vaccine.
- Vaccination rates, when calculated using data from primary health care centers (PHCC), may be overestimated.
- The vaccination rate of the population in this study was < 95%.

Introduction

The Portuguese Nacional Vaccination Program (PNVP) was established in 1965 as universal, free of charge, and accessible to all Portuguese citizens.[1] Vaccination of children under 16 years of age requires the presence of the individual who has custody of the minor or to whom the minor has been entrusted, and it is possible to refuse vaccination, with all or any one vaccine.[1] The measles, mumps and rubella (MMR) vaccine is a trivalent live attenuated vaccine, which is included in the World Health Organization (WHO) immunization schedule and protects against three viral infections that generally occur in childhood.[2] In 1974, the first combined MMR vaccine was added to the WHO immunization program.[3]

According to the most recent WHO recommendations, the first dose of the MMR vaccine should be administered between nine and 15 months of age, with the second dose given either at least 28 days later or between four and 10 years of age. Two doses of the MMR vaccine are associated with a seroconversion rate of 95-98%.[4] Globally, between 2000 and 2019 vaccination coverage rates for the first dose of the measles vaccine increased from 72% to 85%, and from 18% to 71% for the second dose. Between 2000 and 2017, the annual incidence of measles reduced by 83% and mortality reduced by 80%.[4] In Portugal, the measles vaccination was included in the PNVP in 1973. Later, in 1987, the MMR vaccine was added to the PNVP, initially with a single dose at 15 months of age, and a second dose, administered between five and six years of age, was added three years later.[5] Through universal MMR vaccination, Portugal achieved measles and mumps elimination status in 2017, as verified by the WHO European Regional Commission for Verification of the Elimination of Measles and Rubella.[6]

In the 2012 PNVP update, the age to administer the first dose of the MMR vaccine was changed from 15 to 12 months.[7] Since then, various social, political, and public health developments may have affected the optimal timing of vaccination. Although European countries have high vaccination rates, over the last two decades, there has been a reemergence of measles outbreaks, with several European Union (EU) member states experiencing renewed community transmission of measles, mumps, and rubella.[2,3,8] One of the main reasons has been the growth of anti-vaccine movements and the decline in children's vaccination adherence due to parental refusal.[9] The COVID-19 pandemic may have introduced new concerns about vaccines, although Portugal continues to have the highest levels of confidence in vaccines in Europe.[10,11]

The objectives of this study were to evaluate compliance with MMR vaccination following the 2012 update of the PNVP, and to identify factors that may be associated with incorrect vaccination.

Methods

An observational, cross-sectional study was carried out through the application of an anonymous, voluntary survey, to a convenience, random sample of children's parents or caregivers who went to the Pediatric Emergency Department of one of Lisbon's public hospitals (PERLPH) between January and March 2023.

The study included children born between January 2012 and March 2022, and considered the updated 2012 scheme recommended by the PNVP regarding the first dose of the MMR vaccine. Questionnaires (Supplementary data) were delivered in person to caregivers who accompanied children to the PERLPH, between the ages of one year and 11 years and two months, and those caregivers were asked by the main investigator to review the Vaccination Bulletin (VB). The VB of these children was analyzed and, if unavailable, their vaccination calendar was consulted on the Health Data Platform. Participation was voluntary, although an informed consent form had to be signed prior to survey completion.

The confidentiality of the data obtained was respected. Ethical issues were considered during the course of this study, and it was approved by the Ethics Committee of the Institution where this study took place and the Medical Academic Center of Lisbon. Data collection took place over a period of three months, between January 10 and March 16, 2023.

The exclusion criteria were the absence of a signed informed consent form and data that was incomplete or poorly collected.

Sociodemographic data was collected, including the child's nationality (Portuguese, Brazilian, Sao Tomean, Angolan, Cape Verdean, Colombian, Chinese, Moroccan, Ukrainian, Russian, Algerian, French, and Turkish), date of birth (from January 2012 to March 2022), county of residence (Lisbon, Amadora, Odivelas, Loures, Sintra, Oeiras, Almada, Torres Vedras, Mafra, Salvaterra de Magos, Grândola, Cascais, Olhão, Alenquer, Seixal, Crato, Setúbal, Moita, and Vila Franca de Xira), and whether there was a delay or failure in being administered the primary MMR vaccination.

In cases of delayed vaccination, the duration of the delay in months and the underlying reasons for the delay or non-vaccination were documented. A vaccination delay was considered to be when the first dose of the MMR vaccine was administered after 12 months and 30 days of age. Primary MMR vaccination failure was defined as the absence of any documented administration of the vaccine. Incorrect vaccination was defined as when a vaccination delay or failure occurred.

Children who were born and/or whose parents were born outside the national territory were considered as immigrant population. Children who were born in Portugal and whose parents were also born in Portugal were considered as non-immigrant population.

The collected data was analyzed using the "Statistical Package for the Social Sciences" program (SPSS, Chicago, IL, USA), version 28.0 for Windows.

As this was predominantly an exploratory study, descriptive statistics were applied, including absolute and relative frequencies and measures of central tendency (average). To assess the independence of variables, a Chi-Square test (x^2) was performed to compare the immigrant and non-immigrant population regarding vaccination with the first MMR dose within or after 12 months and 30 days of age. A p value of < 0.05 was considered statistically significant.

Results

During the survey period, 211 caregivers were contacted, of whom eight declined to participate. Between January and March 2023, 203 surveys were included in the study, comprising 121 (59.6%) children of the non-immigrant population and 82 (40.4%) of the immigrant population. The sociodemographic characteristics of the population are presented in table 1.

In the studied population, 27.1% of children received the first dose of the MMR vaccine after 12 months and 30 days of age, with a minimum delay of one and a maximum of nine months, with an average delay of 2.24 months.

Out of the total population of this study (n = 203), born between January 2012 and March 2023, 14 (6.9%) children had not been vaccinated with the first dose of the MMR vaccine whereas 189 (93.1%) were vaccinated. Overall, 72.9% of the population received primary vaccination at the recommended age (12 months and zero to 30 days of age, according to the current PNVP). Among the unvaccinated children, 92.9% (n = 13) were from the immigrant population.

The three main reasons reported by caregivers for the delayed or non-administration of the first dose of the MMR vaccine were: no known reason (43.6%), lack of awareness of the PNVP (20%), and absence of a family doctor or difficulty scheduling an appointment

Table 1. Sociodemographic characteristics of the studied population

Variable		Absolute value	%
Year of birth	2012	12	5.9
	2013	14	6.9
	2014	11	5.4
	2015	25	12.3
	2016	15	7.4
	2017	24	11.8
	2018	30	14.8
	2019	21	10.3
	2020	25	12.3
	2021	22	10.8
	2022	4	2.0
County of residence	Lisbon	105	51.7
	Amadora	23	11.3
	Odivelas	20	9.9
	Loures	18	8.9
	Sintra	17	8.4
	Oeiras	5	2.5
Nationality	Portuguese	172	84.7
	Brazilian	15	7.4
	Sao Tomeans	5	2.5
	Angolan	2	1.0
Immigrant and/or with immigrant parents	Yes	82	40.4
	No	121	59.6

at the PHCC (14.5%). Only two caregivers (3.6%) refused vaccination.

Regarding birth cohorts, failure to receive the first dose of the MMR vaccine on time was most frequent among children born between 2012 and 2015. Data from the 2022 cohort was not considered valuable due to the small sample size. Table 2 presents the proportions of children vaccinated on time or with a delay/failure, according to their year of birth, county of residence, and inclusion in the immigrant population.

In terms of the county of residence, only data from Sintra, Loures, Lisbon, Amadora, and Odivelas was valued, as the number of respondents residing in each of the remaining counties was too small for meaningful interpretation (Table 2). The population density and proportion of immigrants with resident status in each of those specific counties are presented in table 3.[12]

Considering the immigrant population, 36.6% did not receive the first MMR dose at the correct time, compared with 20.7% in the non-immigrant population.

A statistically significant association between the immigrant population and receipt of the first MMR dose after 12 months and 30 days was established (p value = 0.012) (Table 4).

Discussion of the results

According to WHO, vaccination coverage of at least 95% is needed for herd immunity against measles in a population.[3,11] The General Directorate of Health (GDH)

Table 2. Was the child vaccinated at the correct time?

Variable			Yes	No	Total
Year of birth	2012	Absolute value	8	4	12
		%	66.7	33.3	-
	2013	Absolute value	6	8	14
		%	42.9	57.1	-
	2014	Absolute value	5	6	11
		%	45.5	54.5	-
	2015	Absolute value	17	8	25
		%	68.0	32.0	-
	2016	Absolute value	11	4	15
		%	73.3	26.7	-
	2017	Absolute value	21	3	24
		%	87.5	12.5	-
	2018	Absolute value	22	8	30
		%	73.3	26.7	-
	2019	Absolute value	15	6	21
		%	71.4	28.6	-
	2020	Absolute value	22	3	25
		%	88.0	12.0	-
	2021	Absolute value	17	5	22
		%	77.3	22.7	-
	2022	Absolute value	4	0	4
		%	100	0.0	-
	Total	Absolute value	148	55	203
		%	71.9	27.1	-
County of residence	Lisboa	Absolute value	76	29	105
		%	72.4	27.6	-
	Amadora	Absolute value	17	6	23
		%	73.9	26.1	-
	Odivelas	Absolute value	16	4	20
		%	80.0	20.0	-
	Loures	Absolute value	13	5	18
		%	72.2	27.8	-
	Sintra	Absolute value	9	8	17
		%	52.9	47.1	-
Immigrant and/or with immigrant parents	Yes	Absolute value	52	30	82
		%	63.4	36.6	-
	No	Absolute value	96	25	121
		%	79.3	20.7	-
	Total	Absolute value	148	55	203
		%	72.9	27.1	-

Table 3. Counties of residence included in the discussion of the results

Counties of residence	Population density (average number of individuals per km2)	Proportion of immigrants with resident status (%)
Lisbon	5466	19.9
Amadora	7310	13.9
Odivelas	5642	14.0
Loures	1215	10.7
Sintra	1215	11.0

Table 4. Link between the immigrant population and the delay in the first dose of the MMRV

Variable	Value	df	Asymptotic significance (bilateral) - p
Pearsons chi-square	6.275	1	0.012
Continuity correction	5.494	1	0.019
Number of valid cases	203	-	-

calculates the vaccination coverage as the proportion (as a percentage) of vaccinated users in certain birth cohorts. Those vaccination coverages are assessed using data from the VACINAS platform by Shared Services of the Ministry of Health, a platform where nurses enter information when a vaccine is administered. All the NVP vaccines are administered in PHCCs.[13] According to the last annual vaccination report released by the GDH, the vaccination coverage rate for the first dose of the MMR vaccine was 98% (in the 2021 cohort) and 95% for the second dose (in the 2017 cohort). Data presented by the GDH in the 2021 and 2022 PNVP bulletin was superimposable.[13,14]

The median age of our sample is 5.79 years. The vaccination coverage of primary vaccination with MMR in this study sample was slightly lower, namely 93.1%, and at 12 months of age it was only 72.9%, which may indicate the existence of susceptible pockets with children being vaccinated after 12 months and 30 days, in the district of Lisbon. Of the 14 (6.9%) children aged between two and seven years who did not receive any doses of the MMR vaccine, 13 were part of the immigrant population. Of those 13, 12 were not born in Portugal, but in Brazil, China, Algeria, Colombia, Sao Tome and Principe, and Cape Verde.

The primary reason reported by caregivers was not knowing or not remembering the reason for the delay/absence of vaccination with the first dose of the MMR vaccine (24 caregivers; 43.6% of participants). Some of these delays may have been caused by false contraindications regarding vaccination, either by the general population or by healthcare professionals.[1] As such, an information campaign was conducted for the caregivers who responded to the survey, providing an information leaflet detailing false contraindications regarding vaccination presented in the PNVP 2020.[1] The second most frequent reason for incorrect MMR vaccination was lack of awareness of the PNVP (11 caregivers; 20% of participants). All those who gave this reason were part of the immigrant population. Administrative and economic barriers, fear of discrimination, lack of information, unfamiliarity with the Portuguese healthcare facilities, language barriers, intercultural barriers, and religious beliefs may contribute to underutilization of health care services within the immigrant population. The third most frequent reason was the absence of a family doctor or difficulty scheduling an appointment at the PHCC (eight caregivers; 14.5% of participants). In 2010, a report from the Central Administration of the Health System estimated that approximately 1.5 million users did not have an assigned family doctor, and by April 2023, this value has increased to over 1.6 million.[15-18] Only two respondents refused the first dose of the MMR vaccine, supporting a study carried out by the European Commission in 2020 as Portugal having the highest rate of confidence in vaccination.[10,19]

Children born after January 1, 2011 began to follow the 2012 PNVP update.[7] The first years of implementing the PNVP that was updated by bringing the first dose of the MMR vaccine forward from 15 to 12 months (birth cohorts from 2012 to 2015), showed the highest rates of incorrect vaccination, which could be indicative of a period of adaptation to the updating of the PNVP by PHCC. Subsequent cohorts in 2016, 2018, and 2019 demonstrated a similar proportion of children not vaccinated at the correct time: 26.7% in 2016 and 2018, and 28.5% in 2019. The period between 2017 and 2019 coincided with several measles outbreaks in Europe, including Portugal, as well as in the USA and Brazil.[3,9,20-22]

Portugal faced five waves of COVID-19 between 2020 and 2022.[23] Although there was a national decrease in the number of administered doses of PNVP vaccines,[24] MMR vaccination in the children's cohort born in 2020 was not affected by this factor, with only 12% of cases being incorrectly vaccinated. In the 2019 cohort, vaccinated in 2020, there was a proportion of 23.8% of children with a delay in primary vaccination, and in the 2021 cohort, 22.7% of children were not vaccinated with the first dose of the MMR vaccine on time, possibly a

reflection of confinement measures and a reduction in visits to the PHCC,[4,24-26] Even with this percentage increase in the 2019 and 2021 cohorts, these values are not greater than those recorded in pre-pandemic years. Therefore, in this study, the COVID-19 pandemic does not appear to have had a major impact on vaccination delays in primary MMR vaccination.

The counties of Lisbon, Amadora, Odivelas, Loures, and Sintra displayed the highest percentages of incorrect primary MMR vaccination.[12] These municipalities are among the most densely populated in Portugal, which may facilitate the spread of MMR-related infectious diseases. The immigrant population in these municipalities is particularly vulnerable, as most originate from developing countries, according to the Human Development Index (HDI) (Guinea-Bissau, Pakistan, Angola, Nepal, Sao Tome and Principe, Cape Verde, India, Brazil, and China, from the lowest HDI to the highest HDI), often with endemicity and/or a high incidence of infectious diseases such as measles and, on average, they have a low socioeconomic level, live in crowded conditions, and have poor housing conditions.[27] In this study, analysis of survey results revealed a statistically significant association between the immigrant population and incorrect primary MMR vaccination, with immigrant children tending to have more delays/failure in the administration of this vaccine than the non-immigrant population.

However, this study had some limitations. The population consisted primarily of children residing in the Lisbon Metropolitan Area and attending the PERLPH. The relatively small number of children in each subpopulation restricts the representativeness of those specific subpopulations. Children's parents or caregivers may also misstate the reasons for incorrect vaccination with the first dose of the MMR vaccine. There is a scarcity of studies conducted in Portuguese populations, and much of the available published data on the MMR vaccine is outdated. Finally, the methodology applied in this study differs from that of the GDH, as we calculated vaccination coverage using cohorts from multiple birth years, whereas the GDH estimates coverage based on a single birth cohort for each vaccine.

In conclusion, this study found that vaccination coverage among the analyzed population was below the threshold needed for herd immunity against measles, with even lower coverage at 12 months of age. The greater discrepancy observed between the immigrant population and non-immigrant population may demonstrate inequalities in adequate immunization, suggesting the need for targeted information campaigns on the vaccines included in the PNVP and the benefits of completing the full vaccination schedule. Concurrently, in Portugal, vaccination coverage rates are primarily calculated based on PHCC records, which may overestimate actual coverage by excluding individuals not yet registered at a PHCC, and, consequently, not yet vaccinated. Therefore, collecting data in a hospital may have revealed lower coverage rates, by including such individuals. Hence, future research should assess vaccination rates across health institutions that cover all users of the Portuguese National Health System and who live in Portugal, ensuring that unregistered populations are also accounted for in national estimates.

Author contributions

All authors participated in the conception and design of the study; drafting the article; criticial review of the article; final approval of the version to be published; agreement to be accountable for the accuracy and integrity of the work. L. Veiga additionally participated in the acquisition of data from caregivers; research studies and literature; analysis and interpretation of the collected data, research studies and literature. F. Prata additionally participated in the correction of the data analysis.

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Conflicts of interest

None.

Ethical considerations

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

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

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

Supplementary data

Supplementary data are available at DOI: 10.24875/PJP.24000070. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

Cross-cultural adaptation and psychometric validation of the Children with Special Health Care Needs Screener© for European Portuguese in a school setting

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Abstract

Introduction and Objectives: Children with special health care needs (CSHCN) constitute a growing and heterogeneous group. The Children with Special Health Care Needs Screener© (CSHCN Screener©) is a brief (five-item), reliable, and clinically useful instrument for identifying these children. The objective of this study was to culturally adapt and evaluate the psychometric properties of the CSHCN Screener© for Portuguese children in a school setting, based on the translation and adaptation of the instrument validated for Brazilian Portuguese. **Method:** The study comprised two phases: (a) cross-cultural adaptation with experts and a pre-test, including face validity, with 54 parents/guardians (PG); and (b) reliability assessment in a sample of 301 PG through internal consistency (Cronbach's alpha), test-retest (kappa coefficient), and content validity with experts, using the content validity index (CVI). **Results:** The final instrument is culturally appropriate. The items demonstrated adequate reliability (α = 0.75 and 0.77). The overall test-retest concordance coefficient (Test 1 – Retest 1 to Test 5 – Retest 5) demonstrated considerable temporal stability (kappa > 0.8). Face validity indicated that the CSHCN Screener© is easily understood by PG. Experts agreed on the relevance, comprehensibility, and comprehensiveness of the content (CVI = 1.00). **Discussion:** The CSHCN Screener©, culturally adapted to European Portuguese, is reliable and useful for identifying CSHCN who present one or more of the five consequences included in the questionnaire, and will contribute to developing policies that promote health, with an emphasis on transdisciplinary intervention, specifically in the school context. It shows high potential for adaptation and applicability in different care contexts.

Keywords: Child health. School health services. Reproducibility of results.

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Adaptação transcultural e validação psicométrica do Children with Special Health Care Needs Screener© *para o português europeu em contexto escolar*

Resumo

Introdução e Objetivo: As crianças com necessidades de saúde especiais (NSE) constituem um grupo crescente e heterogéneo. O Children with Special Health Care Needs Screener© (CSHCN Screener©) é um instrumento breve (cinco itens), fiável e com utilidade clínica para identificar estas crianças. O objetivo foi adaptar culturalmente e avaliar psicometricamente o CSHCN Screener© para crianças portuguesas, em contexto escolar, com base na tradução e adaptação do instrumento validado para português do Brasil. **Método:** O estudo compreendeu duas fases: (a) adaptação transcultural com especialistas e um pré-teste, incluindo a validade de face com 54 pais/encarregados de educação (PEE); (b) avaliação da fiabilidade com 301 PEE através da consistência interna (alfa de Cronbach), do teste-reteste (índice kappa) e validade de conteúdo com especialistas, utilizando o índice de validade de conteúdo (IVC). **Resultados:** O instrumento final é culturalmente apropriado**.** Os itens demonstraram adequada fiabilidade (α = 0.75 e 0.77). O coeficiente geral de concordância teste–reteste (Teste 1 – Reteste 1 a Teste 5 – Reteste 5) demonstrou bastante estabilidade temporal (kappa > 0,8). A validade facial indicou que o CSHCN Screener© é facilmente compreendido pelos PEE. Os especialistas concordaram quanto à relevância, compreensibilidade e abrangência do conteúdo (IVC = 1.00). **Discussão:** O CSHCN Screener©, culturalmente adaptado para o português europeu, é fiável e útil para identificar as crianças com NSE que apresentam um ou mais das cinco consequências do questionário, e contribuirá para o desenvolvimento de políticas que promovam a saúde, com destaque para a intervenção transdisciplinar, especificamente em contexto escolar. Evidencia um elevado potencial de adaptação e aplicabilidade em diferentes contextos de cuidados.

Palavras-chave: Saúde da criança. Serviços de saúde escolar. Reprodutividade dos testes.

Keypoints

What is known

- The CSHCN Screener© is considered the "gold standard" for identifying special health needs. The European Portuguese version lacks psychometric validation.

What is added

- This study provides the first psychometric validation of the European Portuguese version of the CSHCN Screener©, building on the Brazilian adaptation and applying it to a school-based, regionally distinct context.
- The findings confirm the instrument's reliability, validity, and practical usefulness, reinforcing its applicability across different educational and healthcare settings in Portugal.

Introduction

Children with Special Health Care Needs (CSHCN) represent a heterogeneous and growing population.[1] Since 1998, in international literature, CSHCN have been broadly defined as children who have, or are at increased risk for, a chronic physical, developmental, behavioral, or emotional condition and who require health-related services beyond those used by children generally.[2] Up until then, and for many years, this concept remained limited to children with formal clinical diagnoses or defined disabilities, failing to encompass the broader consequences of chronic health conditions or to include children whose needs fall outside traditional diagnostic categories.[3]

The original Children with Special Health Care Needs Screener© (CSHCN Screener©) was developed in the United States (US) between 1998 and 2000 as part of a national collaborative program, led by the Child and Adolescent Health Measurement Initiative (CAHMI) and supported by the David and Lucile Packard Foundation and the Agency for Healthcare Research and Quality, using this more comprehensive federal definition of CSHCN from the Maternal and Child Health Bureau (MCHB).[4,5] The MCHB later endorsed the CSHCN Screener as a standardized way to operationalize the definition of CSHCN, and it has since been incorporated into several national and state surveys.[6,7] Specifically, the 2023 National Survey of Children's Health (NSCH) was the eighth annual production following the redesign and merging of the previous NSCH and National Survey of CSHCN.[8] This survey assesses the prevalence and impact of special health care needs among children in the US, as well as changes over time.[9]

The CSHCN Screener© is a five-item tool based on a parent survey that addresses the need for an efficient and flexible standardized method to identify these children.[5] The first consequence, medication use, is

represented by an item that assesses the need for prescribed medication for a current chronic condition, excluding vitamins (a period of one year or more is considered as classifying a chronic condition). The second domain, use of health services, is represented by three items: the need for more medical care, mental health services, or educational services than most children of the same age; the need for special therapy, such as physical, occupational, or speech therapy; and whether the child has any type of emotional, developmental, or behavioral problem for which he or she needs or receives treatment or counselling. The last domain, functional limitation, is represented by an item that assesses the presence of any limitation or disability in performing activities common to most children.[5,10] The domains in this definition are not mutually exclusive, meaning that a child may qualify in one or more domains.[5]

Studies indicate that allergies, asthma, attention deficit, and emotional issues are among the most common conditions affecting CSHCN. Most of these children live with two or more chronic conditions. In 2019-2020, nearly one in five children (19.4%) in the US had a special health care need, representing 14.1 million children.[6,10]

However, despite being widely used since its inception, until 2011 there were no published studies analyzing the internal psychometric properties of the CSHCN Screener©. It was in that year that its internal psychometric validation was formally established, using classical and modern test theory methods, confirming the instrument's reliability and accuracy in identifying these children.[6] This evidence reinforced the method, consolidating it as the "gold standard" for defining these needs and supporting prevalence estimates in national and state contexts.[11]

But despite the growing international interest in this population, an analysis of Portuguese scientific production on this group, particularly within the school context, reveals a notable lack of studies focused on screening and caring for children with chronic conditions or special health care needs.[12]

The CSHCN Screener© was recently translated and semantically and culturally adapted from the originally published US version into Portuguese. Psychometric properties such as internal consistency and temporal stability were not evaluated.[13] This study therefore complements the validation carried out previously by establishing the psychometric properties of the CSHCN Screener© for European Portuguese, similar to what was done with the original instrument in 2011[6] and applying it to a sample from a different geodemographic area than that of the previous study.

The development of this methodological study arises from the lack of reliable and accessible records, as well as the absence of official estimates regarding the number of Portuguese CSHCN, which significantly hinders healthcare planning, particularly in the school setting, an environment where children spend most of their time each day.[14,15] The adaptation and psychometric validation of this instrument within the school context is unprecedented and represents an original contribution to the field, filling the gap in information gathering and enabling international comparisons.

This research is part of a broader, multicenter project, the next stage of which involves conducting a prevalence study of CSHCN in school settings.[16]

The main objective of this phase was to culturally adapt the instrument to European Portuguese, based on the previously translated and adapted version for Brazilian Portuguese (conducted in 2016),[17,18] based on the linguistic similarity between the variants. We also aimed to evaluate its psychometric properties in a sample of Portuguese parents/guardians (PG). The research question is: How do the cultural adaptation and psychometric evaluation of the CSHCN Screener ensure its suitability for Portuguese children?

The complete CSHCN Screener© instrument for European Portuguese resulting from this study is available upon request from the authors.

Method

Design

We conducted a methodological study in two phases: cross-cultural adaptation and psychometric assessment. These phases include several consecutive steps and are based on the Brazilian Portuguese translation and adaptation of the CSHCN Screener©.

Phase 1: cross-cultural adaptation

The first phase included the cross-cultural adaptation of the instrument-based Beaton methodology.[19] The cross-cultural adaptation into European Portuguese was based on the Brazilian Portuguese version, as they are variants of the same language.[19] We checked whether the instrument items were understood in the same way (lexical and idiomatic equivalence) and had the same meaning (conceptual and cultural equivalence),[20] that is, we analyzed the impact the terms have in the Portuguese cultural context.

In January 2022, the CSHCN Screener© was independently adapted from Brazilian Portuguese to European Portuguese by two professionals: 1) a Portuguese teacher who was not familiar with the instrument, who aimed to increase linguistic and cultural accuracy; 2) a Brazilian health researcher living in Portugal for more than ten years, also not familiar with the instrument, who compared the version adapted into Portuguese by the Portuguese teacher with the original Brazilian version. This process took place in February 2022. The suggestions and considerations regarding the adaptation were subsequently noted in a comparative table with four columns, constructed by the researchers for discussion and the construction of a consensus version by the panel of experts. In the first column, the validated translation and adaptation from Brazil was entered; in the next two columns, the versions with the adaptations and considerations of the language professionals were placed; and in a fourth column, the adapted parts of the items were highlighted using colors, thus facilitating a comparative analysis.

A preliminary consensus adaptation was agreed at an online expert committee meeting on May 10, 2022. The panel included a methodologist, a linguist, a health professional, and the research team, which included three Portuguese professors with a PhD in Nursing Sciences, the main investigator, and the author of the Brazilian translation and adaptation of the instrument, who has a PhD in Public Health Epidemiology.

Items and terms with 90% agreement between experts were accepted as equivalent.[21] The language used was the most semantically appropriate to the concepts of health in Portugal.

After the preliminary consensus version, we carried out a pre-test to assess face validity. The participants, PG, were asked about the clarity of the content and if they had any difficulties in answering the specific questions.

The standard for reviewing and modifying an item was that less than 80% of the PG understood the item or more than 20% of the participants suggested modifications.[22] As it turned out, the questionnaire did not require any changes as the suggestions the participants made were marginal.

On December 19, 2022, the final adaptation of the CSHCN Screener© tool for European Portuguese was agreed after a further consensus meeting with the panel of experts. Once again, items and terms with 90% agreement between the experts were accepted as equivalent.[21]

Phase 2: psychometric assessment

In the second phase, a pilot study was conducted to assess the quality of the psychometric properties of the European Portuguese adaptation of the CSHCN Screener©.

To assess the methodological quality of the instruments, we selected measurement properties according to the criteria of the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) taxonomy in the most studied domains: reliability and validity.[23]

The internal consistency of the complete set of instrument questions was assessed using the same procedure to assess the psychometric characteristics of the original US instrument.[6] The Cronbach's alpha was first calculated for the five main questions, and a combination of the responses to the items of each consequence was then created in a testlet, which is a set of test items presented together but that can be answered independently.[24]

A child or young person received a score of 1 on the testlet if they met all the criteria for a consequence (e.g., if the child needs or takes prescribed medication as a result of a condition lasting at least 12 months); otherwise, they received a score of 0.[6]

Cronbach's alpha results were classified using weighted data as unacceptable (< 0.6), weak (0.6 and 0.7), fair (0.7 and 0.8), good (0.8 and 0.9), and excellent (0.9 and 1).[25]

The kappa coefficient was used to assess the test-retest reliability, which is recommended for variables that are relatively stable over time and in circumstances in which changes in study variables cannot be predicted.[21]

Considering the above, reliability coefficients above 0.70 are considered as satisfactory and 0.85-0.95 as preferable.[21] In general, research tool test-retest reliability coefficients above 0.9 are considered high and 0.7-0.8 are considered acceptable.[26]

As for the application of the questionnaire, this included general information with two sections: 1) demographic data about the PG and child/young person (only the PG were interviewed and provided information about the child); and 2) final CSHCN Screener© adaptation for European Portuguese.

In the pre-test phase, to check for face validity, the principal investigator and three duly trained nursing students, aware of the purpose of each question, administered the questionnaire by telephone to the PG. In the pilot study phase, the survey was conducted using an online questionnaire in Google Forms, which

was answered by the PG; the questionnaire was administered in schools by the school health teams.

The research team maintained close contact with the school health teams. The research team held a preparatory meeting to provide information and supporting documentation so that the teams' contact persons could implement the data collection process. The documentation included the questionnaire, which contained the Informed Consent Form. An invitation email was also sent so that the contact persons could select, contact, and invite the heads of the school groups to take part in the study. Then, the school health teams contacted the school teaching teams.

To simplify communication between the school and the PG, the teachers were responsible for sending the invitation email with the link to fill in the questionnaire.

For test-retest, the invitation email asked the PG to complete the questionnaire again two weeks later, using the same link. Several reminders were sent to ask participants to do so. As a result, 34 PG repeated the questionnaire.

Survey data were encrypted to ensure the participants' security and anonymity. Unanswered questions were not taken into consideration. "Yes" was scored as one point and "no" as zero points.

The second important validation criterion was validity, which briefly assesses the degree to which the instrument measures the construct it is supposed to measure.[23] Validity was complemented by content validity, which assessed whether the CSHCN Screener© for European Portuguese covers all aspects of CSHCN, and was evaluated by the qualitative judgments of a panel of experts[27] comprising three to five participants.[28]

The experts had to be nursing professionals with a master's degree in nursing and more than five years of experience, who worked in the field of school health and participated in intervention projects focused on CSHCN. To meet these requirements, three nurses from different Community Care Units (CCU) in the Regional Health Administration of Lisbon and the Tagus Valley (RHALTV) were invited.

The assessment used the content validity index (CVI) between the experts as a validity indicator, classifying each item individually into the following categories: 1 = not relevant; 2 = not very relevant; 3 = relevant; and 4 = quite relevant.[28] More specifically, it analyzed whether the instrument measures what it is supposed to measure and covers all aspects related to the CSHCN, highlighting that the instrument should not include items not related to this construct.

Thus, the experts were asked to rate the relevance, comprehensibility, and comprehensiveness of each item in the instrument using a four-point scale and to record these ratings in a table created for this purpose. This process culminated on July 12, 2023. Content validity included no statistical treatment, and the index was calculated for the general instrument.[26,29] The CVI is calculated by the number of items scoring 3 and 4 in relation to the total number of items or questions over the total number of statements or questions, with a result greater than 0.80 considered acceptable.[29]

Data collection

In the first phase, for face validity, during the pre-test, we compiled a non-probabilistic convenience sample of 54 PG of children aged between three and 17 years, enrolled from preschool to secondary school, who were users of a CCU belonging to the central Portuguese Regional Health Administration (RHA). Subjects that were representative of the population analyzed were included but not chosen for the main study. The pre-test was conducted on August 6, 2022.

In the second phase, in the pilot study, the target population included PG in public school groups associated with the corresponding Health Centre Groups (HCG). A non-probabilistic convenience sample was adopted, statistically calculated at a 10:1 ratio, that is, each instrument question equals 10 research subjects.[25] In line with methodological guidance, several authors propose securing more than 100 participants as a very good criterion for assessing internal consistency, estimating measurement error and reliability, testing construct-validity hypotheses, and comparing subgroups;[30] others recommend sample sizes of between 100 and 200 respondents[31] or at least 200 participants.[32] A rule of thumb of 10 participants per instrument item is also frequently cited as appropriate.[33] Furthermore, convenience sampling is considered suitable for this type of study provided that participants exhibit characteristics aligned with the intended use of the instrument.[32,34-35]

Of the five school groups from the corresponding pilot HCG, six schools were included, with a sample of 301 participants. The online questionnaire was administered between January 2 and March 31, 2023.

Data analysis

Data analysis was performed using IBM SPSS statistical software (version 29.0, IBM, New York, USA). Cronbach's alpha was used to assess reliability through internal consistency. The kappa coefficient was used to analyze the agreement of nominal dichotomous

Table 1. Discrepant items and sub-items identified during the semantic, idiomatic, conceptual, and cultural equivalence of the CSHCN Screener© for European Portuguese

Original item/sub-item/term	Consensus version item/sub-item/term
1a, 2a, 3a, 4a. Is this due to ANY medical, behavioral, or other health condition?	1a, 2a, 3a, 4a. Is this due to ANY disease, behavioral problem, or other health problem?
2. Does (child's name) need or use more medical, psychosocial, or educational services than most children of the same age?	2. Does (child's name) need or use more medical, mental health, or education services than most children of the same age?
1, 2, 3, 4, 5. (Child's name)	1, 2, 3, 4, 5. (Your child)

variables. To assess the instrument's temporal stability, the test–retest agreement coefficients (kappa) between the items in both applications (Test 1 – Retest 1 and Test 5 – Retest 5) were analyzed, allowing for consistency of responses over time.

Ethical considerations

In both phases, the inclusion criterion was to be a PG for children aged between three and 17 years, enrolled from preschool to high school, who was familiar with the child's health and signed the Informed Consent Form after the study objectives were explained. This study was approved by the Research Ethics Committee of the Health Sciences Research Unit: Nursing (UICISA-E) of the Nursing School of Coimbra (ESEnfC) (decision dated December 15, 2021; opinion No. 8811_10_2021), and by the Directorate General of Education – Monitoring of School Surveys on February 25, 2022 (Registration No. 0812200001). The Health Ethics Committee of RHALTV issued a favorable conditional opinion on August 17, 2022 (opinion No. 3255/CES/2022). The instrument was adapted with permission from the CAHMI, Baltimore, MD, US, which created the CSHCN Screener©.

Results

The terms modified in the cross-cultural adaptation phase were "clinical, behavioral, or other health condition," which was repeated four times in dichotomous instrument sub-items 1a, 2a, 3a, and 4a, and the term "psychosocial," contained in item 2. The sub-items and the item showing discrepancies at this stage are presented in table 1. For the four sub-items, we opted for an adaptation similar to the one described in the Brazilian Portuguese translation and adaptation of the instrument.[18] In the second item, the decision was made after comparing the term psychosocial in the preliminary version with the original term in the original US instrument and its suitability for health concepts in Portugal.

In the items marked 1, 2, 3, 4, and 5, the panel of experts decided to replace the term "(child's name)" with "your child," as this choice reflects language that is more appropriate to the school context. The decision was made after comparing the wording of the original instrument with the proposed final adaptation, as presented in table 1.

The results of the pre-test face validity assessment suggest that the CSHCN Screener© for European Portuguese instrument has strong face validity, since participants reported that it is easy to understand and complete. Therefore, the five domains and nine dichotomous items of the original instrument, which correspond to the classification criteria for identifying CSHCN, were maintained.

Respondents in the pilot study for the instrument psychometric assessment were predominantly adult highly educated mothers, as presented in table 2.

Most children were girls in elementary school: 26.6%, 28.2%, and 20.9% in the first (six to 10 years of age), second (10-12 years), and third (12-15 years) cycles, respectively, as presented in table 3.

The overall standardized internal consistency for the first questions was $\alpha = 0.75$ (Table 4). The item "medication" had the lowest item-total correlation. However, excluding this item would not increase the alpha to the point of justifying its removal.

Testlets had an α of 0.77. The item "medication" had the lowest item-total correlation. However, excluding this item would not increase the alpha to the point of justifying its removal. The Cronbach's alpha values after excluding each item are reported in table 4.

The use of the main questions and testlets to calculate internal consistency revealed results comparable to those of the original English instrument, with $\alpha = 0.72$ and 0.78, respectively.[6] The values were also similar to those of the translation and adaptation into Brazilian Portuguese, achieving an overall internal consistency of $\alpha = 0.8$.[17] Likewise, the psychometric characteristics show high test-retest agreement.

Table 2. Sociodemographic profile of PG who completed the CSHCN Screener© for European Portuguese, Portugal, 2023

Variables	n	%	
Sex			
Female	269	89.4	
Male	32	10.6	
Relationship			
Mother	267	88.7	
Father	29	9.6	
Another family member	5	1.7	
Age	Min.	Max.	M_e
Years	19	58	40.8
Education			
University	134	44.5	
High school	118	39.2	
Elementary school	48	16	
No education	1	0.3	

N: number of participants/observations; %: percentage; Min.: minimum; Max.: maximum; Me: median.

Table 3. Sociodemographic profile of children and young adults screened by the CSHCN Screener© for European Portuguese, Portugal, 2023

Variables	n	%	
Sex			
Female	165	54.8	
Male	136	45.2	
Age	Min.	Max.	M_e
Years	3	17	10.8
Education			
Preschool	29	9.6	
Middle school	148	49.1	
High school	44	14.6	

N: number of participants/observations; %: percentage; Min.: minimum; Max.: maximum; Me: median.

The level of agreement regarding the stability of instrument items was measured through the analysis of the test-retest reliability using the kappa coefficient of agreement. The analysis of the correlation matrix between the items and the total scale established that the instrument is quite stable (kappa agreement coefficient between 1.0 and 0.8), except for question 5 (kappa agreement coefficient = 0.38), which obtained a lower value, as shown in table 5. The total cross-tabulation indicates a high kappa, reflecting good overall agreement and stability of the instrument (kappa > 0.80).

After the statistical tests, all the experts classified the items of the CSHCN Screener© instrument in European Portuguese with a relevance scale of 3 or 4. In this content assessment, the CVI reached 100% consensus, which is considered a perfect consensus (CVI = 1.0).

Table 4. Cronbach's alpha and descriptive statistics for the main questions and testlets

First question approach				
Item	Mean	SD	α = 0.75	
			Correlation with total	α with item deleted
Medications	0.11	0.32	0.37	0.76
Services	0.13	0.34	0.69	0.63
Activity limitation	0.06	0.23	0.48	0.72
Therapy	0.12	0.33	0.48	0.71
Counseling	0.13	0.33	0.58	0.68
Testlet approach				
Item	Mean	SD	α = 0.77	
Medications	0.1	0.27	0.40	0.78
Services	0.1	0.30	0.71	0.66
Activity limitation	0.04	0.20	0.52	0.74
Therapy	0.07	0.25	0.54	0.72
Counseling	0.09	0.29	0.56	0.72

α: Cronbach's alpha; SD: standard deviation.

Table 5. Test-retest agreement matrix. Kappa coefficient of agreement values for each item of the instrument between the two applications and total cross-tabulation (test and retest)

Cross-tabulation per item (T × R)	Kappa coefficient of agreement
T1 and R1 cross-tabulation	0.89
T2 and R2 cross-tabulation	0.87
T3 and R3 cross-tabulation	0.78
T4 and R4 cross-tabulation	1.000
T5 and R5 cross-tabulation	0.38
Total cross-tabulation	0.82

T: test; R: retest.

Discussion

This study highlights the relevance of cross-cultural adaptation and psychometric evaluation of the CSHCN Screener© into European Portuguese, especially considering that health promotion in schools is a strategic

priority.[14] In this context, governments and policymakers are showing increasing concern for equity and inclusion in education, with the aim of ensuring that all students can develop their potential and participate constructively in increasingly diverse and complex societies.[36]

These principles are particularly relevant for CSHCN, whose inclusion requires intersectoral and multidisciplinary approaches, as their higher rates of school absenteeism may negatively impact their academic performance.[37] In Portugal, intervention with CSHCN must be based on specific, integrated strategies. These include, among others, the National Child and Youth Health Program,[38] the Health Action for Children and Youth at Risk,[39] the National School Health Program,[40] and the National Early Childhood Intervention System.[41]

To support this intervention, healthcare professionals need valid, reliable screening tools that are adapted to the clinical context, such as the CSHCN Screener©, which enables the early identification of CSHCN. The standardized use of this type of tool makes it possible to characterize the profile of this population and guide priorities in terms of surveillance, research, program planning, and public policy formulation.[3] In addition, the data collected are relevant across the board, given that children often interact with different sectors, namely health, education, and social action.[42]

Conducted specifically in the school context, this study is highly relevant and could contribute significantly to identifying these children, characterizing their areas of need, and subsequently defining strategic guidelines that promote health.

From the implementation of this project and the results obtained, namely the cross-cultural adaptation, psychometric validation, and the prevalence study conducted across several regions of Portugal using this version of the CSHCN Screener©, significant progress was achieved in strengthening the coordination between the health and education sectors.

In fact, our team and the group responsible for the recent translation, cultural adaptation, and validation of the CSHCN Screener© into Portuguese, developed from the original US version and carried out in a different region of Portugal, joined efforts to develop a consensual version of the instrument. This new version builds upon the work independently conducted by both teams during the cross-cultural adaptation process and incorporates the psychometric validation performed in this study. This process underscores the collaborative, continuous, and evolving nature of the validation of the CSHCN Screener© in Portugal, thereby consolidating its applicability and relevance in both educational and health contexts.

The original instrument is incorporated into the NSCH, the main source of national estimates in the US.[3,11] It has also been translated, adapted, validated, and implemented in countries such as Brazil,[18] Egypt,[43] Canada,[44] Switzerland,[45] and Poland.[46] With its recent adaptation and validation for the Portuguese context, it is now possible to obtain standardized and comparable estimates of the health needs of this population in Portugal too, contributing to a better understanding and response by health professionals and decision-makers, thereby promoting practices aligned with clinical reality.[6] Furthermore, the content of the instrument aligns with the inclusive multidimensional measure of CSHCN according to Portuguese guidelines. The instrument assesses the consequences of health conditions duly focused on the technical-normative guidelines of the Portuguese School Health Program.[40] Additionally, it considers the legal framework that supports the recent paradigm of inclusive education, as established in Article No. 1, of Decree-Law No. 54/2018 of July 6,[47] as amended by Law No. 116/2019, of September 13,[48] and Decree-Law No. 62/2023, of July 25.[49] This legislation defines the legal framework for inclusive education within primary and secondary education across public, private, cooperative, and solidarity-based networks in Portugal, outlining the support measures for learning and inclusion, as well as the specific resources to be mobilized in order to address the educational needs of children and young people throughout their school journey.

Moreover, it is a simple, quick-to-administer, and self-administered instrument that can also be applied by health professionals.[5]

From a methodological standpoint, throughout the cross-cultural adaptation process, we followed international guidelines and used psychometric methods similar to those used in the original 2011 US validation of the CSHCN Screener©, based on the validated Brazilian version. This last part of the methodology is also interesting and somewhat unprecedented, as it is uncommon to find instruments validated in the same language but across different cultures.

Limitations

This study had limitations. First, the population was obtained by a non-probabilistic convenience sampling technique, with data collection limited to children and young people from six schools in a single region of the country, which resulted in particularities of their sociocultural and socioeconomic context. This means that this sample is not representative of all Portuguese

children and young people. Thus, future studies should include a representative number of participants, geographically distributed, and covering different cultural and socioeconomic realities.

Second, this study included only PG of children and young people in a school context; therefore, future research must include other healthcare settings. We suggest the inclusion of the context of functional healthcare units, specifically in Portuguese primary healthcare and hospital care, involving the parents and family members of children and young people.

Furthermore, the expert panel was restricted to three nurses, all from the same region of the country. Other studies should extend the validation to other professionals and to different regions of the country.

Finally, there were limitations regarding the self-administration of the instrument, which may have raised questions during completion.

Conclusion

The European Portuguese CSHCN Screener© demonstrated adequate reliability and validity for screening CSHCN and could identify if the child has one or more of the five conditions related to special health care needs. Content validity and face validity were the initial steps in establishing the instrument's validity. Additionally, other psychometric properties, such as internal consistency and test-retest reliability, contributed to obtaining robust and comparable conclusions regarding the validity and reliability of the CSHCN Screener© for European Portuguese.

The screening and epidemiological results will be a key organizational planning component to develop a set of interventions for the inclusion of CSHCN, including the school context. Use of the instrument can potentially support the decision-making of other healthcare teams in various clinical practice settings and inform important public health policies.

Author contributions

M.C. Coelho Monteiro Pires: conceptualization, data curation, formal analysis, investigation, methodology, resources, validation, visualization, writing (original draft), and writing (review and editing). M.C. Barbieri-Figueiredo: conceptualization, data curation, formal analysis, investigation, methodology, resources, supervision, validation, visualization, and writing (review and editing). A. Silva: data curation, formal analysis, investigation, methodology, software, validation, supervision, and writing (review and editing). A. Arrué: data curation, formal analysis, investigation, methodology, validation, visualization, and writing (review and editing). J. Guarda-Rodrigues: formal analysis, investigation, methodology, validation, visualization, and writing (review and editing). E. Neves: formal analysis, investigation, validation, methodology visualization, and writing (review and editing). E. Menino: conceptualization, data curation, formal analysis, investigation, methodology, resources, supervision, validation, visualization, and writing (review and editing).

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Previous presentations

This research has been previously presented on the following occasions: 16th International Conference on Nursing Research, Lisbon, Portugal, 2022. 1st National Meeting of the Portuguese Association of Primary Care Nurses, Lisbon, Portugal, 2023. 27th International Meeting on Nursing Research | 10th Ibero-American Research Congress, Valladolid, Spain, 2023.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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

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REVIEW ARTICLE

Automated oxygen control in preterm infants: a new frontier in neonatal respiratory care. A review

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Abstract

Maintaining optimal oxygen saturation (SpO_2) in preterm infants remains a critical yet challenging aspect of neonatal intensive care. Manual adjustment of inspired oxygen (FiO_2) is both labor-intensive and prone to human error, often resulting in significant fluctuations in oxygen levels that may increase the risk of complications such as retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and long-term neurodevelopmental impairment. Emerging evidence indicates that automated oxygen control (AOC) systems enhance the stability of SpO_2, reduce the frequency of hypoxic and hyperoxic episodes, and minimize the need for manual FiO_2 adjustments. Despite these promising physiological improvements, high-certainty evidence demonstrating a positive impact on short- and long-term clinical outcomes remains lacking. Current data on mortality, severe ROP, BPD, and neurodevelopmental outcomes are limited and often of low certainty. AOC technology shows significant potential to improve oxygen management in preterm infants by maintaining target saturation ranges more consistently. However, robust, high-quality multicenter trials are essential to confirm its clinical benefits, assess its feasibility in various healthcare settings, and assess cost-effectiveness. This review synthesizes the current evidence surrounding the use of AOC in preterm infants, with a focus on its efficacy, safety profile, and potential role in advancing neonatal respiratory care.

Keywords: Automated oxygen control. Hyperoxia. Hypoxia. Neonatal intensive care. Oxygen saturation. Preterm infants.

Controlo automatizado do oxigénio em recém-nascidos pré-termo: uma nova fronteira nos cuidados respiratórios neonatais. Revisão

Resumo

Manter a saturação periférica de oxigénio (SpO_2) na faixa desejada em recém-nascidos prematuros permanece um aspeto crítico, porém desafiador, dos cuidados intensivos neonatais. O ajuste manual do oxigénio inspirado (FiO_2) é trabalhoso e suscetível a erros humanos, e resulta, frequentemente, em flutuações significativas na SpO_2, o que pode aumentar o risco de complicações como a retinopatia da prematuridade (ROP), displasia broncopulmonar (DBP) e compromisso do desenvolvimento neurológico a longo prazo. Evidências emergentes indicam que os sistemas de controlo automatizado de oxigénio (CAO) melhoram a estabilidade da SpO_2, reduzem a frequência de episódios de hipóxia e hiperóxia e minimizam a necessidade de ajustes manuais da FiO_2. Apesar das melhorias fisiológicas promissoras, ainda faltam evidências de qualidade que demonstrem um impacto positivo nos desfechos clínicos de curto e longo prazo. Os dados atuais sobre mortalidade, ROP grave, DBP e efeitos no neurodesenvolvimento são limitados e, muitas vezes, de baixa qualidade. A tecnologia CAO demonstra um potencial significativo para melhorar o manejo do oxigénio em prematuros, mantendo os intervalos-alvo de saturação

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de forma mais consistente. No entanto, são necessários ensaios multicêntricos robustos e de alta qualidade para confirmar seus benefícios clínicos, avaliar sua viabilidade em diferentes contextos clínicos e analisar sua relação custo-benefício. Esta revisão sintetiza as evidências atuais sobre o uso do CAO em recém-nascidos prematuros, com foco em sua eficácia, perfil de segurança e potencial papel no avanço dos cuidados respiratórios neonatais.

Palavras-chave: Controlo automatizado de oxigénio. Hiperóxia. Hipóxia. Cuidados intensivos neonatais. Saturação de oxigénio. Recém-nascidos prematuros.

What is known
- It is well established that maintaining optimal oxygen saturation in preterm infants is a major challenge due to frequent fluctuations between hypoxia and hyperoxia.
- Automated oxygen control (AOC) systems have been shown to improve the stability of SpO_2 and reduce the frequency of both hypoxemic and hyperoxemic episodes compared with manual control.
- Despite these physiological benefits, current evidence remains insufficient to confirm improvements in key clinical outcomes.

What is added
- This review compiles and critically analyzes the most recent evidence on AOC systems in preterm infants, highlighting their efficacy, safety, and practical implications for neonatal care.
- It identifies existing research gaps, including the need for large multicenter randomized trials to establish the clinical benefits and cost-effectiveness of AOC.
- The review also outlines future research priorities aimed at optimizing control algorithms, improving sensor technology, and integrating AOC into routine NICU practice worldwide.

Introduction

The vast majority of extremely preterm infants require oxygen therapy in their early days of life due to pulmonary immaturity.[1] Maintaining peripheral oxygen saturation (SpO_2) within the desired range in preterm newborns receiving invasive or non-invasive mechanical ventilation is a challenge in neonatal care, particularly during the first days of life.[2] This difficulty is due to several factors, notably the respiratory instability related to the severity of respiratory distress syndrome (RDS) and the relentless work of nurses in the neonatal unit, which prevents them from adjusting the fraction of inspired oxygen (FiO_2) manually in a timely manner.[2]

The European Consensus for the treatment of RDS in preterm neonates recommends maintaining SpO_2 within the 90-94% range.[3] Several important studies have shown that extremely preterm infants receiving oxygen frequently spend time outside the target SpO_2 range, experiencing frequent episodes of both hypoxemia and hyperoxemia.[4-7]

Intermittent hypoxemia (IH) events in preterm infants have been linked to various morbidities, including retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), sleep-disordered breathing, neurodevelopmental impairment, and even mortality.[8-10] Additionally, these infants are especially vulnerable to oxidative stress because of their insufficient enzymatic and non-enzymatic antioxidant defenses, making them more susceptible to the detrimental effects of hyperoxemia, including the development of bronchopulmonary dysplasia (BPD).[11-13] Furthermore, severe ROP has been associated with prolonged exposure to high FiO_2 levels and iatrogenic hyperoxemia, particularly in infants with extremely low birth weight, despite the efforts to titrate FiO_2 more frequently.[14]

In an attempt to overcome the difficulty of maintaining FiO_2 within the desired values, especially during the first days of life in preterm neonates under oxygen therapy, systems of closed-loop automated control (CLAC) of FiO_2 were developed, and have been increasingly used in neonatal intensive care units (NICUs).[15]

The objective of this review is to compile and analyze the available evidence on automated oxygen control (AOC) in preterm infants, focusing on its advantages, limitations, and clinical impact. For this purpose, a review was conducted in the PubMed database, with no time limit and up until April 25, 2025, searching for articles on the topic. The search used the following keywords: automated oxygen control, closed loop automated oxygen control, manual oxygen control, hyperoxia, normoxia, hypoxia, and preterm infant.

Manual method of FiO_2 adjustment

Traditionally, FiO_2 was manually adjusted based on clinical observation of the neonate's SpO_2 levels. This process involves continuous monitoring of SpO_2 and adjusting FiO_2 on ventilators or oxygen therapy devices accordingly. Healthcare providers, including doctors and nurses, are responsible for frequently adjusting the ventilator settings or oxygen systems based on SpO_2

readings, clinical signs (such as respiratory rate and effort), and the perceived needs of the patient. The goal is to maintain SpO_2 within the desired range. A study by Lim K. et al., involving 45 infants with a gestational age of 30 weeks (IQR: 27-32) receiving nasal continuous positive airway pressure (NCPAP), demonstrated that FiO_2 adjustments were required a median of 25 times per day (interquartile range: 16-41).[16] This number of adjustments is difficult to achieve with precision in units caring for extremely preterm infants due to the high number of tasks nurses are in charge of.[2] Additionally, the nurse-to-infant ratio also affects the effectiveness of manual control.[16]

There are several disadvantages to the manual FiO_2 control. Preterm infants often experience rapid changes in oxygen saturation, and manual control cannot respond immediately to these fluctuations.[2] This increases the risk of both hypoxemia and hyperoxemia.[2] Manual adjustment requires continuous attention from healthcare providers, especially nurses, who often manage multiple tasks simultaneously in the NICU.[2] This can lead to delays in FiO_2 adjustment or even missed interventions. Also, continuously adjusting SpO_2 levels can result in overcorrection, potentially leading to unintended hyperoxia.[2] The high-pressure clinical environment, combined with fatigue or competing demands, can result in inaccurate or inconsistent FiO_2 titration, increasing the likelihood of errors.[2] FiO_2 adjustments can vary between caregivers and across shifts, leading to inconsistent care and fluctuations in oxygen exposure.[2] Continuous monitoring of SpO_2 and frequent manual FiO_2 adjustments add significantly to the workload of clinical personnel, potentially diverting attention from other critical aspects of neonatal care.[2] Finally, studies have proven that with manual control, preterm infants often spend a significant amount of time outside the recommended SpO_2 range, which can range between 18% and 68%.[1,17] On the contrary, NICUs that implemented AOC reported that the children spent less time with saturations outside the target range, ranging from 9% to 60%, depending on the system used and the infant's clinical condition.[1,18]

Automatic control of FiO_2

The AOC is currently used in the NICU for infants receiving invasive mechanical ventilation, non-invasive ventilation (nasal CPAP, nasal IPPV), and high-flow nasal cannula. The closed loop AOC is a technology used automatically adjust the amount of oxygen delivered to neonates, usually preterm infants, based on their continuously monitored SpO_2 levels. A sensor continuously measures the baby's SpO_2, and an automated system compares this value to a predefined target range (e.g.: 90-94%). These systems use software algorithms that automatically adjust the FiO_2 in response to fluctuations in the infant's SpO_2, aiming to maintain a predetermined target oxygen saturation range. If the SpO_2 is outside the target range, the system automatically adjusts the FiO_2, increasing or decreasing the oxygen being carried.[19]

Currently available algorithms include CLiO™$_2$ (Closed Loop inspired Oxygen) integrated into the Avea® infant ventilator; CLAC (Closed Loop Automatic Oxygen Control), incorporated into the Leoni plus® ventilator; IntellO$_2$™, part of the Oxygen Assist Module in the Vapotherm® Precision Flow; VDL 1.1 OxyGenie on the SLE6000® ventilator; PRICO (Predictive Intelligent Control of Oxygenation) on the Fabian® Acutronic ventilators; and SPOC on the Sophie® neonatal ventilator (MEDACX).[1,20-21] Each algorithm has a different design for processing the input and computing adjustments in FiO_2.[21] Fathabadi et al. described the main characteristics of algorithms developed for automated FiO_2 control in preterm infants and classified them into four categories: rule-based (fuzzy or non-fuzzy), proportional-integral-derivative (PID), adaptive, and robust, though the latter is not currently available in clinical practice.[22] Among the most widely used systems, PRICO® employs a rule-based, non-fuzzy control algorithm; the OxyGenie® system uses a PID algorithm; and the AVEA™-CLiO$_2$™ system utilizes an adaptive algorithm.[1,21] It is important to emphasize that the clinical outcomes of systems for AOC in preterm infants can vary depending on several factors such as the study population, the type of respiratory support, and the chosen target range, as well as the effectiveness of the algorithm itself.[1,21] Also, the experience of the medical team, the available ventilation technology, and the specific clinical needs are crucial factors influencing the outcome. Although there are minor differences in the functioning of the algorithms, the most effective is currently unknown. All algorithms proved to maintain FiO_2 more consistently and accurately within the desired range by continuously adjusting oxygen levels based on real-time measurements, minimizing fluctuations, and ensuring optimal oxygenation.[21]

AOC systems can minimize the need for frequent manual adjustments by continuously monitoring and adjusting oxygen levels in real time. This, in turn, becomes a technology that supports and facilitates the work of nurses. However, it is important to emphasize that the AOC does not replace the nurse's work and, moreover, it itself needs to be supervised by the nurse,

since in the event of a technical issue, they shall ensure the control of the oxygen. Despite the advantages, technological and financial challenges remain significant obstacles to the widespread implementation of these systems. The high cost of advanced monitoring equipment, coupled with limited access to such technologies in certain NICUs, can impede their adoption, particularly in resource-limited environments.[21]

A commonly mentioned limitation of AOC is the possibility of masking a clinical deterioration in the patient.[21] This aspect is usually detected more quickly with manual adjustment. However, this limitation may be mitigated by implementing protocols that include periodic assessment of the FiO_2 delivered by the ventilator, or by setting an upper FiO_2 limit that facilitates early detection of increasing oxygen requirements in the patient.[21] With the continued use of AOC, caregivers become more familiar with both the technique and the assessment of the clinical status of the patient receiving this AOC, making the masking of clinical deterioration no longer a real issue.[2,21]

Results of studies comparing automatic FiO_2 control with manual control

Since the 1950s, studies have emphasized the detrimental impact of excessive oxygen supplementation and hyperoxia in preterm infants.[23,24] The most evident condition associated with this practice is ROP, which develops as a result of the exposure of the immature retinal vasculature to high oxygen concentrations.[23-25] In subsequent years, studies showed that the preterm lung condition of chronic lung disease (CLD) was associated with prior exposure to higher concentrations of oxygen.[26-28] Also, the harmful effects of hypoxia in preterm infants became evident when prolonged periods of low oxygen were found to increase the risk of death or neurological impairment.[29,30]

The introduction of transcutaneous oxygen electrodes in the 1970s to measure partial pressure of oxygen (PaO_2), followed by the development of pulse oximetry in the 1980s, enabled clinicians to titrate oxygen therapy based on non-invasive assessments of oxygenation.[31,32] Pulse oximetry is now the standard method for monitoring oxygenation in NICUs. To prevent both hypoxia and hyperoxia, maintaining SpO_2 within an admissible range has become a widely accepted practice. However, the optimal target range for preterm infants continues to be a topic of ongoing debate.[30]

In routine clinical practice, NICU personnel – typically nurses – manage oxygen therapy by manually adjusting the fraction of inspired oxygen (FiO_2) or the flow rate based on fluctuations in the infant's SpO_2. However, this manual approach can be challenging due to the numerous factors that influence its effectiveness.[2,33]

The implementation of AOC in neonatal care began in the 1970s.[34-36] Since then, advancements in ventilation technology led to the development of the first AOC systems, designed to enhance the precision of oxygen delivery to newborns, particularly preterm infants.[37]

Over the past two decades, many studies have assessed the effectiveness of AOC in the care of preterm infants. Meanwhile, systematic reviews and meta-analyses have already been conducted using several of these studies. A systematic review by Hummler H et al. in 2014, wich included nine studies, found that AOC allows SpO_2 to remain within the target range for longer periods, reduces the number of episodes of hyperoxemia and severe hypoxemia, and decreases nurses' manual workload.[38] Additionally, a systematic review and meta-analysis by Mitra S et al. up to December 2016, published in 2018, including ten studies, also concluded that AOC improves the maintenance of target oxygen saturations.[17] Another systematic review and meta-analysis by Denault MH et al., conducted in 2018 and published in 2019, included seven studies in preterm infants and two in adults, and reached the same conclusion: AOC allows for a greater percentage of time within the target saturation range.[39] Also, a systematic review by Abdo M et al., conducted in December 2020 and published in 2022, included 13 studies and 343 preterm infants on respiratory support. It concluded that AOC is fast and effective in regulating SpO_2 and may be used to reduce nurses' workload.[40]

A recent Cochrane systematic review, published on January 23, 2023, aimed to assess the benefits and harms of AOC systems (integrated into ventilators or oxygen delivery devices) for preterm infants with respiratory dysfunction requiring respiratory support or supplemental oxygen therapy.[41] This review included 18 studies that enrolled a total of 457 infants, of which 13 studies (339 infants) contributed data to meta-analyses.[15,37,42-57] The included studies were randomized controlled trials and randomized cross-over trials that compared AOC versus manual oxygen delivery, or that compared different automated oxygen delivery systems head-to-head. Seventeen studies involved preterm infants of both genders, with an average gestational age at birth between 25 and 29 weeks (ranging from 23 to 36 weeks), and birth weights ranging from 350 g to 2460 g. One study (Kaltsogianni, 2023) included late preterm or term infants born after 34 weeks of gestation.[47] Across studies, the mean age

at enrolment varied between eight and 33 days postbirth. The duration of the period in which AOC was used ranged from 90 minutes to 24 hours, except in one study (Nair 2023)[56] in which the infants remained on AOC while being ventilated. Three main comparisons were made: one (1) AOC versus standard manual delivery; two (2) AOC versus enhanced manual delivery with additional personnel (a dedicated research nurse or research assistant adjusting FiO_2 to provide a level of care beyond routine practice); and three (3) comparisons between different AOC systems. The results indicated that AOC, compared to routine manual administration, likely increases the percentage of time that SpO_2 remains within the target range (mean difference 13.54%; 95% CI: 11.69-15.39; I^2 = 80%; 11 studies, 284 infants; moderate-certainty evidence). No studies assessed in-hospital mortality. Regarding the risk of severe ROP, AOC may have little or no effect compared to routine manual administration (risk ratio 0.24; 95% CI: 0.03-1.94; one study, 39 infants; low-certainty evidence). No studies assessed neurodevelopmental outcomes. When compared with enhanced manual oxygen delivery, AOC may show no clear increase in the time spent within the target SpO_2 range (mean difference 7.28%; 95% CI: –1.63-16.19; I^2 = 0%; two studies, 19 infants; low-certainty evidence). No studies reported on in-hospital mortality, severe ROP, or neurodevelopmental outcomes. A comparison was also made between AOC algorithms: CLACfast, which allows up to 120 automated adjustments per hour, and CLACslow, which allows up to 20 adjustments per hour. CLACfast may result in little or no increase in the percentage of time within the target SpO_2 range compared to CLACslow (mean difference 3.00%; 95% CI: –3.99-9.99; one study, 19 infants; low-certainty evidence). Again, no studies mentioned in-hospital mortality, severe ROP, or neurodevelopmental outcomes. The authors' conclusion was that AOC likely increases the amount of time that preterm infants on respiratory support spend within the target SpO_2 range when compared with routine manual delivery (with an average increase of 13.54%). However, it remains uncertain whether this improvement translates into meaningful clinical benefits. The available evidence on outcomes such as CLD and severe ROP is of low certainty, with minimal or no differences observed between interventions. Current data are also insufficient to draw firm conclusions regarding comparisons between AOC and enhanced manual delivery, or between different automated systems.

At our center, we conducted a prospective study over a three-year period (2020-2023), enrolling preterm infants born at less than 33 weeks' gestation who required supplemental oxygen within the first 24 hours of life and received either invasive or non-invasive respiratory support.[58] The closed-loop AOC system used was the PRICO feature integrated into Fabian® ventilators. Infants were randomized into two groups: one receiving combined automatic and manual FiO_2 control, and the other receiving standard manual control. The study included 89 patients: 45 received combined automatic and manual FiO_2 control, while 44 received routine manual control. Compared to the manual control group, the combined control group required fewer manual FiO_2 adjustments [median 0 (range 0-4) versus 4 (range 0-12), $p < 0.001$], had fewer episodes of hypoxemia [median 0 (range 0-4) versus 2 (range 0-8), $p < 0.001$] and hyperoxemia [median 0 (range 0-0) versus 1 (range 0-6) ($p < 0.001$)], and spent significantly more time within the target SpO_2 range [median (min - max), in minutes: 1440 (1424-1440) versus 1406 (936-1440), $p < 0.001$]. After adjusting for potential confounders, the time spent in normoxemia remained significantly higher in the combined control group (β = 81.5; 95% CI: 47.9-115.2; $p < 0.001$). The use of AOC was feasible and was associated with fewer episodes of both hypoxia and hyperoxia, resulting in longer periods of SpO_2 within the target range. Furthermore, its use was associated with a reduction in the need for manual FiO_2 adjustments.

Several other studies are currently underway.[41] Their results will be available soon, potentially providing more relevant information.

A related study was that of Dani C. et al. which assessed the impact of the PRICO system on cerebral (rSO_2 C) and splanchnic (rSO_2 S) oxygenation in a cohort of 20 preterm infants (< 32 weeks gestational age) experiencing frequent desaturation episodes.[59] The infants were randomly assigned in sequence to 12 hours of either automated or manual FiO_2 adjustment. Throughout this period, continuous monitoring was conducted using near-infrared spectroscopy (NIRS). While AOC with the PRICO® system did not improve cerebral or splanchnic oxygenation compared to manual control, it reduced SpO_2 fluctuations and shortened the duration of both hypoxemia (% of time SpO_2 < 80%: 1.6 ± 0.9 vs 3.0 ± 2.9, p = 0.46) and hyperoxemia (% of time SpO_2 > 95%: 17.6 ± 12 vs 30.9 ± 18.9, p = 0.014). The total percentage of time in normoxemia (SpO_2 90-95%) was significantly higher with AOC (66.0 ± 14.1% vs. 50.0 ± 20.6%, p = 0.009).

Assessing the clinical potential of automated oxygen control in neonatal care

Most studies have shown that AOC allows neonates to spend more percentage of time within the target SpO_2 range, although this period of time varies among studies, ranging from 40% to 91% with automatic control and from 32% to 82% with manual control[1]. Also, the width of the SpO_2 target range does not seem to have influence on the effectiveness of AOC[1]. Additionally, some studies showed that the AOC performs less favorably with hypoxia than with hyperoxia[1]. It should be noted, however, that while AOC can respond to hypoxia, it cannot prevent it[1].

Although current evidence suggests that AOC in preterm infants results in longer time spent within the target SpO_2 range, fewer episodes of hypoxemia and hyperoxemia, and reduced need for manual FiO_2 adjustments, several important questions remain before this technology can be widely adopted in NICUs.

It remains unclear whether improved oxygen saturation control translates into better clinical outcomes. The studies conducted to date have predominantly employed crossover designs rather than randomized controlled trials, are highly heterogeneous, and lack sufficient statistical power to assess the impact of AOC versus manual oxygen control on neonatal morbidities. Further studies are necessary to assess the effect of AOC on key short and long-term outcomes, including mortality, BPD, severe ROP, intraventricular hemorrhage, and long-term neurodevelopmental outcomes. The FiO_2-C study group trial (www.ClinicalTrials.gov: NCT03168516) is ongoing and will address questions related to neonatal outcomes and neurodevelopment at 24 months of corrected age, ensuring an appropriate assessment of safety and efficacy before AOC can be implemented as standard therapy[60].

Most existing trials compare AOC with routine manual adjustment. Evidence is still lacking on how AOC systems perform against enhanced manual protocols involving well-trained personnel and standardized oxygen management strategies.

The safety and effectiveness of AOC in different clinical settings and patient subgroups – such as those receiving invasive versus non-invasive respiratory support – require further exploration.

Before widespread adoption, comprehensive analyses of cost-effectiveness are needed. Additional considerations include equipment compatibility, training requirements, and the availability of technical support.

Standardized guidelines and regulatory frameworks must be developed to ensure its safe and consistent implementation across institutions. Validation of AOC systems across different ventilators and NICU environments is essential.

To support clinical decision-making and guideline development, larger and higher-quality multicenter randomized controlled trials are necessary to provide more robust evidence of effectiveness and safety.

Until these gaps are addressed, the routine use of AOC in NICUs should be approached with caution and guided by ongoing research findings.

Suggestions for future research

Future research in preterm infants should prioritize the inclusion of both short- and long-term clinical outcomes, including mortality, BPD, ROP, patent ductus arteriosus (PDA), intraventricular hemorrhage, periventricular infarction, sepsis, necrotizing enterocolitis, duration of mechanical ventilation, and time on oxygen therapy, as well as neurodevelopmental outcomes at two years of corrected age. To allow meaningful comparisons between clinical outcomes and physiological parameters such as SpO_2, researchers should favor parallel-group randomized controlled trial designs over crossover approaches. Moreover, these studies should involve large patient cohorts and clearly defined nosocomial groups. Finally, clinical trials are necessary to assess and compare the effectiveness of different oxygen regulation algorithms.

Conclusion

AOC in neonatology represents a significant advancement in care, with growing evidence indicating improved oxygen targeting, fewer episodes of hypoxia and hyperoxia, and reduced workload for clinicians. While the results to date are promising, current AOC systems still face important challenges, including individual patient variability, sensor limitations, and difficulties in integrating these technologies into routine clinical workflows. Future research should prioritize the optimization of control algorithms, the development of more accurate and reliable sensors, and the execution of large-scale parallel-group randomized clinical trials to assess long-term outcomes. These efforts will be essential to determine whether AOC systems should become the standard of care. As neonatal intensive care continues to evolve, investing in and refining these technologies will be critical to improving both the safety and effectiveness of care for preterm infants.

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G. Rocha: literature research, writing, and review of the manuscript.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. 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 or creation of the content of this manuscript.

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CASE REPORT

Breast milk jaundice: when to cease investigation in the jaundiced neonate?

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Abstract

Introduction: Breast milk jaundice is a benign condition in breastfed newborns, characterized by an increase in indirect bilirubin levels, resulting in yellowish discoloration of the skin and sclerae. It usually appears in the first week of life, with a peak incidence in the second week, and can persist for up to twelve weeks. This physiological condition is a diagnosis of exclusion and is not associated with any underlying pathology. **Case report:** A full-term previously healthy newborn presented with jaundice in the first week of life, which persisted beyond 14 days, requiring several cycles of phototherapy. After pathological conditions were excluded, the diagnosis of breast milk jaundice was confirmed, with complete resolution by two months of age. **Discussion:** This case highlights the importance of recognizing and properly managing this condition, emphasizing the need to educate parents about its benign nature and encouraging the continuation of breastfeeding.

Keywords: Neonatal jaundice. Breastfeeding. Neonatal hyperbilirubinemia. Phototherapy. Bilirubin. Infants.

Icterícia do leite materno: quando interromper a investigação no recém-nascido com icterícia?

Resumo

Introdução: A icterícia do leite materno é uma condição benigna em recém-nascidos amamentados; caracteriza-se pelo aumento dos níveis de bilirrubina indireta, resultando na coloração amarelada da pele e escleróticas. Geralmente surge na primeira semana de vida, com um pico de incidência na segunda semana, podendo persistir até às doze semanas. Esta condição fisiológica é um diagnóstico de exclusão, não estando associada a nenhumapatologia subjacente. **Relato de caso:** Recém-nascido de termo, previamente saudável, com icterícia na primeira semana de vida, que persistiu além dos 14 dias, com necessidade de vários ciclos de fototerapia. Após exclusão de causas patológicas,assumiu-se o diagnostico de icterícia do leite materno, com resolução da icterícia aos dois meses de vida. **Discussão:** O caso sublinha a importância de reconhecer e orientar corretamente esta condição e destaca a necessidade de educar os pais sobre a sua natureza benigna, incentivando a continuação da amamentação.

Palavras-chave: Icterícia neonatal. Aleitamento materno. Hiperbilirrubinemia neonatal. Fototerapia. Bilirrubina. Recém-nascido.

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Keypoints

What is known
- Breast milk jaundice is a benign condition that occurs in breastfed newborns.
- It appears in the first week of life and can persist for up to 12 weeks.
- It is a diagnosis of exclusion that rarely requires treatment.

What is added
- An atypical presentation, with extremely high bilirubin levels and multiple cycles of phototherapy with a small initial response to treatment.
- Description of a practical management approach to breastfeeding jaundice.
- Systematic review of the diagnostic assessment required to rule out pathological conditions of neonatal jaundice.

Introduction

Jaundice is characterized by yellow pigmentation of the skin and eyes caused by increased bilirubin levels in the blood. Almost all newborns have circulating bilirubin levels above 1 mg/dL and changes in the skin and sclerae are visible when levels are above 5 mg/dL. This makes jaundice one of the most prevalent conditions of the neonatal period, arising from elevated bilirubin production due to the short lifespan of fetal erythrocytes and immature hepatic enzymes.

Breast milk jaundice is a benign condition identified in healthy newborns who are being breastfed, and is marked by an increase in unconjugated bilirubin. This usually emerges after the first week of life, reaching its peak between the second and third weeks, and can persist – albeit with gradual improvement – for up to twelve weeks. Considered a diagnosis of exclusion, other potential causes must be ruled out, such as hemolytic disease, infections, or liver abnormalities. Despite its duration, this condition does not reflect any underlying illness, nor does it require the cessation of breastfeeding.[1,2]

This case is reported due to its atypical course of severe hyperbilirubinemia, responding to phototherapy but with repeated rebounds, requiring multiple treatment cycles. Despite extensive diagnostic evaluation, the final diagnosis was breast milk jaundice. This case demonstrates the difficulty of diagnosing neonatal jaundice and outlines a practical approach managing breastfeeding-associated hyperbilirubinemia.

Case report

A four-day-old newborn was seen at the pediatric emergency department with jaundice and excessive sleepiness. The pregnancy progressed without complications, and a fetal ultrasound at 22 weeks and six days detected an aberrant right subclavian artery. Group B *Streptococcus* screening was negative.

According to the obstetric history, this was the first infant of an O, Rh-negative mother, who received Rho (D) immune globulin at 32 weeks and had hypothyroidism managed with levothyroxine. The newborn was delivered via vacuum extraction at 38 weeks and five days, with a birth weight of 3130 grams, Apgar score of 10/10/10, and a small occipital cephalohematoma. The infant's blood type was A, Rh-positive, and the direct Coombs test was negative. The newborn remained hospitalized with her mother and was discharged on day three, exclusively breastfed, with a maximum weight loss of 8.5%. Jaundice was noted at discharge and a transcutaneous bilirubin assessment registered 11.8 mg/dL – below the threshold for phototherapy according to the 2022 American Academy of Pediatrics guidelines.

At the emergency department, blood testing revealed hemoglobin 18.3 g/dL, leukocytes 11,800/µL (Neutrophils 5,020/µL, Lymphocytes 5,060/µL), no reticulocytosis (67 G/L), platelets 279,000/µL, total bilirubin 26.8 mg/dL, direct bilirubin 0.5 mg/dL, lactate dehydrogenase 531 U/L, aspartate transaminase 53 U/L, alanine transaminase 29 U/L, gamma-glutamyl transferase 111 U/L, total proteins 5.2 g/dL, albumin 3.5 g/dL, C-reactive protein 0.37 mg/dL, and procalcitonin 0.09 ng/mL. The blood culture was negative. The urine sample obtained via bladder puncture showed normal urinalysis and a negative culture. Respiratory secretions tested negative for respiratory viruses.

According to the guidelines applied, the threshold for phototherapy at that time was 20.8 mg/dL, so treatment was initiated. After 24 hours, bilirubin levels declined, allowing for safe discontinuation.

Despite initial improvement, serial evaluations after cessation showed slight bilirubin rebounds, with values of 13.8 mg/dL at 12 hours and 16.3 mg/dL at 36 hours. These levels did not meet treatment criteria.

By day seven, total bilirubin increased to 21.4 mg/dL, crossing the threshold of 21.1 mg/dL, prompting phototherapy. After 24 hours, phototherapy was discontinued as total bilirubin decreased to 12.7 mg/dL. A cerebral ultrasound was performed with no abnormal findings.

On day eight, further lab investigations showed a decrease in lactate dehydrogenase from 531 to 432 U/L, no increase in transaminases, gamma-glutamyl transferase, or liver function abnormalities, no thyroid abnormalities, and no signs of hemolysis or anemia. The newborn screening test performed on day four was negative. Elevated lactate dehydrogenase prompted an evaluation for hemoglobinopathies. A hemoglobin electrophoresis showed 78.6% fetal hemoglobin and the remainder was hemoglobin A, which was consistent with the patient's age.

Approximately 48 hours after phototherapy cessation, on day 10, bilirubin rebounded to 21.7 mg/dL, just above the threshold of 21.5 mg/dL, leading to the resumption of phototherapy. A subsequent liver profile and cholestatic enzyme study showed no abnormalities. Another blood typing and direct Coombs test retrieved the same results as before.

The case was discussed with specialists in Medical Genetics and Hepatology, leading to an investigation to rule out Crigler-Najjar and Gilbert syndromes, which were both negative. DNA sequencing of the UGTA1 gene excluded Lucey-Driscoll syndrome and its variants.

On day 12, after 36 hours of therapy, double phototherapy was discontinued as bilirubin levels normalized. A follow-up re-evaluation on day 15 showed total bilirubin at 14.1 mg/dL. Urinary *cytomegalovirus* DNA was not detected; alpha 1 antitrypsin levels, cryotest, and eosin-5-maleimide test results were normal.

Throughout hospitalization, the newborn was breastfed exclusively, maintained good sucking reflexes, normal urination and defecation, adequate weight gain, and remained clinically stable with a normal physical examination. After three cycles of phototherapy, bilirubin levels stabilized, and multiple secondary causes were ruled out. The newborn was discharged on day 17. Outpatient follow-up showed a downward bilirubin trend and the patient became anicteric by two months, with no recurrence of jaundice.

Discussion

Bilirubin is a product of heme protein breakdown from erythrocytes. In the bloodstream, bilirubin is primarily bound to albumin and transported to the liver, where it binds to ligandins (Y proteins), which are in lower concentrations at birth. It is transported to the smooth endoplasmic reticulum, where it undergoes conjugation. This process attaches glucuronic acid to bilirubin under the action of the enzyme uridine diphosphoglucuronate glucuronosyltransferase (UDPGT), making it water-soluble and allowing excretion in the bile. However, UDPGT activity is significantly reduced in newborns, leading to less efficient conjugation.[2]

A genetic mutation in the *UGT1A1* gene, which encodes UDPGT, can further impair bilirubin conjugation. After conjugation, bilirubin is excreted into the duodenum via the bile ducts and metabolized by intestinal bacteria into urobilinogen. A portion is reabsorbed into the enterohepatic circulation, while the rest is excreted as stercobilin in feces or filtered by the kidneys as urobilin in urine. Unconjugated bilirubin, being lipophilic, can cross the blood-brain barrier and cause central nervous system damage. In severe hyperbilirubinemia (levels above 25-30 mg/dL), there is a significant risk of kernicterus, a form of neurological dysfunction.[3,4]

The exact cause remains unclear; there is scientific evidence that genetic and environmental factors have a role in breast milk jaundice. Certain components of breast milk, such as pregnane-3α,20β-diol, might inhibit UDPGT activity, reducing bilirubin conjugation and excretion. Additionally, ß-glucuronidase in the intestinal mucosa hydrolyzes conjugated bilirubin back into its unconjugated form, increasing enterohepatic circulation. This is aggravated by lower intestinal bacterial enzyme levels in newborns, which limit bilirubin degradation into stercobilin.[1,3]

Inflammatory cytokines, particularly interleukin-1β (IL-1β), can suppress *UGT1A1* gene expression and increase intestinal permeability, promoting bilirubin reabsorption. IL-1β also modifies the intestinal microbiome, intensifying the enterohepatic cycle of bilirubin.[2,3]

Epidermal growth factor (EGF), another breast milk component, enhances gastrointestinal tract development but slows intestinal transit, favoring bilirubin reabsorption. EGF also interferes with bilirubin transport in hepatocytes, impairing its excretion into bile.[1,2]

Elevated alpha-fetoprotein (AFP) levels are often found in newborns with breast milk jaundice. AFP inhibits *UGT1A1* activity, interferes with bilirubin transporters like MRP2, and influences genes responsible for bilirubin metabolism and excretion.[1,2,4,5]

Breast milk jaundice is a multifactorial condition involving enzymatic inhibition, increased enterohepatic circulation, and altered bilirubin metabolism.

Treatment depends on the infant's total serum bilirubin level but the prognosis is favorable. First-line treatment is phototherapy, initiated if bilirubin levels exceed the thresholds recommended by the 2022 American Academy of Pediatrics' guidelines, except in cases requiring immediate exchange transfusion.

Table 1. Differential diagnosis of breast milk jaundice

Pathological causes of indirect hyperbilirubinemia	Laboratory exams/tests in the newborn
Increased production	
Immune-mediated hemolysis	
ABO incompatibility Rh incompatibility	Blood type and Rh factor typing Positive direct coombs test Decreased hematocrit and hemoglobin Reticulocytosis Peripheral blood smear with microspherocytes
Non-immune-mediated hemolysis	
Congenital defects of the erythrocyte membrane (e.g., spherocytosis, elliptocytosis)	Decreased hematocrit and hemoglobin Reticulocytosis Peripheral blood smear with spherocytes, elliptocytes EMA binding test, cryotest, erythrocyte osmotic fragility test
Erythrocyte enzymatic defects (e.g., G6PD, pyruvate kinase deficiency, and congenital porphyria)	Decreased hematocrit and hemoglobin Reticulocytosis Peripheral blood smear with bite cells, "prickle" cells Blood G6PD level measurement (outside the acute phase)
Hemoglobinopathies	Decreased hematocrit and hemoglobin Reticulocytosis Peripheral blood smear with target cells Hemoglobin electrophoresis
Infection/sepsis	Leukocytosis, neutrophilia Increased C-reactive protein/procalcitonin Positive blood culture/urine culture
Polycythemia (children of diabetic mothers, LGA, IUGR, high altitudes)	Increased hematocrit and hemoglobin
Blood sequestration in closed areas (e.g., cephalohematoma)	Decreased hematocrit and hemoglobin CT/MRI of the Head
Decreased clearance	
Crigler-Najjar syndrome Type I and II Gilbert's syndrome	Genetic test (sequencing of the UGTA1 gene)
Congenital hypothyroidism	Newborn screening Thyroid function
Inborn errors of metabolism (galactosemia, tyrosinemia)	Newborn screening Extended analytical assessment with uric acid, ammonia, lactate Capillary glucose and ketone levels Arterial blood gas Urine sample collection Genetic tests (for confirmation)
Breastfeeding jaundice	Hypovolemia and hypernatremia

EMA: eosin-5-maleimide; G6PD: glucose-6-phosphate dehydrogenase; CT: computed tomography; MRI: magnetic resonance imaging.

The gravest complication of neonatal jaundice, although rare in breast milk jaundice, is acute bilirubin encephalopathy and kernicterus (chronic bilirubin encephalopathy) due to its potential for severe neurological damage.[6]

Parents should be informed about the nature of breast milk jaundice and its likely clinical progression. Additionally, breastfeeding should be continued unless contraindicated.

In cases of elevated and recurrent jaundice after phototherapy, as described in this case, further investigation must exclude pathological conditions. It is key to rule out secondary causes of unconjugated hyperbilirubinemia, such as hemolysis due to isoimmunization (e.g., ABO or Rh incompatibility), erythrocyte membrane/enzyme defects, hereditary hemolytic diseases (e.g., hemoglobinopathies), infections, polycythemia, thyroid disorders

(e.g., hypothyroidism), metabolic diseases related or unrelated to bilirubin metabolism, blood sequestration in closed areas (e.g., cephalohematoma), or breastfeeding-associated jaundice (by assessing breastfeeding techniques and weight gain).[1-3]

In neonatal jaundice, investigations should be guided by the clinical presentation, the progression of hyperbilirubinemia, and the exclusion of key pathological conditions, as outlined in table 1. In the absence of significant family history and other clinical manifestations such as anemia, lethargy, anorexia, or neurological changes, it is considered jaundice with no alarming signs. Furthermore, an adequate clinical and laboratory response to treatment, along with the exclusion of risk factors (e.g., blood incompatibilities, hemolytic diseases, infections, and genetic disorders) and a normal neonatal screening test, supports the diagnosis of breast milk jaundice.[1,6]

Nonetheless, clinical follow-up is essential to monitor the emergence of warning signs.

In this case, given the infant's excellent clinical condition, adequate weight gain, clinical evolution consistent with breast milk jaundice and exclusion of pathological conditions of neonatal jaundice due to unconjugated bilirubin, a diagnosis of breast milk jaundice was established. After discharge, clinical monitoring was chosen, with further investigation reserved if warning signs were identified.

In summary, breast milk jaundice is a benign condition that can persist for several weeks in breastfed newborns. Accurate diagnosis and identification are essential, as is the exclusion of serious pathological conditions, to reach the final diagnosis. Distinguishing it from other forms of jaundice is crucial for properly managing the newborn and ensuring the safe continuation of breastfeeding.

Author contributions

C. Gomes: planning; resources; writing; F. Curinha: planning; writing; R. Castelo: planning; supervision; validation; writing.

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Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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CASE REPORT

Leukoerythroblastosis in sickle cell disease: think about parvovirus B19 infection!

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Abstract

Introduction: Leukoerythroblastosis is a rare condition characterized by leukocytosis and myeloid and erythroid precursors in the peripheral blood. Only a few cases of parvovirus B19 associated leukoerythroblastosis in a context of SCD have been reported. **Case report:** A 27-month-old girl with HbSS presented with fever and non-specific symptoms; a WBC of 92,300 × 109/L, hemoglobin 3.3 g/dL, platelets 607 × 109/L, and 113 NRBCs/100 WBCs; her reticulocyte count (RC) was 11,000/uL. A marked leukoerythroblastosis and thrombocytosis were evident on the blood smear. After appropriate treatment and within 48 hours her RC rose to 391,000/uL, her WBC had fallen to 19,500 and her platelets to 419,000. The PB19 IgM was positive. **Discussion:** This case describes the unusual association between leukoerythroblastosis and thrombocytosis, in conjunction with a transient aplastic crisis secondary to PB19 infection. It also illustrates the clinical utility of the IRF parameter in documenting marrow recovery. PB19 should be considered in the laboratory examinations of children with leukoerythroblastosis.

Keywords: Leukoerythroblastic. Thrombocytosis. Sickle cell disease. Parvovirus B19. Aplastic anemia.

Leucoeritroblastose na doença falciforme: pense em infecção por parvovírus B19!

Resumo

Introdução: A reação leucoeritroblástica é uma condição rara caracterizada por leucocitose e percursores mielóides e eritróides no sangue periférico. Estão descritos poucos casos de leucoeritroblastose associada ao parvovirus B19, no contexto de Drepanocitose. **Relato do caso:** Menina de 27 meses com hemoglobinopatia SS procura cuidados médicos por febre e sintomas inespecíficos. Tinha 92,300 × 109/L leucócitos, hemoglobina de 3,3 g/dL, plaquetas de 607 × 109/L, e 113 eritroblastos/100 leucócitos; reticulocitopenia de 11,000/ul; na morfologia do sangue periférico observava-se leucoeritroblastose e trombocitose. Após tratamento a contagem reticulocitária subiu em 48h para 391,000/ul, com descida dos leucócitos e plaquetas. A IgM para PB19 foi positiva. **Discussão:** O caso descreve a associação invulgar entre leucoeritroblastose e trombocitose, no contexto de crise aplástica secundária a PB19. É ilustrativo da utilidade do parâmetro IRF (immature reticulocyte fraction) na documentação da recuperação medular. A infeção a PB19 deve ser considerada no estudo de crianças com leucoeritroblastose.

Palavras-chave: Reação leucoeritroblástica. Trombocitose. Drepanocitose. Parvovirus B19. Anemia aplástica.

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Keypoints

What is known

- A leukoerythroblastic reaction is always an abnormal finding and may indicate a myeloproliferative neoplasia among other non-malignant causes.
- PB19 infection causes an aplastic crisis in SCD patients
- Immature reticulocyte fraction (IRF) is used to document bone marrow response in different scenarios, mainly following transplant.

What is added

- Additional evidence of parvovirus B19 as an etiologic agent of leucoerythroblastic reaction in SCD (third case described in the literature).
- Association of leucoerythroblastic reaction and thrombocytosis
- *Wait and see* approach in the described scenario, before conducting invasive exams to exclude malignancy.
- Clinical utility of immature reticulocyte fraction (IRF) to document marrow recovery following an aplastic crisis.

Introduction

Leukoerythroblastosis (LEB) is a rare condition, particularly in pediatric ages. It is characterized by leukocytosis and the presence of myeloid and erythroid precursors in the peripheral blood.[1] Leukoerythroblastic reaction (LER) has been poorly described in various clinical scenarios, mostly in association with malignancies.[2] The association of parvovirus B19 (PB19) with LEB has rarely been reported.[3-7]

In a setting of sickle cell disease (SCD), PB19 infection can cause a transient aplastic crisis, which can be life threatening. However, there are only two reported cases of an association between leukoerythroblastic reaction and PB19 in SCD patients.[8-9]

We report the case of a 27-month-old girl with SCD, hemoglobin SS disease (HbSS), who presented with severe anemia, LEB and thrombocytosis, secondary to a parvovirus B19 infection.

Case-report

A 27-month-old girl with HbSS was seen at the emergency department due to intermittent fever over the previous week. She also had a cough, vomiting and felt progressively unwell. Her SCD was diagnosed at 11 months of age in a context of dactylitis. Her medical history showed a vaso-occlusive crisis at 19 months of age and a fever with no localizing signs when she was 24 months old; she was on amoxicillin prophylaxis and she was receiving the recommended standard of care. On examination, she was prostrated, pale, mildly dehydrated with a grade 3/6 systolic ejection murmur. No splenomegaly was observed.

Her full blood count (FBC) showed a white blood count (WBC) of 92,300 × 10^9/L (36% neutrophils, 42% lymphocytes), hemoglobin (Hb) 3.3 g/dL (baseline 7.5 – 8 g/dL), platelets (PLT) 607 × 10^9/L, and 113 nucleated red blood cells (NRBCs)/100 WBCs; her reticulocyte count (RC) was 11,000/uL which raised the suspicion of PB19 infection. Morphologic examination

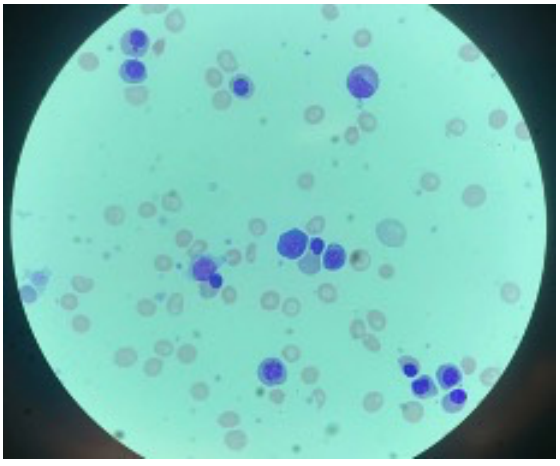

Figure 1. Peripheral blood showing marked leukoerythroblastosis.

of the peripheral blood showed marked leukoerythroblastosis, low myeloblasts (< 2%), high NRBCs, and thrombocytosis (Fig. 1); C-reactive protein was 1.49 mg/dL and lactate dehydrogenase (LDH) was 1870 U/L. The patient was transfused with packed red blood cells, and received intravenous hydration and ceftriaxone. Within 48 hours, the RC rose to 391,000/uL (652,000/uL at 72 hours) and 325 NRBCs/100 WBC; the WBC had fallen to 19,500/uL and the platelets to 419,000. Two weeks later her FBC showed baseline values (Table 1). Seroconversion to PB19 was documented: IgM positive (index > 48, rf > = 1.1), as well as IgG (24); IgG and IgM one month before were both negative and four months after the episode, her IgM was 1.4 and IgG was > 46. The search for other infectious agents, namely EBV, was negative. From a clinical point of view, the outcome was excellent with a full recovery.

Discussion

The child described presented with blood counts suggesting a myeloproliferative neoplasia, but was

Table 1. Red cell parameters, WBC and platelet count, upon admission and at follow-up

	Days of admission				Days after discharge	
	1	2	3	4	10	16
GV (x10^{12}/L)	1.12	2.20	2.27	2.40	3.31	3.00
HGB (g/dL)	3.3	6.2	6.5	6.7	8.9	8.2
HTC (%)	9.4	18.6	20.4	21.7	27.8	23.6
RET (%)	1	2.9	17.2	27.2	9.1	10.3
RET (x10/L)	11,000	62,000	391,000	652,000	301,000	319,000
RPI	0.5	2.4	15.4	26.2	14	10.8
IRF (%)	36.8	57.1	63.8	44.9	18	23.1
HFR (%)	14	22	38.8	23	5.8	8.8
MFR (%)	22.8	35.1	25	21.9	12.2	14.3
LFR (%)	63.2	42.9	36.2	55.1	82	76.9
EB/100 L	113	272	325	183.8	3.8	1.2
WBC (x 10^9/L)	92,300 (36.8%N 42.7%L 17%M)	37,300 (41.8%N 47.2%L 9.7%M)	19,500 (21.2%N 72.4%L 5.1%M)	14,400 (20.5%N 70.2%L 7.2%M)	14,900 (25.5%N 64.4%L 8.4%M)	24,400 (19.1%N 71.7%L 7.1%M)
Plat (x 10^9/L)	607,000	494,000	419,000	334,000	547,000	306,000

ultimately diagnosed with transient leukoerythroblastosis. This scenario overlaps with the one with two children with SCD, parvovirus B19 infection and a leucoerythroblastic reaction, described in the literature.[8-9] These children were three and 12 years old, both splenectomized, with the following laboratory values at presentation: WBC 62.3 × 10^9/L, Hb 5 g/dL, PLT 586 × 10^9/L, 111 NRBCs per 100 WBCs and WBC 72.2 × 10^9/L, Hb 3.9 g/dL, PLT 1533 × 10^9/L, and 15.3 NRBCs per 100 WBCs, respectively. They also demonstrated signs of laboratory recovery at 24-48 hours after treatment, and baseline values within one week. As the leukoerythroblastic peripheral blood findings seen in this patient were transient, there was less concern about a primary bone marrow disease or bone marrow necrosis, and therefore a bone marrow biopsy was not performed. It is also important to highlight that focal bone marrow necrosis can be a complication of a vaso-occlusive crisis in SCD patients, paradoxically more frequent in patients affected by less severe heterozygote genotypes,[10] and they can present with a leukoerythroblastic blood picture.

A recent systematic review of the causes of LEB showed two principal groups of diseases, corresponding to solid and hematological malignancies.[2] Although it is typically associated with marrow infiltrative processes, it may also represent marrow response to stressors such as hypoxia, peripheral destruction/sequestration, or sepsis. Other etiologies, in order of frequency, were hemolytic diseases and infection. The authors concluded that its presence in malignant disease is an indicator of adverse prognosis. On the other hand, in cases where LER had neither underlying hematological or solid neoplasms, its manifestation, prognosis, and impact on daily clinical practice was undetermined due to insufficient data. The child described had a favorable outcome in the setting of a transient viral infection, as previously reported.

The most common causes of LER in children and young adults are viral infections and juvenile myelomonocytic leukemia (JMML); less frequently observed, but also important are osteopetrosis, myelofibrosis, and neuroblastoma.[11-14] Leukoerythroblastosis that mimics juvenile myelomonocytic leukemia has been reported in children with viral diseases, such as Epstein-Barr virus,[15-16] cytomegalovirus,[17] and parvovirus B19, as mentioned before.[3-7] Several groups have recently shown a leukoerythroblastic peripheral smear in COVID-19 adult patients without any history of an underlying hematological malignancy,[18-20] with this being more rare in children.[21] Other conditions rarely described in association with a leucoerythroblastic reaction include Kawasaki disease and severe malaria.[22-23]

Specifically regarding parvovirus B19, it shows tropism to bone marrow, particularly erythroid progenitor cells, and

is responsible for erythema infectiosum (fifth disease) in immunocompetent children and for transient red cell aplasia (aplastic crisis) in those who have an underlying hemolytic disease, such as SCD. Infection suppresses erythropoietic activity and infected cells fail to proliferate and mature, thereby compromising the production of new red blood cells. Reticulocytopenia is a cardinal sign, but also the quantity of RNA found in reticulocytes quantified by flow cytometry (IRF, immature reticulocyte fraction) is a measurable change within the cell that can define the maturity of the various subpopulations in circulation. Bone marrow 'stress or shift' reticulocytes are primarily defined by high RNA within the cell. It has been shown that sequential IRF measurements entail a practical significance in their ability to assess the status of engraftment during the post-transplant period because IRF increases three to five days prior to the increase seen in reticulocyte counts and therefore can assess marrow erythropoietic activity earlier than the reticulocyte count.[24,25] This earlier increase was also seen in our patient (Table 1), although less strikingly, providing further evidence of the transient nature of the clinical condition. IRF behaved as an early and sensitive indicator of erythropoiesis and a useful parameter for monitoring the regenerative bone marrow response, following an aplastic crisis.

In conclusion, a leukoerythroblastic reaction is always an abnormal finding. This case is unique as it describes the unusual association between leukoerythroblastosis and thrombocytosis, in conjunction with a transient aplastic crisis secondary to parvovirus B19 infection. Moreover, it perfectly documents the reticulocyte/erythroblastosis response in the timeline of a PB19 infection, specifically in the setting of SCD. Our patient's presentation suggests that PB19 serology should be considered in the laboratory examinations of children who present with leukoerythroblastosis and that watchful waiting might be a wise initial approach. The IRF is a useful tool in documenting marrow recovery and can potentially provide additional information in the diagnostic work-up.

Author contributions

A. Figueiredo: data collection, critical reviewing; S. Mota Faria: data collection, bibliographical search, critical reviewing; F. Salazar: bibliographical search, critical reviewing; A. Santos: bibliographical search, analysis and interpretation, critical reviewing.

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Morphea: insights into a rare skin condition

Morfia: percepções sobre uma condição de pele rara

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Keypoints

What is known

- Morphea is a rare connective tissue disease, characterized by skin inflammation and fibrosis.
- Genetic predisposition, immune dysregulation, and environmental factors are recognized triggers.
- Treatment can be challenging, especially in moderate to severe cases requiring systemic therapy.

What is added

- Morphea can present with characteristic painful lesions in pediatric patients.
- A multidisciplinary approach, involving dermatology, is essential for accurate diagnosis and management.
- Although diagnosis is clinical, skin biopsies are useful for confirming the diagnosis, especially in complex cases.

The authors describe the case of a previously healthy seven-year-old female with no suggestive family history, who was admitted to the Emergency Department (ED), with hyperpigmented, thickened, longitudinal band-like lesions on the right lateral arm and axillary regions, which had appeared six weeks prior to the ED visit.

The patient reported localized pain, although there was no history of significant medical or trauma.

Upon examination, the lesions measured approximately 15 centimeters on the long axis, had a central waxy area, surrounded by an erythematous margin, were of a brownish color, and appeared to increase in size (Figs. 1A and B). They did not, however, affect joint mobility.

There were no other manifestations, namely arthralgia, loss of mobility, Raynaud's phenomenon, or other cutaneous alterations.

She had been admitted two weeks previously for the same symptoms.

During her first visit to the ED, an ultrasound was performed, which revealed no significant findings and the patient was discharged with flucloxacillin.

Morphea was suspected and the collaboration of the Dermatology Department was then requested.

During the patient's time on the ED, a skin biopsy was performed, showing thickening of the dermis, with lymphocytic and plasma cell infiltrates at the edges, with an area of central sclerosis, confirming the diagnosis of active linear morphea (or juvenile localized scleroderma [JLS]).

There were no other extracutaneous symptoms.

The patient was transferred to Outpatients and was treated with prednisolone (1 mg/kg/day for two months with subsequent gradual tapering), along with topical treatment with calcipotriol, tacrolimus, and betamethasone, with satisfactory resolution of both lesions.

Morphea is an inflammatory fibrotic skin disorder.[1] Although its etiology remains poorly understood, it involves genetic predisposition, immune dysregulation, and environmental factors.[2]

It is more common in girls and typically appears around the age of five to seven.[1]

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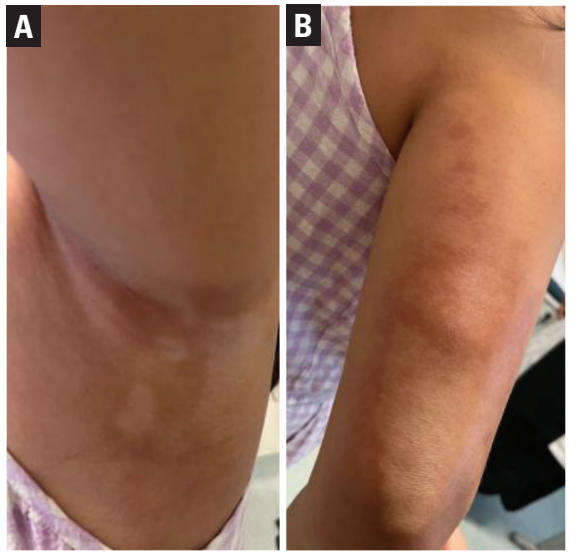

Figures 1. Lesions on **A:** the axillary and **B:** external right arm regions.

According to recent classification systems, morphea is divided into five different types: circumscribed (plaque), linear, generalized, pansclerotic, and mixed.[1]

A diagnosis can usually be made from a clinical history and physical examination alone. However, a skin biopsy may be helpful in establishing a definitive diagnosis, especially in complex or atypical cases.[3]

Certain diagnostic tools, such as the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) can be used to evaluate disease activity and severity.[4]

Diagnosis and treatment should be prompt so as to prevent the development of any sequelae of the disease.[5]

The differential diagnosis is broad, including conditions such as systemic sclerosis, lichen sclerosus, and keloids.[6]

Treatment aims to arrest disease activity and prevent disfigurement, joint contractures, and restriction to mobility.[7]

Types of therapy depend on the level of disease activity, subtype, and depth of the lesions.[6]

Mild variations of the disease can be managed by topical or intralesional steroids, tacrolimus, calcipotriol, or a combination of calcipotriol and a steroid, imiquimod, and/or phototherapy.[7]

As for the disease-modifying antirheumatic drugs that should be started in combination with corticosteroids, experts recommend methotrexate as first-line treatment.[4]

In moderate to severe morphea, recommendations include methotrexate in combination with systemic steroids as an initial "bridge therapy". In cases of resistance, the options are mycophenolate mofetil, cyclosporine, and biological agents.[7]

Most patients have a good prognosis and achieve remission.[7] However, relapses are common, reported in 15 to 53% of JLS patients, so patients need to be monitored over the long term.[8] Extracutaneous complications are also frequent.[8]

Children with suspected JLS should be referred to specialized pediatric rheumatology centers to ensure accurate assessment and effective management.[4]

Author contributions

C.M. Francisco: conceptualization, data curation, methodoloy, writing – original draft; J. Frade: data curation, methodoloy, validation, writing – review and editing; I. Correia: project administration, validations, writing – review and editing; S. Fonseca: supervision, validation, writing – review and editing.

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Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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

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A rare case of neonatal molluscum contagiosum

Um caso raro de molusco contagioso neonatal

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Keypoints

What is known

- Molluscum contagiosum is a common skin infection seen in children.
- In rare circumstances, it can be transmitted during labor from an infected mother.
- There are defined risk factors that increase the risk of transmission.

What is added

- Unlike school-aged children, molluscum contagiosum in neonates tends to affect the scalp.
- Dermoscopy plays an important role on the differential diagnosis of this infection in neonates.
- Off-label topical treatment with 5% potassium hydroxide is a possible treatment option in this group.

A previously healthy six-week-old female infant presented at a pediatric consultation with multiple round, non-coalescing papules (< 1 cm in diameter) with an umbilicated center, affecting the scalp (Fig. 1 and 2). The lesions first appeared in small numbers over the two preceding weeks. No other skin alterations were found.

The infant was delivered via vacuum-assisted vaginal delivery. During the pregnancy and labor, the mother had similar lesions in the perineal region (Fig. 3). These lesions were left untreated by the obstetric team due to the perceived low risk of transmission. The physical examination of the newborn at birth was unremarkable. No specific measures were taken during delivery to prevent skin-to-skin contact between the mother and newborn.

Dermoscopy of the lesions revealed polylobulated whitish-yellow amorphous structures with peripheral linear vessels surrounding a central depression, consistent with the diagnosis of neonatal molluscum contagiosum (Fig. 4). The patient was referred to a pediatric surgery consultation and started on off-label topical treatment with a 5% potassium hydroxide solution, which resulted in progressive improvement (Fig. 5).

Molluscum contagiosum is common in school-age children. Its presentation during the first weeks of life is extremely rare, with fewer than 20 cases described in the scientific literature.[1-2]

This condition is caused by a double-stranded DNA virus of the *poxvirus* family and is typically transmitted through person-to-person contact or autoinoculation. However, in rare circumstances, it can be vertically transmitted through the birth canal of an infected mother.[2] Prolonged rupture of membranes and prolonged or instrumental delivery are risk factors for viral transmission.[1-4] The incubation period can range from two to eight weeks.[2] In the first months of life, the lesions are typically located on the scalp rather than the torso, arms, or limbs, as in older children.[2,3]

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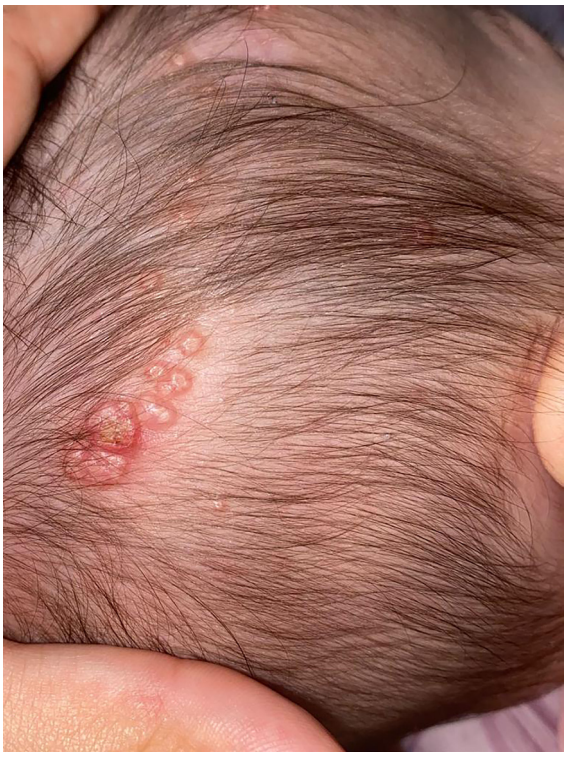

Figure 1. Molluscum contagiosum lesions located at the scalp of a newborn.

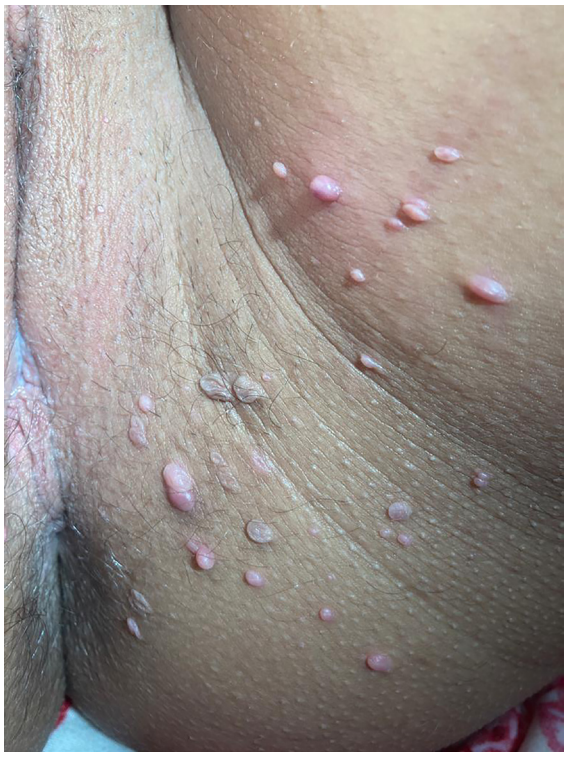

Figure 3. Multiple papules on the perineal region of the mother before labor.

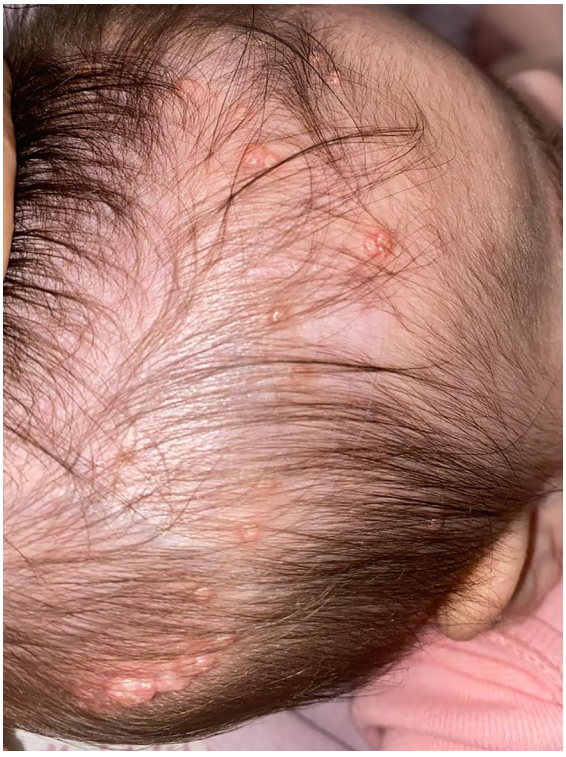

Figure 2. Multiple umbilicated papules scattered on the scalp.

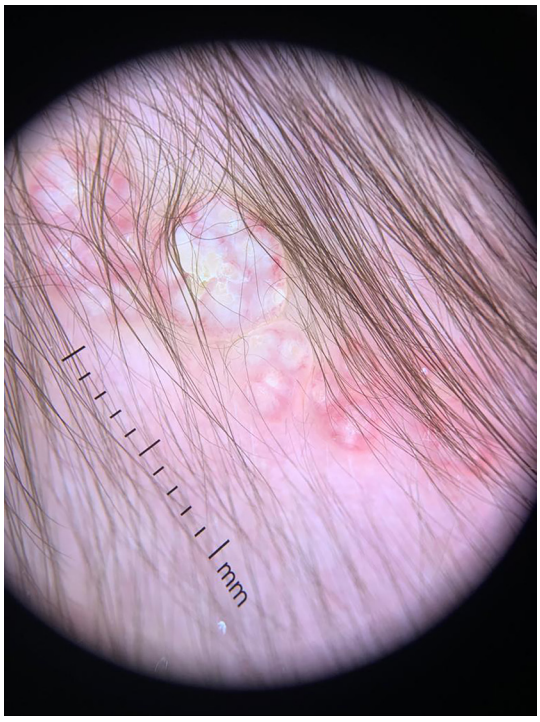

Figure 4. Dermoscopy of the lesions showing polylobulated whitish-yellow amorphous structures with peripheral linear vessels surrounding a central depression.

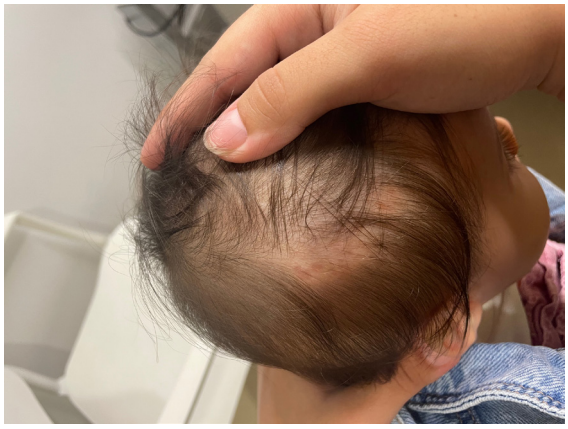

Figure 5. Residual lesions after treatment.

The diagnosis is primarily clinical; however, a biopsy may be indicated in cases of uncertainty.[3]

The prognosis is generally good, with spontaneous remission of the lesions occurring after two to four years in immunocompetent hosts.[5] However, to prevent transmission and auto-inoculation, topical therapies or the removal of the lesions with cryotherapy, curettage, or electrosurgery may be indicated.[3] In the literature, curettage is typically the preferred method of treatment for these cases.[1-4] Although there are no studies on the use of 5% potassium hydroxide in this age group, its apparent efficacy compared to other topical treatments made it a viable option in this case, with no side effects such as stinging or burning reported.[6,7]

Author contributions

L.P. Soares: came up with and designed the study, report, review, or other types of paper; acquired data from patients, research studies, or literature; analyzed and interpreted data from patients, research studies, or literature; drafted the article; critically reviewed the article for important intellectual content; provided final approval of the version to be published; agreed to be held accountable for the accuracy and integrity of the paper. B.B. Pedreira: acquired data from patients, research studies, or literature; critically reviewed the article for important intellectual content; provided final approval of the version to be published; agreed to be held accountable for the accuracy and integrity of the paper. B. Pereira: analyzed or interpreted data from patients, research studies, or literature; critically reviewed the article for important intellectual content; provided final approval of the version to be published; agreed to be held accountable for the accuracy and integrity of the paper. A. Cavaco: analyzed or interpreted data from patients, research studies, or literature; critically reviewed the article for important intellectual content; provided final approval of the version to be published; agreed to be held accountable for the accuracy and integrity of the paper.

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