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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 hídro-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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ORIGINAL ARTICLE

Exclusive breastfeeding and the impact of the NICU stay - a pilot prospective study

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Abstract

Introduction and Objectives: The World Health Organization aims for a prevalence of exclusive breastfeeding (EBF) at six months of ≥ 50%. Difficulties in EBF associated with Neonatal Intensive Care Unit (NICU) admission are documented, although with limited data in Portugal. The objective is to estimate the prevalence of EBF up to six months of age following NICU admission in the neonatal period and to evaluate factors related to EBF success. **Methods:** A prospective study was conducted on newborns admitted to a level III hospital NICU within the first 24 hours of life between October 2022 and January 2023. Data was collected by reviewing clinical records and interviews with caregivers during hospitalization and by telephone up to six months of age. **Results:** A total of 65 newborns were included with a mean gestational age of 35 weeks (SD ± 4) and a mean birth weight of 2411 g (SD ± 836). The primary reasons for hospitalization were prematurity (46%) and congenital anomalies (25%). At NICU discharge, 39% were under EBF. The prevalence of EBF was higher in newborns with a birth weight of < 1500 g (p = 0.025) and younger mothers (p = 0.020), but lower in cases of multiple pregnancies (p = 0.047). At two months of age, 29% maintained EBF, of which 53% were already on EBF at discharge. Up until six months of age, the prevalence of EBF was 14% while 29% continued with breastfeeding. **Discussion:** The prevalence of EBF at discharge was much lower than national data published regarding maternity unit discharge figures for healthy newborns. Determinants of EBF success were not identified and future studies with larger sample sizes are needed.

Keywords: Exclusive breastfeeding. Breastfeeding. Neonatal intensive care. Newborn. Prematurity.

Aleitamento materno exclusivo e o impacto do internamento na UCIN - um estudo piloto prospetivo

Resumo

Introdução e Objetivos: A Organização Mundial da Saúde tem como objetivo a prevalência do aleitamento materno exclusivo (AME) aos seis meses ≥ 50%. Estão descritas dificuldades no AME associadas ao internamento em Unidade de Cuidados Intensivos Neonatais (UCIN), embora existam dados limitados em Portugal. O objetivo é estimar a prevalência de AME até aos 6 meses de vida após internamento em UCIN no período neonatal e avaliar fatores relacionados com o sucesso de AME. **Métodos:** Estudo prospetivo, incluindo RN admitidos na UCIN de um hospital nível III nas primeiras 24 horas de vida, de Outubro 2022 a Janeiro 2023. Dados obtidos por consulta dos processos clínicos e entrevista aos cuidadores durante o internamento e por via telefónica até aos 6 meses. **Resultados:** Foram incluídos 65 RN com idade gestacional média 35 semanas (DP ± 4) e peso médio 2411g

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(DP ± 836). Os principais motivos de internamento foram prematuridade (46%) e anomalias congénitas (25%). À alta da UCIN, 39% encontravam-se sob AME. A prevalência de AME foi superior nos RN com peso ao nascimento < 1500g (p = 0,025) e mães mais jovens (p = 0,020) e inferior nos casos de gravidez múltipla (p = 0,047). Aos dois meses de idade, 29% mantinham o AME, dos quais 53% já estavam em AME à alta. Até aos seis meses, 14% mantinham o AME e 29% mantinham leite materno. **Discussão**: A prevalência de AME à data de alta foi inferior aos dados nacionais publicados à alta da maternidade de RN saudáveis. Não foi possível encontrar determinantes do sucesso do AME, sendo necessários estudos futuros com maior poder amostral.

Palavras-chave: Amamentação materna exclusiva. Amamentação. Cuidados intensivos neonatais. Recém-nascidon. Prematuridade.

Keypoints

What is known
- Exclusive breastfeeding continues to be the optimal method for nourishing newborns.
- Difficulties in exclusive breastfeeding associated with Neonatal Intensive Care Unit admission are recognized.

What is added
- The exclusive breastfeeding rates after NICU stays were much lower than national data published regarding maternity unit discharge figures for healthy newborns.
- The prevalence of exclusive breastfeeding at discharge was higher in newborns with a birth weight of < 1500 g.
- NICU practices must be improved, extending beyond premature newborns, where there have been more efforts to reinforce breastfeeding.

Introduction and objectives

Human milk has a unique composition, with antimicrobial, anti-inflammatory, and immuno-regulatory functions, relevant to a child's developing immune system[1].

Exclusive breastfeeding continues to be the optimal method for nourishing newborns, serving as the cornerstone for infant health by supplying essential and irreplaceable nutrients that are vital to a child's growth and development[1-5]. The World Health Organization (WHO) advocates for exclusive breastfeeding up to six months of age[4,5], with a WHO target of increasing the rate of exclusive breastfeeding in the first six months up to at least 50% by 2025[6].

Breastfeeding, even if partial or for a shorter period than desirable, has a beneficial effect when compared to exclusive feeding with infant formula[7].

According to the National Health Survey, the prevalence of exclusive breastfeeding in Portugal has shown un upward trend, yet it consistently falls below the recommended levels[8].

National data reveals exclusive breastfeeding rates ranging from 76.7% to 78.8% at the time of maternity unit discharge, followed by a subsequent decline to 51.6% and 22.1% at two and five months of age, respectively[9]. Literature describes similar trends, with various factors identified as contributors to the early cessation of exclusive breastfeeding[10-12]. There is also a link between neonatal intensive care unit (NICU) admission and heightened challenges in exclusive breastfeeding[13-16], although available data for Portugal is limited.

The objectives of this pilot study were to estimate the prevalence of exclusive breastfeeding up to six months of age following NICU admission in the neonatal period at the time that the Human Milk Bank was implemented and to assess clinical factors (pertaining to pregnancy, delivery, and NICU admission) and/or sociodemographic variables linked to exclusive breastfeeding success.

Methods

A prospective longitudinal observational study was conducted, with the study population consisting of newborns admitted to the NICU of a level III hospital within the first 24 hours of life. Systematic random sampling was used, based on the list of NICU admissions and in line with the inclusion criteria. These included all newborns admitted to the NICU (both inborn and outborn infants) between October 2022 and January 2023, with hospitalization within the first 24 hours of life. Exclusions comprised newborns contraindicated for breastfeeding, those who died during hospitalization or the follow-up period, caregiver refusal to participate in the study, loss of follow-up, and newborns with brief hospital stays for elective procedures. Five losses of follow-up were recorded due to failure to respond to telephone calls.

Written information was given to caregivers and after informed consent was obtained, clinical records were reviewed and caregivers were interviewed during hospitalization and by telephone up to six months of age, using a structured questionnaire. Variables included data

pertaining to pregnancy, family context, delivery, NICU admission, and associated problems.

Statistical analysis was performed using the SPSS® program (IBM, USA) v.28. In the descriptive analysis, normally distributed continuous variables were characterized by the mean (± standard deviation), while non-normally distributed variables were characterized by the median and interquartile range. Categorical variables were described by absolute and relative frequencies. The comparison between a continuous and a categorical variable was conducted through an independent t-test and Mann-Whitney U test for paired and independent samples, respectively. The comparison of two categorical variables was carried out using a chi-squared test and Fisher's exact test. Imputation was used to substitute reasonable guesses for missing data.

A p value of less than 0.05 was considered statistically significant.

Authorization was obtained from the hospital's Ethics Committee.

Results

A total of 70 newborns were recruited, with five lost at follow-up, resulting in a total sample of 65 participants. A descriptive analysis of the sample is summarized in table 1.

The mean birth weight was 2411 grams (± 836 grams), with a minimum of 940 grams and a maximum of 4065 grams. The mean gestational age was 35 (± 4) weeks, ranging from a minimum of 26 weeks and two days to a maximum of 40 weeks and five days.

The primary reasons for hospitalization were prematurity (46%), followed by congenital anomalies (25%), predominantly cardiac and digestive (Table 2).

During hospitalization in the NICU, 62 newborns received their mother's milk, 16 met the criteria for donor human milk (DHM) of which 11 (69%) were fed with DHM, and 45 received formula milk at some point during their hospital stay.

At NICU discharge, 62 newborns (95%) were being breastfed and 25 (39%) were being exclusively breastfed. At two months of age, 19 (29%) were exclusively breastfed, of which 10 (53%) were already on exclusive breastfeeding at discharge. Nine (14%) continued with exclusive breastfeeding until six months and 19 (29%) maintained breastfeeding (not exclusive). At four months of age, nearly 23% had initiated complementary feeding and by six months of age, all newborns had started it. Figure 1 illustrates the evolution of exclusive breastfeeding and any breastfeeding rates up to six months, compared to the WHO target for 2025 (above the red line).

Table 1. Sample descriptive analysis (n = 65)

	n (%)	Mean (± SD) or median (IQR)
Maternal age years		31 (± 5)
Multiparous mother	20 (31)	
Mother with higher education	27 (42)	
Employed mother	54 (83)	
Previous breastfeeding experience	22 (34)	
Multiple pregnancy	8 (12)	
Caesarean delivery	39 (60)	
Skin-to-skin contact in the first hour	26 (40)	
First contact with mother hours		1 (1-10)
Female newborn	35 (54)	
Newborn birth weight g		2411 (± 836)
Gestational age weeks		35 (± 4)
Length of stay days		12 (5-23)
Donor human milk use	11 (18)	
Need for surgery	6 (9)	

SD: standard deviation; IQR: interquartile range.

Table 2. Summary of reasons for NICU admission

Reasons for NICU admission	n (%)
Prematurity	30 (46)
Congenital anomalies	
Cardiac	6 (10)
Digestive	4 (6)
Polimalformative	3 (5)
Central nervous system	1 (1)
Other	2 (3)
Non-malformative cardiac pathology	1 (1)
Non-malformative neurologic pathology	3 (5)
Infectious risk/sepsis	7 (11)
Other	8 (12)

NICU: Neonatal Intensive Care Unit.

Table 3 presents a comparative analysis of exclusive breastfeeding at NICU discharge concerning factors related to the mother and pregnancy. At NICU discharge, exclusive breastfeeding was more common in younger mothers (p = 0.020) and less common in cases

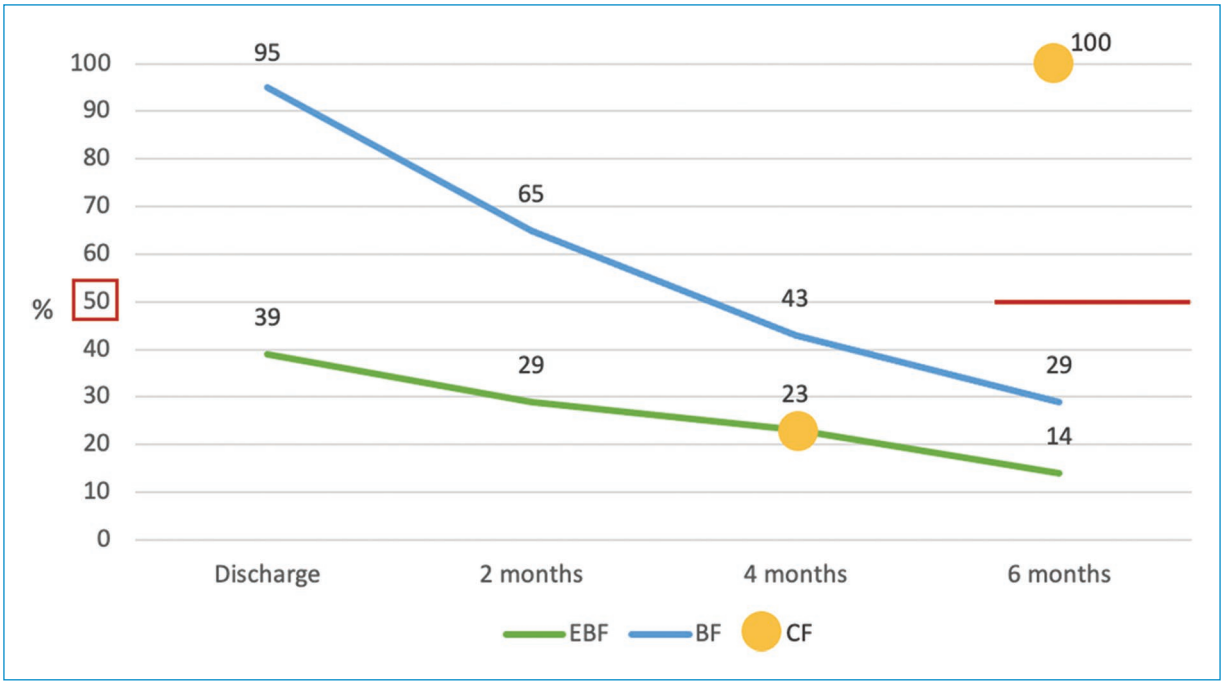

Figure 1. Evolution of exclusive breastfeeding and breastfeeding rates up to six months of age.
EBF: exclusive breastfeeding; BF: breastfeeding; CF: complementary feeding.

Table 3. Comparative analysis of exclusive breastfeeding rate at discharge from the NICU and factors relating to the mother and pregnancy

	NICU discharge		
	EBF n (%)		p
	Yes 25 (39)	No 40 (61)	
Maternal age mean, years	29.1	32.2	0.020†
Mother with higher education, n (%)	8 (32)	19 (48)	0.217*
European nationality, n (%)	22 (88)	34 (85)	0.987†
Employed mother, n (%)	18 (72)	34 (85)	0.202*
Previous breastfeeding experience, n (%)	9 (36)	13 (33)	0.772*
Multiparous mother, n (%)	7 (28)	13 (33)	0.702*
Multiple pregnancy, n (%)	2 (5)	6 (24)	0.047‡
Caesarean delivery, n (%)	16 (64)	23 (58)	0.603*

*Chi-squared test.
†Fisher's exact test.
‡Independent t-test
EBF: exclusive breastfeeding; NICU: Neonatal Intensive Care Unit.

of multiple pregnancies (0.047). Nevertheless, the limited number of cases of multiple pregnancies (two with exclusive breastfeeding and six without) is relevant and should prompt a careful interpretation of this finding.

No statistically significant differences were found regarding the mother's education or professional status, or prior breastfeeding experience. Similarly, no statistically significant differences were observed in factors related to the

Table 4. Comparative analysis of EBF at discharge from the NICU and factors relating to the newborn and the NICU stay

	NICU discharge		
	EBF n (%)		p
	Yes 25 (39)	No 40 (61)	
Sex, n (%) Female Male	 15 (60) 10 (40)	 20 (50) 20 (50)	0.431*
Birth weight mean, g	2267	2501	0.312‡
Gestational age/weight relationship, n (%) Small for gestational age Large for gestational age	 1 (4) 1 (4)	 5 (13) 3 (8)	 0.393† 0.889†
Gestational age mean, weeks	34	35	0.412‡
Need for surgery, n (%)	2 (8)	4 (10)	0.898†
Length of stay median, days	17	10	0.335‡
Skin-to-skin contact in the first hour, n (%)	11 (44)	15 (38)	0.603*
First contact with mother median, hours	4	2	0.141‡
Donor human milk	5 (20)	6 (15)	0.308†

*Chi-squared test.
†Fisher's exact test.
‡Mann-Whitney U test.
EBF: exclusive breastfeeding; NICU: Neonatal Intensive Care Unit.

Table 5. Comparative analysis of exclusive breastfeeding at discharge from the NICU, two months and six months, in relation to a newborn weight of < 1500 g and a gestational age of < 32 weeks

	NICU discharge			2 months			6 months		
	EBF n (%)		p	EBF n (%)		p	EBF n (%)		p
	Yes	No		Yes	No		Yes	No	
Birth weight of < 1500g	9 (36)	5 (12.5)	0.025*	2 (10.5)	12 (26.1)	0,203†	1 (11.1)	13 (23.2)	0.670†
Gestational age of < 32 weeks	8 (32)	5 (12.5)	0.056*	1 (5.3)	12 (26.1)	0.087†	1 (11.1)	12 (21.4)	0.674†

*Chi-squared test.
†Fisher's exact test.
EBF: exclusive breastfeeding; NICU: Neonatal Intensive Care Unit.

newborns and the NICU stay, including birth weight, gestational age, main diagnosis, need for surgery, duration of hospitalization, skin-to-skin contact, and DHM use (Table 4).

When analyzing the type of breastfeeding at NICU discharge, two and six months, taking a newborn weight of < 1500 grams and a gestational age of < 32 weeks into account (Table 5), we found that the prevalence of exclusive breastfeeding at discharge was higher in newborns with a birth weight of < 1500 grams (p = 0.025). In a gestational age of < 32 weeks, we observed a similar trend at the threshold of statistical significance (0.056). These links, however, were subsequently lost at two and six months.

Discussion

Despite breastfeeding being a priority in the NICU, exclusive breastfeeding rates tend to be low for hospitalized newborns[15], failing to meet the WHO recommendations. In line with international literature, the prevalence of exclusive breastfeeding at discharge was

much lower than the latest national data published regarding maternity unit discharge figures for healthy newborns[9]. A 2019 study from the same department[17] that investigated the prevalence of exclusive breastfeeding at maternity unit discharge and at two months in a population of healthy newborns reported rates of 80.5% and 59.7%, respectively.

In the population studied, no statistically significant differences were found concerning factors known to be associated with higher exclusive breastfeeding rates in healthy newborns, such as skin-to-skin contact, prior breastfeeding experience, or higher education status, a situation also noted in some international studies in the NICU[11,15].

Moreover, no statistically significant differences were found when comparing the reasons for NICU admission. However, in this study, prematurity and congenital anomalies, including cardiac and digestive anomalies requiring surgical correction in the neonatal period, accounted for 71% of the NICU admissions. Both of these conditions are potentially associated with added challenges to breastfeeding, but the literature on breastfeeding rates in relation to specific conditions requiring NICU admission is scarce, underscoring the need for further studies with larger samples.

According to a retrospective multicentric study involving Portuguese very preterm infants[18], 25.2% of newborns < 32 weeks of gestational age were exclusively on breast milk at hospital discharge. These results are similar to our data (32%). We also found that the prevalence of exclusive breastfeeding at discharge was higher in newborns with a birth weight of < 1500 grams. These findings are in line with an international study in a level II NICU[14] that also found better exclusive breastfeeding rates in premature infants at discharge, while gestational age did not significantly associate with exclusive breastfeeding rates during follow-up. The better rates of exclusive breastfeeding in smaller infants might be explained by NICU practices such as family-centered and neurodevelopment-focused care involving caregivers, which is particularly personalized to premature infants. It is also important to note that one of the criteria for DHM was a birth weight of < 1500 grams and the use of DHM instead of formula in this population might have served as a bridge to achieving exclusive breastfeeding at discharge. However, this study was not designed to address this matter and further studies are needed to clarify this.

The most relevant limitation of this study is the short recruitment period, leading to a small sample size. Further studies, both multicentric and with larger sample sizes, are needed to confirm these results and to identify the determinants of breastfeeding success in newborns admitted to Portuguese NICUs. Moreover, an extension of this pilot study conducted to evaluate the impact of the implementation of the Human Milk Bank on breastfeeding rates could provide an important insight.

This study is the first prospective publication on exclusive breastfeeding rates up to six months of age in NICU-admitted newborns in Portugal, encompassing both medical and surgical admissions. These preliminary results are presented to highlight the need for improvement in NICU practices, extending beyond premature newborns, where more efforts are made to reinforce breastfeeding.

Previous presentation

51º Congresso Português de Neonatologia (23 – 24th November 2023).

Author contributions

S. Soares Cardoso: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. S. Catarino: Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. S. Geraldes Paulino: Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article 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. Flor-de-Lima: Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. S. Pissarra: Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. S. Costa: Conception and design of the study, report, review or other type of work or paper; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Critical review of the article for important

intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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

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ORIGINAL ARTICLE

Prevalence and impact of bullying in a portuguese school: insights from a descriptive cross-sectional study

Catarina M. Francisco, Íris Santos Silva, Alexandra M. Rodrigues, Lara Torres, Pedro Fernandes, and Rita S. Oliveira*

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Abstract

Introduction and Objectives: Bullying is defined as peer violence, characterized by repeated aggression over time, the intention to cause suffering to others and an imbalance of power between the two sides. The authors set out to quantify the prevalence of bullying and characterize students' engagement and perception of bullying incidents. **Methods:** Descriptive cross-sectional study, in the form of a survey for students at a local school. A total of 199 children were surveyed, of which 55% were male and the median age was 11. **Results:** Regarding experiences of bullying, 60.3% (n = 120) responded positively, with 41% (n = 81) reporting incidents in the last six months. Approximately 8% reported being attacked in the previous week. **Discussion:** Most of the bullying episodes happened among children from the same class (23.6%), and the most common place of occurrence was the playground. Around 46.5% perceived school as a dangerous place. Regarding gender, bullying was more frequent in males (p = 0.013).

Keywords: Bullying. Social medicine. Pediatrics.

Prevalência e impacto do bullying numa escola portuguesa: perceções de um estudo descritivo transversal

Resumo

Introdução e Objetivos: O bullying é definido como violência entre pares, caracterizada pela repetição de agressões ao longo do tempo, intenção de causar sofrimento ao outro e desequilíbrio de poder entre as duas partes. Os autores avaliaram a prevalência de *bullying* em crianças de uma escola local, bem como a sua perceção do mesmo e o papel adotado **Métodos:** Estudo transversal descritivo, consistindo na aplicação de um questionário. Houve um total de 199 inquiridos. 55% eram do sexo masculino, a mediana foi de 11 anos. **Resultados:** Em relação a episódios de *bullying* sofridos, 60,3% (n = 120) responderam afirmativamente, 41% (n = 81) relataram ter tido episódios nos últimos 6 meses, e 8% na semana anterior. **Discussão:** A maioria dos episódios foi entre crianças da mesma turma (23,6%), ocorrendo mais frequentemente no recreio. Aproximadamente 46,5% classificaram a escola como perigosa. Os casos de *bullying* foram mais frequentes em rapazes (p = 0,013).

Palavras-chave: Bullying. Medicina social. Pediatria.

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Keypoints

What is known
- Bullying involves a pattern of aggression that occurs repeatedly over time.
- Bullying can occur not only in schools, but at home or online.

What is added
- 60% of children suffer from bullying.
- Acts of bullying are related to school performance.
- Around 5% of the surveyed children needed professional psychological help to overcome bullying.

Introduction

Bullying is defined as peer violence, characterized by repeated aggression over time, the intention to cause suffering to others and an imbalance of power between the two sides[1].

It has a negative impact on victims' health and psychosocial development[2].

This power imbalance may stem from physical strength, social status within the group or group size. Power may also be achieved by knowing a person's vulnerabilities[3], and using them to humiliate.

Bullying encompasses not only physical aggression, but also verbal attacks (e.g. name-calling or threats), social aggression (e.g. social exclusion or spreading rumors) or, more recently, attacks through the internet and social media (also referred to as cyberbullying)[3].

Large-scale studies conducted in Western nations suggest that 4–9% of young people frequently engage in bullying behaviors, with 9–25% of school-age children being bullied. Some children may also be both bullies and victims, simultaneously[4].

As bullying is an important issue, the authors sought to evaluate its prevalence and characterize its impact in a local school setting.

The aim of this article was to quantify the prevalence of bullying in our region and to examine students' roles, engagement and perception of bullying incidents.

Materials and methods

Descriptive cross-sectional study, consisting of carrying out a survey through the administration of an anonymous standardized questionnaire, modified from the Costa, P. and Pereira, B. (2010) version[5]. The survey was distributed to students in the 5th and 6th grades at an elementary school in the Guarda region. Children were selected according to their school year (5th or 6th), as the authors believed children in this age range would have a heightened awareness of bullying episodes and aggressive behaviors.

Parents authorized students' participation through written consent. The questionnaire was completed by students in their ordinary classroom settings. Only questionnaires which were completed, with no missing responses, were considered valid for analysis.

The questionnaire comprised three sections: the first section addressed matters from the victim's perspective, the second section from the aggressor's perspective and the final section explored children's perceptions of bullying incidents.

Data analysis was conducted using SPSS® Statistics version 29 for descriptive and statistical analysis.

The authors defined victims as anyone who reported suffering any type of violence from their classmates and aggressors as students who admitted engaging in these same acts.

Acts of violence encompassed various behaviors, including physical attacks (such as beating and kicking), verbal offenses and offensive gestures, threats among students (with or without the use of weapons) and damage or theft of school material; defamation, either to other classmates or through the internet; and exclusion.

Categorical variables were evaluated through absolute frequencies and continual variables were evaluated as an average (min, max and standard deviation). A chi-squared test was used to analyze categorical variables. Statistical significance was considered when $p < 0.05$.

Results

A total of 199 children participated in our questionnaire after parental consent. Of these, 55% were males, the average age was 11.18 and the median age was 11, with a min of 10 and a max of 13. Eleven questionnaires were excluded due to incorrect or incomplete filling in.

About 7% of the children had failed one or more years, and 19.6% (n = 37) of the children were reported to have some kind of poor behavior, such as receiving notes on the school record, facing disciplinary sanctions or experiencing suspensions.

In terms of the questions asked about suffering bullying episodes, 60.3% (n = 120) answered affirmatively, with 41% (n = 81) of the children reporting episodes in the past six months, and of these, 8% mentioned attacks the previous week.

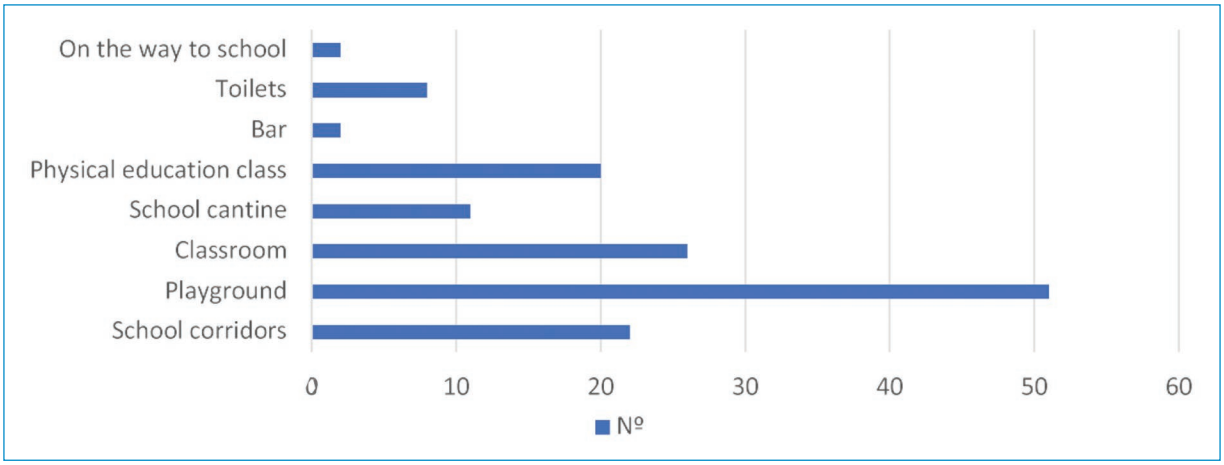

Figure 1. Bullying, place of occurrence.

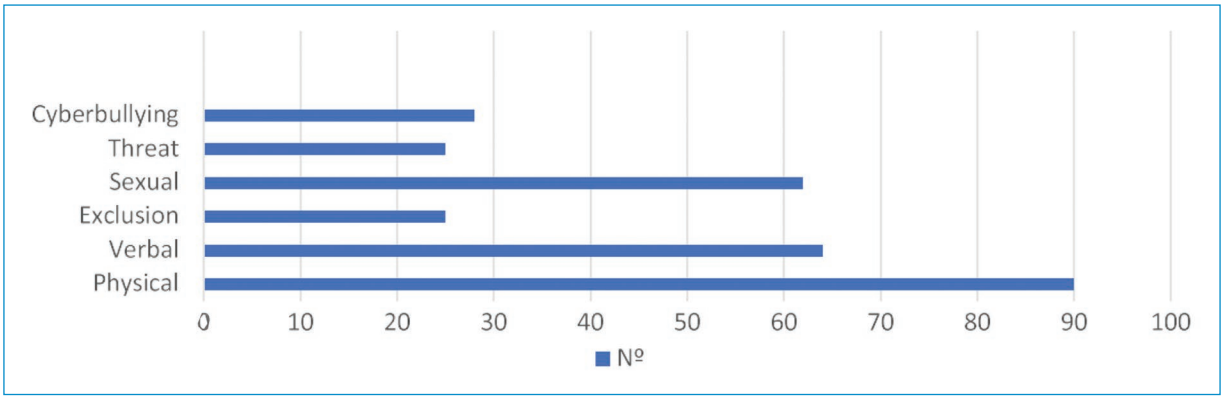

Figure 2. Forms of bullying perceived worst by students.

Most of the bullying episodes occurred among children within the same class (23.6%), while 17.1% reported aggressors from a different class.

The primary location for these incidents was the playground, followed by classrooms (Fig. 1).

The most serious form of bullying identified by children was physical aggression, reported 90 times, followed by verbal aggression, reported 64 times. Sexual aggression was mentioned 62 times (Fig. 2). It is worth pointing out that students were allowed to select multiple forms of aggression.

When asked who they reached out to in these situations, 52% mentioned their parents or a responsible adult at school, 21% preferred to keep it to themselves, and 13% told their teachers. No children went to talk to the school psychologist.

When asked about the dominant feeling after an episode of bullying, the predominant answer was sadness and humiliation (n = 28) followed by shame (n = 15).

About 5.5% of the children reported seeking psychological or medical support to face these types of situations.

When asked from the aggressor's perspective, 26.6% (n = 53) of children admitted to committing acts of violence in the past six months. Of these, 68.5% did so more than once, with 14% occurring in the last week. Most (72.5%, n = 37) claimed they acted in self-defense.

When asked about violent behavior towards a school employee, only 6% (n = 12) answered affirmatively.

Finally, regarding the children's perception of acts of bullying, the worst-considered form of bullying was physical, mentioned 90 times, followed by verbal, mentioned

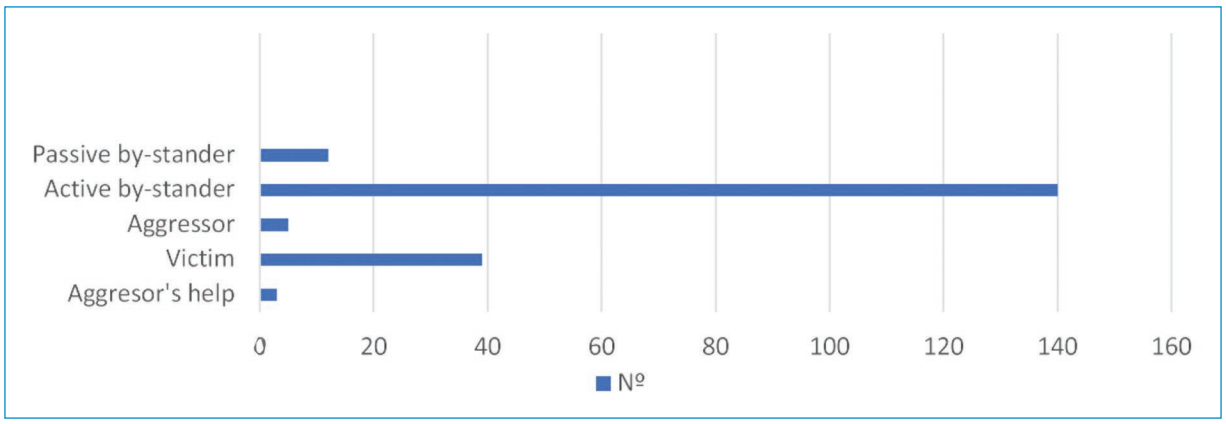

Figure 3. Role adopted during bullying episodes.

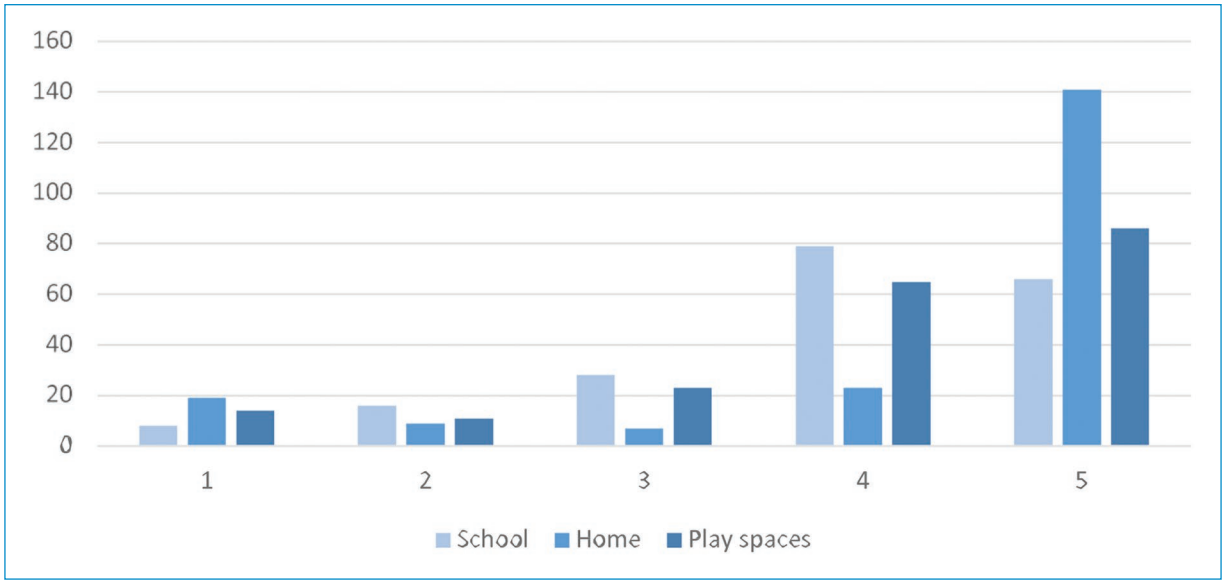

Figure 4. Scores attributed to different environments according to children's affinity for them.

64 times and sexual (considered as performing acts of a sexual nature or any kind of harassment, and insulting others in a sexual manner or making sexual comments), mentioned 62 times (Fig. 2).

The authors also asked about what role most children assumed during episodes of bullying, with about 70% of the children responding that they perceived themselves as active bystanders, i.e. people who tried to end the situation and help the victim (Fig. 3).

Students were also asked to attribute points according to their affinity to different environments (school, home and play spaces), with one defined as "low affinity/total dislike of the space" and five defined as "high affinity/they like the space a lot"; the results are displayed in figure 4. The majority attributed high scores (four or higher) to these spaces.

Students were also asked if they perceived school as a safe place and 46.5% responded negatively.

When analyzing gender, the authors found a statistical significance between children, as males were more frequently bullies ($p = 0.013$ (Table 1)).

Another interesting point was that suffering from bullying did not seem to be related to students' school performance, as children who failed one or more years did not show a significant relation to being victims ($p = 0.377$).

On the contrary, children who failed one or more years are more frequently bullies ($p = 0.04$ (Table 1)).

Table 1. The association between the occurrence of acts of bullying and the following traits: gender, school performance, behavior and being an aggressor/victim (chi-squared test)

Trait	Category	Bullying acts	No bullying acts	p
Gender	Male	37	73	0.013
	Female	16	73	
Disciplinary reports	Reports	17	22	0.026
	No reports	35	122	
Victim of bullying	Academic failure	10	4	0.377
	No academic failure	110	75	
Bully	Academic failure	7	7	0.04
	No academic failure	46	139	
Bully vs victim	Victim	42	78	0.01
	Not victim	11	68	

The authors also found that school behavior was also related to acts of bullying, as students who had more notes on their disciplinary card, as well as school sanctions (suspensions, detentions, etc.), appeared to engage in more acts of violence in the last six months, when compared to others (p = 0.026 (Table 1)).

Another statistically significant finding was that out of the 53 children who reported experiencing bullying, 42 also admitted to engaging in violent behaviors towards others, being simultaneously both victims and bullies (p = 0.01 (Table 1)).

Discussion

The authors found the collected data relevant, not only due to the high prevalence of bullying situations, especially when compared to other series[5,6], but also because of the notable disparity between the number of individuals identifying themselves as bullies (26.5%) and those identifying as victims (46%), the latter being a lot higher. Other studies show a different tendency, with a higher number of bullies compared to victims[5], or even when victims are more prevalent than bullies, the disparity between the two groups is not as high as this[6].

To explain this difference, it could be suggested that only a few individuals are responsible for the aggressive actions but considering the difference in the number of answers, that explanation does not seem to apply here.

The authors believe that, victimization is more intensely perceived by children than in previous series, hence the larger difference between our results.

This, in our opinion, is related to the fact that bullying episodes are always more traumatizing to the victim than to the aggressor, who tends not to value the episodes of poor behaviors toward others, and this may explain why substantially more people report themselves as victims. Also, children who externalize acts of violence may feel ashamed of their behaviors and therefore may not admit to do it.

There was not, at the time of the study, a high prevalence of cyberbullying, although according to what is described in the literature, this is increasing over time[7].

There was a proven male predominance in performing acts of bullying. This is consistent with existing literature, where there is a slight male predominance in bullying[3].

The relationship between poor school behavior and acts of bullying is obvious to the authors, as bad behavior encompasses bullying itself.

The need for medical or psychological support, although small (5.5%), is already significant to the authors, as no child should be placed in an environment so traumatizing that they require professional help.

Being bullied is associated, in the short term, with severe symptoms of mental health problems and, furthermore, has long-lasting effects that can persist until late adolescence[3].

Also, in our study, the percentage of students who keep these episodes to themselves is worrying, and students should be encouraged to speak out. In the literature, results show that adolescents who are bullied report higher loneliness and greater levels of anxiety and depression than their nonvictimized peers[3].

The person who most children reached out to when these episodes happened was their teacher, although the total number of children reporting bullying episodes is relatively low.

This is in line with what is described in the literature., with students allegedly avoiding reporting incidents as they lack faith in staff members' ability to intervene[8].

The authors believe it would be interesting to have more support from school psychologists, i.e. in the form of training activities with children or educational sessions for parents or teachers, to allow for proper recognition of these episodes and correct conduct by all the parties involved.

Also, the perception of a lack of safety among children is, from our point of view, very high. It is important that children feel safe in school, so they can reach max

development at all levels (physical, mental and emotional) and can build meaningful relationships. Some authors suggest that these feelings of insecurity could negatively predict self-disclosure and lead to posttraumatic stress symptoms[9].

Previous studies have already proven a significant association between physical symptoms and psychological complaints like anxiety and depression[10].

Also, many authors have highlighted the relationship between victimization and developing psychiatric issues related to bullying[10].

Finally, the authors found it curious that 42 children are simultaneously victims and aggressors, showing that the percentage of children who engage in acts of violence, even though they suffer from these same acts, is significant.

The main limitation of this study, the authors point to the fact that the survey was filled out by children, who can be rather inconsistent in their answers and recall of past situations.

The definition of bullying might also not be entirely clear to them, particularly the notion of repeated acts of violence, defining bullying.

Despite these limitations, the authors believe the study is relevant due to the sample size and the fact that it allowed us to reach interesting conclusions on the topic, particularly regarding the significant importance children attribute to bullying episodes and how bullying affects their perception of the school environment. Understanding these patterns may enable us to intervene appropriately during future episodes of violence.

Conclusion

Bullying poses a threat to children's well-being and acts of bullying should be stopped at all costs. The percentage of acts of bullying was surprisingly high, with around 60% of children identifying as victims. Additionally, the percentage of children seeking any kind of psychological support underscores the need to address this issue.

The survey highlighted physical aggression as the worst form of violence.

Raising awareness not only among children but also parents, teachers, school directors and the entire school community is crucial to adequately prevent bullying and promote a peaceful environment in schools. The authors suggest incentivizing well-organized support networks and lectures on the topic to help children perceive schools as safe environments.

While some studies suggest that anti-bullying campaigns have limited effects, there are some strategies that can be effective. According to the literature, the most effective interventions are those that address the student as a whole and act on a social, family, education and individual level[11]. In our local school community, organizing lectures on this topic could prepare children and empower them to handle future bullying situations effectively. Similar initiatives could be implemented in other school regions across the country.

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Author contributions

C.M. Francisco: 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 (mandatory for all authors); Agreement to be accountable for the accuracy or integrity of the work (mandatory for all authors). I.S. Silva: Analysis or interpretation of data from patients, research results, or literature search; Drafting the article; Final approval of the version to be published (mandatory for all authors); Agreement to be accountable for the accuracy or integrity of the work (mandatory for all authors). A.M. Rodrigues: Critical review of the manuscript for important intellectual content; Final approval of the version to be published (mandatory for all authors); Agreement to be accountable for the accuracy or integrity of the work (mandatory for all authors). L.M. Torres: Drafting the article; Final approval of the version to be published (mandatory for all authors); Agreement to be accountable for the accuracy or integrity of the work (mandatory for all authors). P. Fernandes: Critical review of the manuscript for important intellectual content; Final approval of the version to be published (mandatory for all authors); Agreement to be accountable for the accuracy or integrity of the work (mandatory for all authors).

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Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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

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ORIGINAL ARTICLE

High-flow nasal cannula effectiveness in acute bronchiolitis: a retrospective study

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Abstract

Introduction and Objectives: Acute bronchiolitis (AB) is a leading cause of hospital admission in pediatric patients. The main objective of this study was to evaluate the effectiveness of high-flow nasal cannula (HFNC) oxygen therapy in AB. **Methods:** Retrospective cohort study. Patients (1–24 months of age) admitted with AB in a tertiary hospital were included, comparing the periods before ('preHFNC: Apr/2018–Nov/2019) and after the introduction of HFNC ('postHFNC: Nov/2019–Apr/2022). The outcome measure of effectiveness was transfer to the intensive care unit (ICU). Effect measures were relative risk (RR), absolute risk reduction (RRA) and number needed to treat (NNT). **Results:** Of the 486 patients included, 196 were preHFNC and 290 were postHFNC. Of the latter, 46 (14.9%) required HFNC. Treatment with HFNC was associated with a significant reduction ($p < 0.001$) in respiratory rate, use of accessory muscles, wheezing and, consequently, an improvement in the WARM score. In the postHFNC period, there were fewer transfers to the ICU (21.4% vs. 13.8%, $p = 0.027$), with RR = 0.66, RRA = 7.6% and NNT = 13. In patients treated with HFNC, daycare attendance ($p = 0.036$; OR 91.7) and a higher WARM score 24 hours after HFNC ($p = 0.009$; OR 16.2) were predictors of transfer to the ICU (Hosmer-Lemeshow: $x 2 = 0.82$, $p = 0.976$). In the survival curve for time to ICU admission, preHFNC patients were transferred earlier ($p = 0.013$). None of the patients under HFNC required invasive ventilation. **Discussion:** The introduction of HFNC in the treatment of AB reduced the need for the ICU and was associated with a clinical improvement in several respiratory parameters. On the basis of the NNT, it is estimated that three to four ICU admissions were avoided in the postHFNC period.

Keywords: Pediatric respiratory care. Intensive care unit. Invasive ventilation. Respiratory rate. Respiratory distress.

Efetividade da oxigenoterapia de alto fluxo na bronquiolite aguda: estudo retrospetivo

Resumo

Introdução e Objetivos: A bronquiolite aguda (BA) é das principais causas de internamento em idade pediátrica. O principal objetivo deste estudo foi avaliar a efetividade da oxigenoterapia por cânulas nasais de alto fluxo (CNAF) nestes doentes. **Métodos:** Estudo de coorte retrospetivo. Incluídos doentes (1–24 meses) internados com BA num hospital terciário, comparando os períodos antes ('pré-CNAF':Abril/2018–Novembro/2019) e após introdução de CNAF ('pós-CNAF':Novembro/2019-Abril/2022). A medida de efetividade foi a transferência para cuidados intensivos (UCI). As medidas de efeito foram:

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risco relativo (RR), redução risco absoluto (RRA) e número necessário para tratar (NNT). **Resultados:** Incluídos 486 doentes, 196 pré-CNAF e 290 pós-CNAF. Destes últimos, 46 (14.9%) necessitaram de CNAF. O tratamento com CNAF associou-se a uma redução significativa (p < 0,001) na frequência respiratória, uso de músculos acessórios, pieira, alterações dos sons pulmonares e, consecutivamente, melhoria no score de Warm. No pós-CNAF verificaram-se menos transferências para UCI (21,4% vs 13,8%, p = 0,027), com RR = 0,66, RA = 7,2% eNNT = 13. Nos doentes sob CNAF, a frequência de infantário (p = 0,036; OR 91.7) e maior score de Warm às 24 h CNAF (p = 0,009; OR 16.2) foram preditores de transferência para UCI (Hosmer-Lemeshow: x2 = 0,82, p = 0,976). Na curva de sobrevivência para o tempo até admissão na UCI, os doentes pré-CNAF foram transferidos mais precocemente (p = 0,013). Nenhum dos doentes sob CNAF necessitou de ventilação invasiva. **Discussão:** A introdução de CNAF no tratamento da bronquiolite aguda reduziu a necessidade de UCI, associando-se a uma melhoria clínica em diversos parâmetros respiratórios. De acordo com o NNT, estima-se que tenham sido evitados 3–4 internamentos em UCI no pós-CNAF.

Palavras-chave: Cuidados respiratórios pediátricos. Unidade cuidados intensivos. Ventilação invasiva e não invasiva. Frequência respiratória. Dificuldade respiratória.

Keypoints

What is known
- Current guidelines suggest only supportive therapy, such as oxygen therapy, respiratory support and maintaining hydration for AB treatment.
- HFNC therapy has emerged as a new method of respiratory support, due to its good tolerability and safety.
- Studies suggest that HFNC can decrease the work of breathing, the need for intubation and prevent ICU admission, although the evidence is still limited.

What is added
- In our cohort, the introduction of HFNC in the treatment of AB reduced the need for ICU admission.
- The use of HFNC was associated with a clinical improvement in several respiratory parameters.
- It is estimated that three to four ICU admissions were avoided in the postHFNC period.

Introduction

Acute bronchiolitis (AB), a lower respiratory tract infection that is generally caused by respiratory viruses, is one of the leading causes of hospital admission in pediatric patients. Although most cases are self-limiting, between one and 5% will need hospital admission[1], and up to 23.8% of these patients will require critical care due to respiratory impairment or apnea[2]. Respiratory syncytial virus (RSV) is the most common virus identified (63.5%), but coinfection may be present in 35.5% patients[3]. Prematurity and preexisting comorbidities, such as heart disease, chronic respiratory disease, neuromuscular disease or immunodeficiencies were identified as risk factors for severe disease[4]. Various medical therapies have been investigated in patients with bronchio-litis, but none of them have shown efficacy[5]. Current guidelines suggest only supportive therapy, such as oxygen therapy, respiratory support and maintaining hydration[1]. For years, mild AB was limited to noninvasive oxygen therapy with low-flow nasal cannula. Patients with severe dis-ease required noninvasive ventilation (NIV) or invasive mechanical ventilation (IMV)[6]. High-flow oxygen therapy through a nasal cannula (HFNC) has emerged as a new method of supportive treatment with the administration of warm, humidified airflow, with or without oxygen, due to its simplicity, good tolerability and safety[6]. Some studies suggest that HFNC could decrease the work of breathing[7], the need for intubation[8] and prevent high-cost intensive care[9]. However, more recent studies have shown that HFNC may not be as superior compared to single oxygen therapy (SOT)[10]. So, the evidence on its effectiveness and specific indications in AB is still limited. The aim of this study was to evaluate the effectiveness of HFNC in AB treatment by assessing the proportion of intensive care (ICU) admission. We also analyzed the changes in work of breathing and differences in the timing of ICU admission in patients on HFNC. Predictive factors for the need for HFNC and HFNC failure were evaluated.

Materials and methods

Study design, setting and participants

We conducted a retrospective cohort study including patients aged under 24 months with a diagnosis of AB that required hospital admis-sion at our tertiary hospital, Centro Materno-Infantil do Norte, Centro Hospitalar

Universitário do Porto, between April 2018 and March 2022, inclusive. Patients with incomplete electronic medical records, neuromuscular diseases and pulmonary chronic diseases under home oxygen therapy were excluded.

In November 2019, HFNC was introduced in our hospital, with the AIRVO2 Fisher&Paykel® systems. It was started in the pediatric wards following a clinical protocol based on different pediatric societies' recommendations. Study data was collected between September and December 2022.

This study has been reviewed and approved by the Ethics Committee of Centro Hospitalar Universitário do Porto (2022.124(097-DEFI/099-CE). This manuscript followed STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines[11].

Variables

AB diagnosis was defined according to national guidelines criteria[12]. Two groups were made, based on the availability of HFNC. The 'preHFNC' group included the participants admitted before HFNC was available at our hospital [April 2018 – October 2019] and the 'postHFNC' group included participants admitted after HFNC was available [November 2019 – March 2022].

The main outcome measure of HFNC effec- tiveness was admission to the ICU. Secondary outcomes were differences in the timing of ICU admission in patients on HFNC and changes in the work of breathing after starting HFNC.

Data collection

All the data were extracted from the elec- tronic medical records: date of admission, date of discharge, date of birth, age, sex, weight on admission, prematurity, need for respiratory support in the neonatal period, preexisting comorbidities (pulmonary, cardiac, neurologic, immunodeficiency or chromosomal disorders), personal or family history of allergies, exposure to tobacco smoke, daycare attendance, day of illness on admission, clinical presentation on admission (fever, cough, dyspnea, rhinorrhea, vomiting, diarrhea, respiratory rate, oxygen sat- uration, work of breathing and pulmonary auscultation), viral identification in nasopharyngeal aspirate, antibiotic therapy, HFNC use, admission to the ICU, blood gas analysis, ICU length of stay, NIV and IMV. In patients on HFNC we also recor- ded: respiratory rate and work of breathing immediately before and 24 hours after initiating HFNC.

The WARM score was calculated for each participant on admission, and immediately before and 24 hours after initiating HFNC[13].

Statistical methods

We performed statistical analysis using SPSS® version 27 (SPSS IBM, New York, NY, USA). Descriptive statistics are presented as means (M) and standard deviations (SD) for quantitative and symmetrically distributed variables; medians (Mdn) and interquartile ranges (IQR) are presented for quantitative and non-symmetrically distributed variables. Frequencies (n) and proportions (%) are presented for qualitative variables. Normality was assessed using the Shapiro-Wilk test and histogram observation. T-tests were used to compare quantitative variables after checking for homogeneity of variance using Levene's test. When the normality assumption was not met, the Mann-Whitney U test was used. Chi-square tests were used to compare proportions across qualitative variables. The Cochran-Mantel-Haenszel test was used to control the effects of a third variable when evaluating the association between qualitative variables. Fisher's exact test was used when the expected frequency was lower than five in more than 20% of the contingency table cel/mm. Logistic regression was used to measure the association between the dependent variable (HFNC use and failure) and a set of independent variables. The Hosmer-Lemeshow test ($p > 0.05$) assessed the quality of adjusting binomial data to a logistic model-type. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

The impact of introducing HFNC was assessed by using the following effect measures: relative risk (RR), absolute risk reduction (ARR) and the number needed to treat (NNT). We analyzed the changes in quantitative secondary outcome variables (WARM score and respiratory rate) by using the Mann-Whitney U for paired samples. Qual- itative variables (work of breathing and pulmonary sounds) were compared using the Marginal Homogeneity test. We also conducted a survival analysis of the time to ICU admission by calculating adjusted hazard ratios by means of Cox regression. Statistical significance was set at $p < 0.05$. Missing data were omitted and the remaining data analyzed.

Results

There were 502 admissions with AB diagnosis in the study period. Sixteen patients were excluded: 10 with

incomplete data, four with neuro-muscular disease and two under home oxygen therapy (Fig. 1). Of the 486 patients included in the study, 196 were in the preHFNC cohort and 290 in the postHFNC cohort (Table 1). There were no demographic and *a priori* clinical statistical differences between the periods. In the postHFNC group, 46 patients (14.9%) received respiratory support with HFNC.

Comparison of preHFNC vs. postHFNC

There was a significant reduction in the number of ICU admissions in the postHFNC group (21.4% vs. 13.8%, p = 0.027), corresponding to a RR of 0.66 (CI 0.43–0.95), ARR of 7.6% (0.65–14.61) and NNT of 13 (6.84–153.08). There were no significant differences in the respiratory support techniques used in each group, but there was a trend towards a reduction in the need for NIV (17.3% vs. 12.5%) and for IMV (2.6% vs. 2.0%). No differences in overall or ICU length of stay were found between the groups. On the survival analysis, patients that needed ICU admission were transferred earlier in the preHFNC group (mean 0.3 vs. 0.8 days; p = 0.013; Fig. 2).

PostHFNC period analysis

In the postHFNC period, there were no age, gender or preexisting comorbidity differences between patients that received HFNC and those who did not (Table 2). However, patients that needed HFNC were admitted earlier in the course of their disease (median days of illness on admission: 2.8 vs. 4.3; p < 0.001) and had a higher WARM score on admission (median 2.3 vs. 1.7; p < 0.001). Enterovirus and bocavirus were more frequent in the HFNC group (7.8% vs. 3.6%, p < 0.001; 11.1% vs. 2.6%, p = 0.015, respectively).

In the multivariate analysis, exploring predictive factors for the need for HFNC in the postHFNC period, the identification of enterovirus (OR 9.30; 95% – CI 2.90 29.80; p < 0.001), an earlier day of illness on admission (p = 0.005; 95% CI 0.62–0.92; OR 0.76) and a higher WARM score (p = 0.004; 95% CI 1.14–1.96; OR 1.5) were found to predict a higher probability of HFNC use (Hosmer-Lemeshow test: x^2 = 4.7, p = 0.698). Within the participants that used HFNC, there was a significant decrease in respiratory rate (from 57.2 ± 10.3 to 46.3 ± 8.9; p < 0.001) and in the WARM score (from 4.98 ± 0.65 to 2.31 ± 1.18; p < 0.001) 24 hours after initiating HFNC. There was also a significant reduction in muscle use, wheezing and increase in air exchange (p < 0.001). None of the participants on HFNC needed IMV and 10 (21.7%) needed NIV. However, out of those in the nonHFNC group, 26 needed NIV (10.7%; p = 0.038) and six (2.5%; p = 0.282) needed IMV. However, the higher prevalence of NIV in the HFNC group was mediated by a higher severity on admission. After adjusting for the WARM score, there was no statistical difference (p = 0.632).

In the multivariate analysis, HFNC failure (i.e., the need for ICU admission) was associated with daycare attendance (OR 91.7; 95% CI 1.34–6.28; p = 0.036) and a higher WARM score 24 hours after initiating HFNC (OR 16.2; 95% CI 2.01–130.80; p = 0.009), Hosmer-Lemeshow: x^2 = 0.82, p = 0.976.

Discussion

In our study, we found that significantly fewer patients needed ICU admission after the introduction of HFNC in our hospital. We also found a NNT of 13, which means that we may have avoided three to four ICU admissions between November 2019 and April 2022 (postHFNC period). Interestingly, there was a trend towards a reduction in the proportion of patients that needed NIV.

Several studies reported the same rates of ICU admission regardless of the use of HFNC[8,9]. However, Kepreotes et al. demonstrated that HFNC may have a role as a rescue therapy to reduce the proportion of children requiring high-cost ICU care[9].

Also, according to Kepreotes et al. and Franklin et al., there were no differences in overall length of stay or ICU length of stay between the groups[9,14].

When looking at predictive factors for HFNC use, we found that an earlier day of illness on admission, a higher WARM score and the identification of enterovirus were significantly associated with HFNC use. Caliskan et al. also found that a shorter duration between the onset of symptoms and admission is an independent parameter for severe bronchiolitis development[15]. Parker et al. reported that patients with a higher accessory muscle use and tachypnea had a higher risk of needing major intervention[16]. In regard to enterovirus infections, Renois et al. and Asner et al. found a greater clinical severity in bronchiolitis with enterovirus infection[17,18].

In analyzing the response to HFNC oxygen therapy, we verified a significant decrease in respiratory rate, muscle use, wheezing, air exchange and consequently the WARM score. Overall, there was a significant decrease in the work of breathing, which is in line with the study conducted by Pham et al., where HFNC appeared to offload the diaphragm and reduce the work of breathing in bronchiolitis[7].

Table 1. Patients' characteristics by group

	Total sample	PreHFNC	PostHFNC	p
Participants, n	486	196	290	
Age in months, mean (SD)	5.7 (9.4)	5.18 (5.6)	6.05 (11.3)	0.316
Male, n (%)	266 (54.7)	110 (56.1)	156 (53.8)	0.613
Prematurity, n (%)	91 (18.7)	38 (19.5)	53 (18.3)	0.738
Neonatal respiratory support, n (%)	44 (9.1)	22 (11.3)	22 (7.6)	0.165
Preexisting comorbidities, n (%)				
Pulmonary disease	10 (2.1)	6 (3.1)	4 (1.4)	0.200
Cardiac disease	16 (3.3)	7 (3.6)	9 (3.1)	0.777
Immunodeficiency	2 (0.4)	2 (1.0)	0 (0.0)	0.085
Chromosomal disorders	4 (0.8)	2 (1.0)	2 (0.7)	0.692
Neurologic disease	14 (2.9)	6 (3.1)	8 (2.8)	0.845
Family history of allergies, n (%)	199 (41.5)	90 (46.6)	109 (38.0)	0.059
Personal history of allergies, n (%)	22 (4.6)	8 (4.1)	14 (4.9)	0.713
Exposure to tobacco smoke, n (%)	203 (42.5)	87 (45.3)	116 (40.6)	0.303
Daycare attendance, n (%)	98 (21.0)	43 (22.4)	55 (20.0)	0.532
Symptoms on admission, n (%)				
Fever	227 (46.7)	98 (50.0)	129 (44.5)	0.232
Cough	448 (92.2)	180 (91.8)	268 (92.4)	0.816
Dyspnea	271 (55.8)	106 (54.1)	165 (56.9)	0.540
Vomiting	61 (12.6)	18 (9.2)	43 (14.8)	0.065
Diarrhea	31 (6.4)	12 (6.1)	19 (6.6)	0.859
Physical examination on admission, n (%)				
Nasal flaring	46 (9.5)	24 (12.2)	23 (7.6)	0.085
Wheezing	31 (6.4)	16 (8.2)	15 (5.2)	0.186
Retractions, n (%)				0.078
Subcostal or intercostal	257 (53.0)	113 (57.7)	144 (49.8)	
Global	162 (33.4)	64 (32.7)	98 (33.9)	
Lung auscultation, n (%)				0.245
Decreased pulmonary sounds in one area	14 (2.9)	4 (2.0)	10 (3.4)	
Decreased pulmonary sounds in > one area	39 (8.0)	20 (10.2)	19 (6.6)	
Respiratory rate, mean (SD)	50.6 (12.1)	51.6 (12.8)	49.8 (11.7)	0.150
SpO_2, mean (SD)	93.6 (4.4)	93.17 (4.8)	93.8 (4.1)	0.100
Weight on admission in Kg, mean (SD)	6.2 (2.5)	5.9 (2.2)	6.3 (2.6)	0.082
Virus, n (%)				
RSV	299 (68.0)	109 (64.9)	190 (69.9)	0.278
Adenovirus	18 (4.2)	11 (6.8)	7 (2.6)	0.033
Metapneumovirus	32 (7.4)	15 (9.3)	17 (6.3)	0.247
Rhinovirus	86 (20.0)	38 (23.6)	48 (17.8)	0.143
Parainfluenza	24 (5.6)	12 (7.5)	12 (4.4)	0.177
Influenza	4 (0.9)	2 (1.2)	2 (0.7)	0.599
Enterovirus	22 (5.1)	6 (3.7)	16 (5.9)	0.312
Bocavirus	18 (4.2)	6 (3.7)	12 (4.4)	0.719
Coronavirus	6 (1.4)	4 (2.5)	2 (0.7)	0.135
SARS-CoV-2	3 (0.6)	---	3 (1.0)	---
Antibiotics use, n (%)	75 (15.5)	29 (14.8)	46 (15.9)	0.738
Respiratory support, n (%)				
None	98 (20.2)	46 (23.5)	52 (17.9)	0.135
SOT	388 (79.8)	150 (76.5)	238 (82.1)	0.135
HFNC	---	---	46 (15.9)	
NIV	70 (14.4)	34 (17.3)	36 (12.5)	0.133
IMV	11 (2.3)	5 (2.6)	6 (2.0)	0.726
ICU admission, n (%)	82 (16.9)	42 (21.4)	40 (13.8)	0.027
ICU length of stay in days, median (SD)	8.8 (4.7)	10.5 (5.9)	9.6 (2.9)	0.862
Overall length of stay in days, median (SD)	7.8 (22.4)	6.5 (4.3)	8.7 (28.8)	0.288

HFNC: high-flow nasal cannula; ICU: intensive care unit; IMV: invasive mechanical ventilation; NIV: non-invasive mechanical ventilation; RSV: respiratory syncytial virus; SD: standard deviation; SOT: single oxygen therapy.

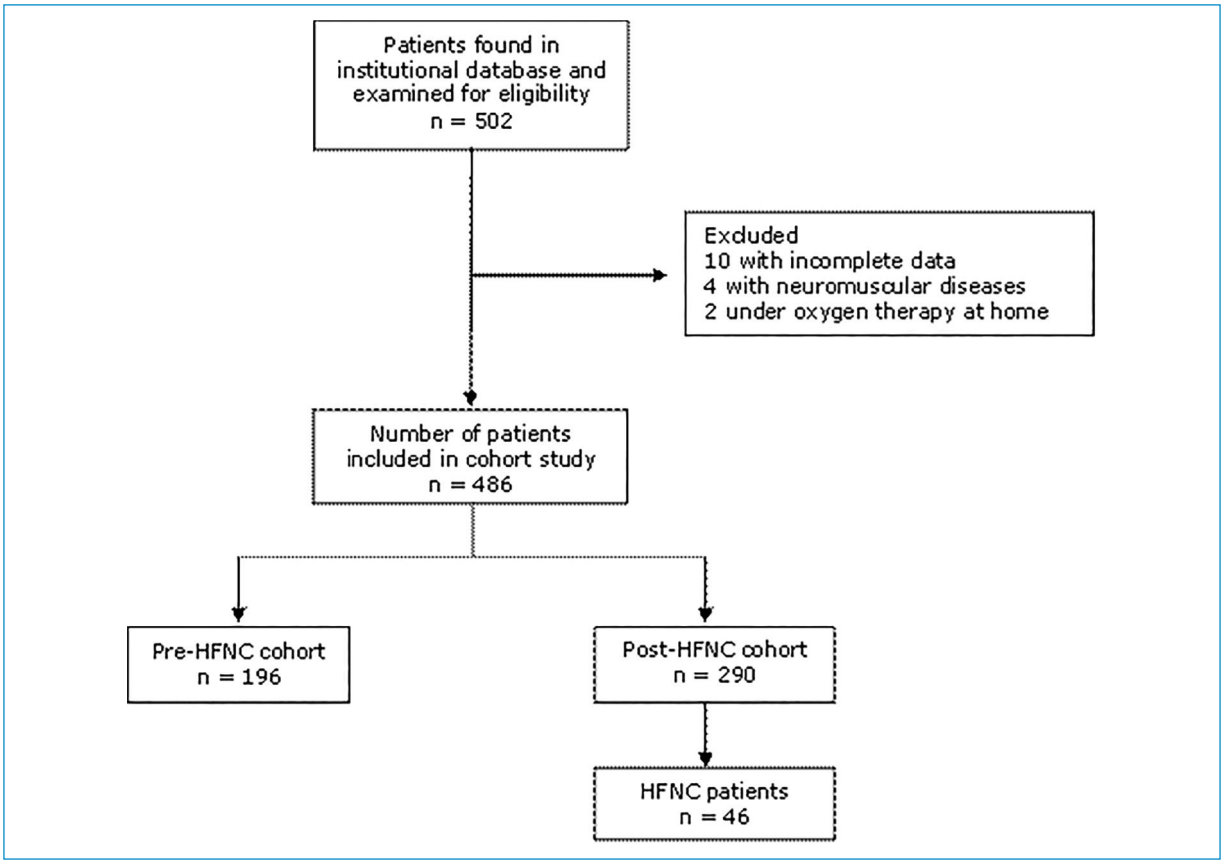

Figure 1. Study profile. Flow chart illustrating the study profile, depicting the progression of participants from enrollment to the final analysis.

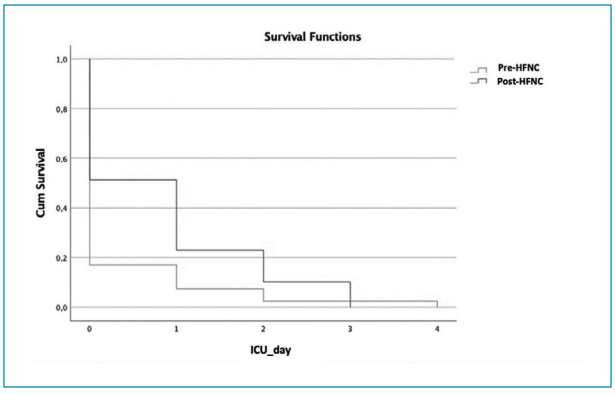

Figure 2. Survival analysis. This figure illustrates the survival analysis depicting the time to Intensive Care Unit (ICU) admission for patients in the preHFNC and postHFNC groups.

In our patients on HFNC oxygen therapy, around 22% needed NIV and none needed IVM. A retrospective study showed that 25% of patients with HFNC therapy required NIV, which is a very similar proportion[8]. The reduction in the need for intubation was also demonstrated in several studies[6].

When looking for predicting factors of HFNC oxygen failure, daycare attendance and HFNC nonresponders, with a higher WARM score 24 hours after initiation were identified. In line with this, Aydin et al. found that the respiratory rate observed in the second hour of the follow-up period could be a predictive factor for HFNC failure[19]. Daycare attendance was never reported as a predictive factor for failure, but it may be explained by the fact that children in daycare are usually at a higher risk of recurrent respiratory tract infections and of more chronic airway inflammation. Besides that, several studies have shown that children at younger ages are particularly vulnerable to daycare-related effects with more severe problems[20].

A strength of this study is that it is the first national study on the use of high-flow oxygen therapy in bronchiolitis, allowing for the adjustment of current national clinical practices to reduce overall length of stay, the

Table 2. Subgroup analysis in the postHFNC period: HFNC therapy vs. nonHFNC subgroups

	HFNC	NonHFNC	p
Participants, n	46	244	
Age in months, mean (SD)	5.18; 5.59	6.15; 11.9	0.738
Male, n (%)	23 (48.9)	133 (54.5)	0.574
Prematurity, n (%)	13 (28.3)	40 (16.4)	0.056
Neonatal respiratory support, n (%)	5 (10.9)	17 (7.0)	0.359
Day of illness, mean (SD)	2.80 (1.72)	4.33 (3.83)	< 0.001
Preexisting comorbidities, n (%)			
Pulmonary disease	2 (4.3)	2 (0.8)	0.060
Cardiac disease	3 (6.5)	6 (2.5)	0.145
Immunodeficiency	0 (0.0)	0 (0.0)	
Chromosomal disorders	1 (2.2)	1 (0.4)	0.185
Neurologic disease	0 (0.0)	8 (3.3)	0.213
Family history of allergies, n (%)	14 (30.4)	95 (39.4)	0.250
Personal history of allergies, n (%)	0 (0.0)	14 (5.8)	0.094
Exposure to tobacco smoke, n (%)	17 (37.0)	99 (41.3)	0.587
Daycare attendance, n (%)	7 (15.2)	48 (21.0)	0.374
Symptoms on admission, n (%)			
Fever	23 (50.0)	106 (43.4)	0.412
Cough	41 (89.1)	227 (93.0)	0.359
Dyspnea	23 (50.0)	142 (58.2)	0.303
Vomiting	7 (15.2)	36 (14.8)	0.935
Diarrhea	3 (6.5)	16 (6.6)	0.993
Physical examination on admission, n (%)			
Nasal flaring, n (%)	5 (10.9)	17 (7.0)	0.359
Wheezing, n (%)	3 (6.5)	12 (4.9)	0.652
Retractions, n (%)			0.098
Subcostal or intercostal	20 (44.4)	124 (50.8)	
Global	21 (46.7)	77 (31.6)	
Lung auscultation, n (%)			0.139
Decreased pulmonary sounds in one area	1 (2.2)	9 (3.7)	
Decreased pulmonary sounds in one area	6 (13.0)	13 (5.3)	
Respiratory rate, mean (SD)	51.52 (13.1)	49.50 (11.4)	0.309
SpO_2, mean (SD)	93.22 (3.63)	93.96 (4.19)	0.269
Weight on admission in Kg, mean (SD)	5.93 (2.23)	6.31 (2.61)	0.820
Warm score, mean (SD)	2.3 (1.4)	1.7 (1.2)	0.002
Virus, n (%)			
RSV	29 (65.9)	161 (70.6)	0.534
Adenovirus	2 (4.5)	5 (2.2)	0.373
Metapneumovirus	6 (13.6)	11 (64.7)	0.028
Rhinovirus	9 (20.5)	39 (17.3)	0.612
Parainfluenza	1 (2.3)	11 (4.9)	0.445
Influenza	1 (2.3)	1 (0.4)	0.195
Enterovirus	9 (20.5)	7 (3.1)	< 0.001
Bocavirus	5 (11.4)	7 (3.1)	0.015
Coronavirus	1 (2.3)	1 (0.4)	0.195
SARS-CoV-2	0 (0.0)	3 (1.2)	0.450
Antibiotics use, n (%)	11 (24.4)	35 (14.3)	0.089
Respiratory support, n (%)			
None	---	51 (20.9)	---
SOT	---	193 (79.1)	---
HFNC	---	---	---
NIV	10 (21.7)	26 (10.7)	0.038
IMV	0 (0)	6 (2.5)	0.282
ICU admission, n (%)	11 (23.9)	29 (11.9)	0.030
ICU length of stay in days, median (SD)	9.5 (2.9)	10.5 (5.9)	0.604
Overall length of stay in days, median (SD)	16.2 (54.2)	7.3 (20.6)	0.278

HFNC: high-flow nasal cannula; ICU: intensive care unit; IMV: invasive mechanical ventilation; NIV: non-invasive mechanical ventilation; RSV: respiratory syncytial virus; SD: standard deviation; SOT: single oxygen therapy.

need for therapeutic escalation, and consequently, the costs involved. However, there are some limitations. One of these lies in the fact that this is a retrospective study. Additionally, we only have three HFNC devices available, which could have influenced their use in the most severe patients or led to ICU transfer without the chance to try HFNC first. Another limitation has to do with the fact that we are a tertiary hospital, which may have conditioned a selection bias, with a population with more severe disease being transferred from other hospitals. Moreover, our timeframe encompassed the period of the pandemic, coinciding with a lower number of patients admitted.

In conclusion, in our cohort, the introduction of HFNC in the treatment of AB reduced the need for the ICU, being associated with a clinical improvement in several respiratory parameters. On the basis of the NNT, it is estimated that three to four ICU admissions were avoided in the postHFNC group. It is imperative that we establish the efficacy of HFNC therapy compared to standard care in the management of AB, assessing potential differences in efficacy according to the time of initiating the HFNC. While a few observational studies have shown promising results for HFNC, the evidence base is limited by the lack of well-designed randomized controlled trials with the measurement of simple and composite outcomes. These studies would enable a more rigorous evaluation of HFNC therapy, allowing for a better determination of its safety and efficacy. Moreover, the use of standardized outcome measures would ensure that results are comparable across studies and settings. Large sample sizes and long-term follow-up periods are particularly desirable, as they would provide robust evidence for the use of HFNC in clinical practice. With such evidence, clinicians and policymakers would be better equipped to make informed decisions about the appropriate use of HFNC therapy, ultimately improving patient outcomes and reducing health care costs.

Previous presentations

This investigation was presented at the 22nd National Pediatric Conference in October 2023 and received the award for the best works at the conference.

Author contributions

J. Costa Leite Baptista de Lima: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. I. Aires Martins, J. Queirós, S. Monteiro: Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. T. Barbosa, M. Guilhermina Reis, L. Morais, A. Ramos: Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. M. Ferreira-Magalhães: Conception and design of the study, report, review or other type of work or paper; Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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

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

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SYSTEMATIC REVIEW AND META-ANALYSIS

Avoidant/restrictive food intake disorder: pediatric comorbidities

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Abstract

Introduction and Objectives: Avoidant/Restrictive Food Intake Disorder (ARFID) is a newly-recognized feeding and eating disorder diagnosis in the DSM-5 (2013) and ICD-11 (2019). This systematic review aims to gather knowledge on prevalent comorbidities in pediatric ARFID patients. **Methods:** Following PRISMA guidelines, a systematic literature review was conducted, focusing on comorbidities in ARFID-diagnosed participants with a mean age inferior or equal to 18 years old. Covering the period from 2013 to September 2023, a search across PubMed and B-On resulted in 20 selected studies from an initial pool of 161 articles. The risk of bias was assessed using the ROBINS-I tool. PROSPERO CRD42024503067. **Results:** Medical comorbidities were detailed in eight studies, revealing that 38% of the comorbidities observed were gastrointestinal symptoms, 25% neurological conditions, and 10% immune system complications. Psychiatric comorbidities were addressed in most of the studies, with 45% of observations displaying anxiety disorders, 33% neurodevelopmental disorders, and 15% mood disorders. Various other medical and psychiatric conditions were also identified. **Discussion:** This review underscores the association between ARFID and diverse comorbidities, including gastrointestinal, neurological, and psychiatric conditions. It highlights the disorder's complexity and the increased medical risks, advocating for early, multidisciplinary interventions and greater awareness among educators and health professionals. The need for comprehensive treatment involving various medical specialists is emphasized, along with the importance of family involvement and further research to enhance understanding and treatment of ARFID.

Keywords: Avoidant restrictive food intake disorder. Comorbidity. Child. Adolescent.

Transtorno evitativo/restritivo da ingestão de alimentos: comorbidades pediátricas

Resumo

Introdução e Objetivos: Perturbação de Ingestão Alimentar Evitativa/Restritiva (ARFID) é um diagnóstico de perturbação alimentar reconhecido recentemente no DSM-5 (2013) e CID-11 (2019). Esta revisão sistemática tem como objetivo reunir conhecimento sobre as comorbilidades mais prevalentes em doentes pediátricos com ARFID. **Métodos:** Seguindo as guidelines PRISMA, foi realizada uma revisão sistemática da literatura focada nas comorbilidades em participantes diagnosticados com ARFID com uma média de idades inferior ou igual a 18 anos. Abrangendo o período de 2013 a setembro de 2023, uma pesquisa na PubMed e B-On resultou em 20 estudos selecionados de um conjunto inicial de 161. O risco de viés foi analisado utilizando a ferramenta ROBINS-I. PROSPERO CRD42024503067. **Resultados:** As comorbilidades médicas foram detalhadas em 8 estudos, revelando que 38% das comorbilidades observadas eram sintomas gastrointestinais, 25% problemas neurológicos e 10% complicações do

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sistema imunitário. As comorbilidades psiquiátricas foram abordadas na maioria dos estudos, com 45% das observações a revelar perturbações de ansiedade, 33% perturbações do neurodesenvolvimento e 15% perturbações do humor. Também foram identificadas outras condições médicas e psiquiátricas. **Discussão:** Esta revisão sublinha a associação entre ARFID e diversas comorbilidades, incluindo doenças gastrointestinais, neurológicas e psiquiátricas. Destaca a complexidade da doença e o aumento dos riscos médicos, defendendo intervenções precoces e multidisciplinares e uma maior consciencialização dos educadores e profissionais de saúde. É realçada a necessidade de um tratamento abrangente que envolva vários médicos especialistas, bem como a importância do envolvimento da família e de mais investigação para melhorar a compreensão e o tratamento da doença.

Palavras-chave: Perturbação de ingestão alimentar evitante/restritiva. Comorbilidades. Crianças. Adolescentes.

Keypoints

What is known
- ARFID, recognized in DSM-5 and ICD-11, details a condition where individuals exhibit limited food intake, impacting nutritional and psychosocial well-being.
- Unlike traditional eating disorders, ARFID lacks body image concerns, emphasizing the need for unique approaches to diagnosis and treatment.
- The prevalence of ARFID varies widely, with existing studies indicating a need for better screening tools and standardized diagnostic criteria.

What is added
- ARFID's association with gastrointestinal, neurological, and psychiatric comorbidities underscores the necessity for early, comprehensive interventions.
- The complexity of ARFID, coupled with its significant comorbidities, demands a multidisciplinary treatment approach and increased awareness among healthcare providers.
- Future research on ARFID should focus on elucidating its etiology, improving diagnostic tools, and developing effective, holistic treatment strategies.

Introduction

Avoidant/Restrictive Food Intake Disorder (ARFID) is a diagnosis introduced in the DSM-5[1] in 2013 and recognized by the ICD-11[2] in 2019, highlighting its acceptance in the global psychiatric community. ARFID outlines a condition where individuals exhibit a significant limitation in food intake, due to a lack of interest in food, fear of aversive consequences, or sensory sensitivities. This disorder extends beyond the limitations set by the DSM-IV, recognizing affected individuals across all age groups, not confined to early childhood. The implications of ARFID are profound, leading to nutritional deficiencies, weight loss, and notable psychosocial difficulties, setting it apart from other eating disorders which typically involve concerns over body image or an explicit desire to lose weight[1].

The epidemiology of ARFID, although increasingly studied, remains inadequately characterized, with reported prevalence rates showing wide variation, ranging from 0.3% to 15.5% in a non-clinical sample and from 5% to 64% in specialized pediatric eating disorder department samples[3]. This variability underscores the urgent need for comprehensive epidemiological studies using standardized diagnostic criteria and assessment tools to better define the disorder's scope and impact[3,4].

The treatment of ARFID demands a comprehensive, multidisciplinary approach that integrates psychological therapies, nutritional guidance and, when necessary, pharmacological support to address the multifaceted nature of the disorder. Effective management often requires customized interventions that consider the unique motivations behind food avoidance for each individual[5-7].

Comorbid conditions are commonly observed with ARFID, including anxiety disorders, obsessive-compulsive disorder (OCD) and various neurodevelopmental disorders[1]. These comorbidities complicate the clinical picture, necessitating an integrated treatment plan that addresses both ARFID and its psychiatric or developmental co-occurrences.

The purpose of this systematic literature review is to synthesize what is already known about the most common comorbidities of ARFID, whilst focusing on children and adolescents. Accurate knowledge of comorbidities is crucial for effective clinical management, treatment planning, and resource allocation. It informs public health strategies, influences research design, and contributes to patient-centered care by recognizing the interconnected nature of health conditions. Overall, understanding comorbidities is essential for improving patient outcomes and optimizing healthcare systems. This knowledge will enable a more comprehensive understanding of the topic, effectively supporting clinical practice and shaping preventive strategies and interventions.

Methods

This systematic review of literature was developed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[8].

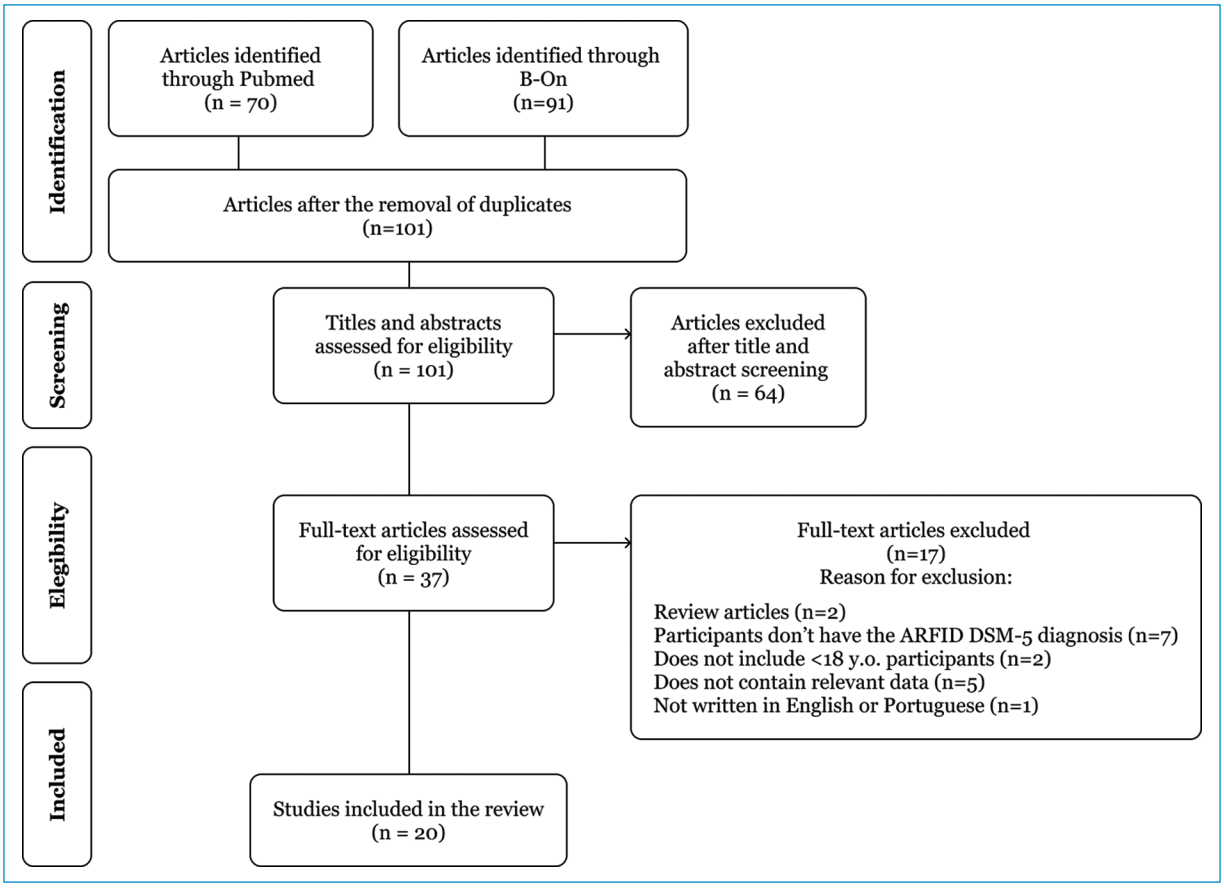

Figure 1. Flow chart of reviewed studies, according to PRISMA[8].

The first search was conducted in July 2023 and the final search was on the 5th of September, 2023.

Two databases were used: Pubmed and B-On - a Portuguese platform, sponsored by the Foundation for Science and Technology - that gives open access to several databases such as Medline, Elsevier and Web of Science.

Articles published between January 2013 and September 2023 were identified. ARFID was introduced as a diagnosis in the DSM-5, published in 2013. Consequently, 2013 was the starting point for the search.

Using the keywords "Avoidant/Restrictive Food Intake Disorder", "Comorbidities", "Child", and "Adolescent", 70 articles were identified in Pubmed and 91 in B-On. After removing duplicates, 101 abstracts were screened and 37 articles remained for full assessment. Applying the inclusion criteria, a total of 20 articles met the requirements and were selected for the final systematic review[9-28].

The review selection process is summarized in the PRISMA flow chart in figure 1.

The review was registered with the international prospective register of systematic reviews (PROSPERO) (PROSPERO CRD42024503067).

Inclusion criteria

- Studies published between 1 January 2013 and 5 September 2023;
- Studies written in Portuguese or English;
- Studies with a mean age of participants below or equal to 18 years old;
- Studies with participants diagnosed with ARFID according to DSM-5 or ICD-11 criteria;
- Studies containing relevant data on the participants' medical or psychiatric comorbidities.

Exclusion criteria

- Studies published before January 2013 and after September 2023;
- Study design: case studies, qualitative studies, letters to the editor, reviews (literature reviews, systematic reviews, and meta-analyses), comments, or manuscripts;
- Studies with a mean age of participants above 18 years old.

Data extraction

Data was extracted from each article as regards the author, country, year of publication, design and method, sample size, gender and age of participants, diagnostic criteria, description of participants, setting of the study, medical comorbidities, and psychiatric comorbidities. Other relevant data was also collected, such as signs of medical instability, family history of psychiatric disorders, criteria A symptoms according to the DSM-5, presence of infection prior to the onset of the eating disorder (ED), trigger for the ED, demonstration of somatic concerns by the participants, and comparisons between different phenotypes.

Quality assessment

The risk of bias was assessed with the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. This tool assesses, for each study, the risk of bias in seven different domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Each domain, as well as the overall risk of bias, is categorized using a traffic light color code: green for low risk, yellow for moderate risk, and red for high risk. Additionally, a question mark indicates that the data for a particular domain was not adequately reported or was unclear (Figs. 1 and 3)[29-31].

Results

Twenty articles were reviewed, with a total of 1178 participants. The selected studies included children and adolescents with a mean age inferior or equal to 18 years old (the maximum age reported was 23 years old), diagnosed with ARFID, using DSM-5 or ICD-11 criteria.

Key aspects of the included studies are presented in tables 1 and 2.

Characteristics of the included studies

The majority were conducted in North America (n = 10) (United States of America (USA) (n = 5)[9,13,15,18,26] and Canada (n = 5))[11,12,23,27,28] and four were carried out in multiple countries[10,20,22,24]. Two studies took place in Japan[16,25] and four in Europe: United Kingdom[17], Italy[14], Spain[19], and Germany[21].

All of the included studies focused on clinical populations, with most drawing on samples from pediatric eating disorder specialized departments (n = 11)[9-15,17,19,23,27] and utilizing retrospective chart reviews (n = 11)[10-15,16,18,23,26,27]. ARFID diagnosis was established using the DSM-5 or ICD-11 criteria.

Quality assessment

The risk of bias, assessed with the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool, is depicted across multiple studies in figure 2, which utilizes a traffic light color code to evaluate individual studies across seven domains of bias and an overall appreciation. Figure 3 summarizes this data in a bar chart, quantitatively presenting the overall proportion of studies falling into low, moderate, or unknown risk categories for each bias domain[29-31].

Results from the included studies: medical comorbidities

From the 20 selected studies, eight provided data on medical comorbidities, giving a total sample of 383 ARFID patients who were assessed for these comorbid conditions[9,10,13,21-23,26,28]. However, only 353 observations of comorbidities were recorded. Due to the consistent methodology employed across the studies, the results were aggregated to provide a more robust body of evidence (Fig. 4).

All eight studies focus on gastrointestinal (GI) symptoms or conditions, showing that about 38% of the observations include a related complaint or disease. Among these observations, there were 117 instances reporting GI symptoms. Of these, 56 mentioned specific issues such as diarrhea, gastroesophageal reflux, early satiety, nausea, gastroparesis, or abdominal pain, while 61 did not specify the symptoms. Additionally, 14 observations involved a GI disease diagnosis, with seven cases of either chronic abdominal pain or inflammatory conditions and seven not specifying the disease.

Secondly, 25% of the observations indicate a neurological-associated condition. Sensory problems were reported 23 times among the patients. There were 18 instances mentioning migraines and cognitive impairment was reported 17 times. Fifteen observations registered episodes of dizziness, four reported chronic pain, three a diagnosis of brain palsy, and two a history of seizures. One observation did not specify a condition.

The immune system was affected in 10% of the observations. Allergies to food and drugs were reported in 19 and six instances, respectively. Asthma was documented in nine observations and atopic dermatitis in one.

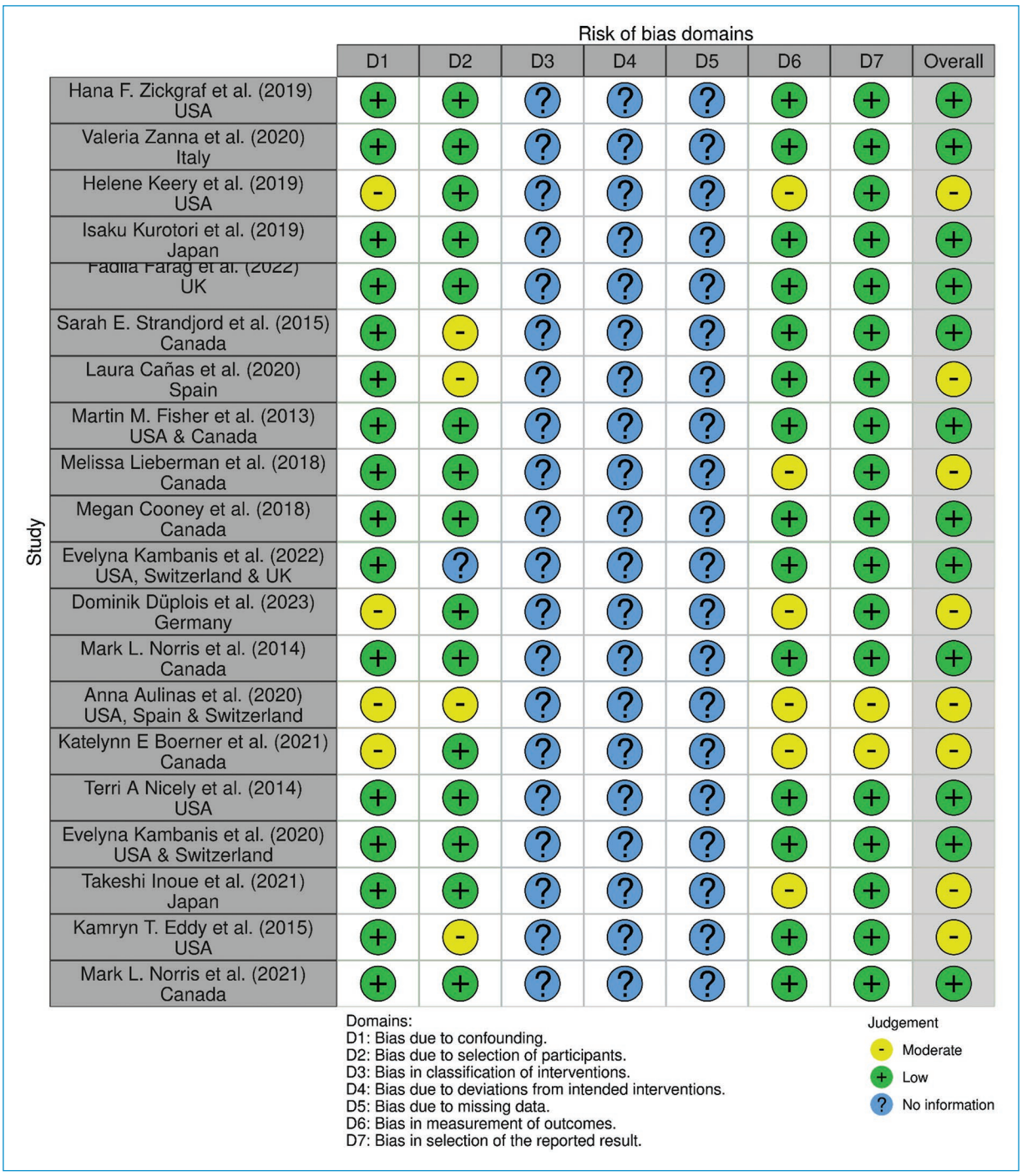

Figure 2. Traffic-light plot with the risk of bias domains assessment for each study, using the ROBINS-I tool[29,31].

Five observations indicated endocrine conditions, three a congenital anomaly, and another three a musculoskeletal problem. One instance referred to an oncological problem, one Lyme disease, and one interstitial cystitis. Lastly, 12 reported pain of some kind, 18 did not specify the symptoms, and 50 referred to an unspecified medical condition.

Results from the included studies: psychiatric comorbidities

All but two studies reported psychiatric comorbidities, giving a total sample of 1125 participants analyzed for psychiatric comorbidities[9-21,23-25,27,28]. However, only 924 observations of comorbidities were recorded.

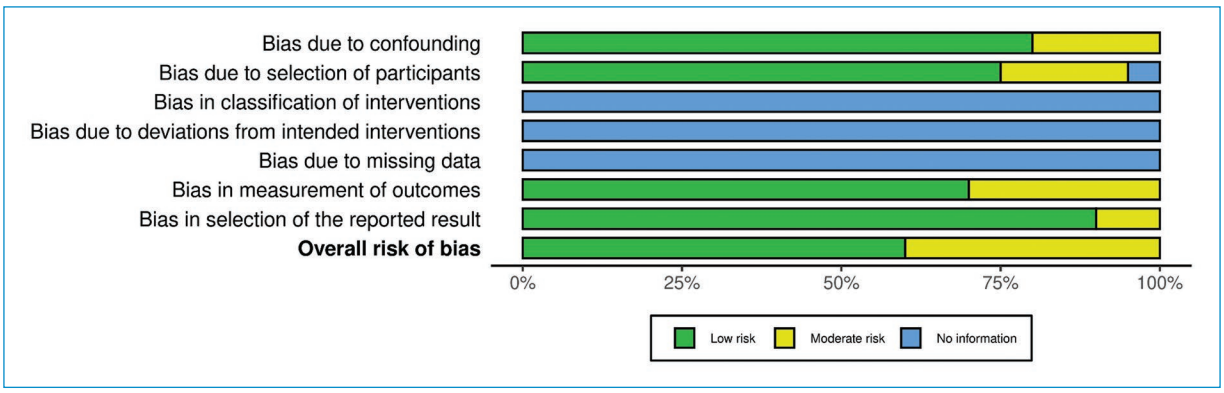

Figure 3. Bar chart with quantitative summary of the risk of bias domains assessment, using the ROBINS-I tool[29,31].

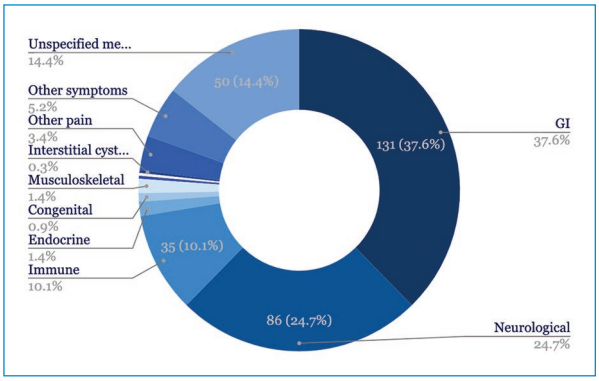

Figure 4. Pie chart depicting the most prevalent medical comorbidities.

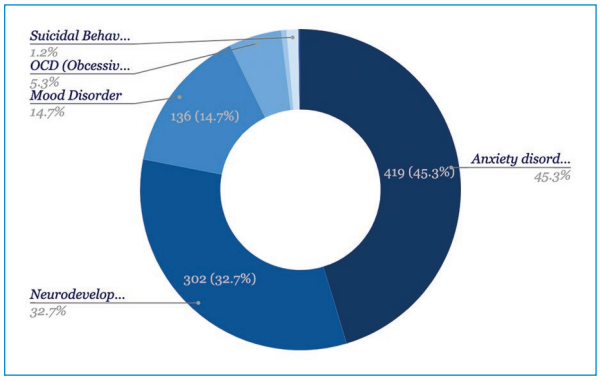

Figure 5. Pie chart depicting the most prevalent psychiatric comorbidities.

Due to the consistent methodology employed across the studies, the results were aggregated to provide a more robust body of evidence (Fig. 5).

From this instance pool, 45% of the observations recorded anxiety disorders, more specifically, 88 instances of generalized anxiety disorder (GAD), 19 a specific phobia, 14 social anxiety disorder, with the same number reporting panic disorder, four post-traumatic stress disorder (PTSD) and 280 an unspecified anxiety disorder.

Secondly, neurodevelopmental disorders were reported in 33% of observations. Autistic spectrum disorder (ASD) was diagnosed in 179 instances, attention deficit hyperactivity disorder (ADHD) in 68, a learning disability in 15, and 40 reported an unspecified neurodevelopmental disorder.

Mood disorders were found in 15% of the observations. Twenty-nine instances presented a depressive disorder or dysthymia, 23 with major depressive disorder (MDD), and 84 did not specify.

Lastly, 5% of the observations mentioned a co-occurring diagnosis of OCD, there were 11 instances of suicidal behavior, five of a conduct disorder, one a dissociative disorder, and ten of an unspecified psychiatric disorder.

Additionally, three studies reported a psychiatric history[15,22,24], four a family's psychiatric and eating disorder history[11,16,18,22], two the use of psychiatric medication[15,22], one showed data on a history of abuse, self-harm, and substance use[23], and one evaluated the distribution of psychiatric comorbidities in the different ARFID phenotypes[27].

Results from the included studies: other findings

In this section, other relevant data that was found through the analysis of the studies is presented.

Three studies reported criteria A from the DSM-5 diagnostic criteria, showing the frequency of each one

Table 1. Characteristics of the included studies

Author, year, and country	Design	Method	Sample description	Sample setting	Sample size	Sample gender	Sample age	How was the ARFID diagnosis made?
Hana F. Zickgraf et al. (2019) USA[9]	Retrospective chart review	Data collected either prospectively since 2013 or retrospectively from 2008 to 2012, from participants	Patients admitted to a Partial Hospitalization Program (PHP) and diagnosed with Avoidant/Restrictive Food Intake Disorder (ARFID)	Pediatric eating disorder Partial Hospitalization Program	n = 83	♂n = 19 ♀n = 64	8-17 (mean of 11.4 y. o.)	Using a checklist of DSM-5 eating disorder symptoms
Valeria Zanna et al. (2020) Italy[14]	Retrospective chart review	Retrospective chart review of patients under the age of 18 who received specific ED diagnoses by the DSM-IV criteria, between January 2010 and September 2017, which were later reclassified as DSM-5 criteria by an expert	Participants were children and adolescents under 18 years old, initially diagnosed according to DSM-IV criteria with Anorexia Nervosa (AN), Feeding Disorder of Infancy or Early Childhood, or Eating Disorder Not Otherwise Specified. Diagnosis later reclassified as ARFID according to DSM-5 criteria by an expert	Pediatric tertiary care ED program	n = 94	♂n = 36 ♀n = 58	mean age < 18 y. o.	Using a checklist of DSM-5 eating disorder symptoms
Helene Keery et al. (2019) USA[15]	Longitudinal study	Data collection was done through interviews, pen-and-paper assessments, and electronic health records	Patients aged 7-19 years old who were diagnosed with a DSM-5 feeding or eating disorder and agreed to participate in outpatient treatment at Children's Minnesota Hospital, between July 2015 and December 2017	Center for the Treatment of Eating Disorders (CTED)	n = 106	♂n = 43 ♀n = 63	7-19	DSM-5 criteria
Isaku Kurotori et al. (2019) Japan[16]	Observational study	Retrospective chart review	Pediatric patients diagnosed with eating disorders, requiring hospitalization due to their medically unstable state	Child and adolescent psychiatric ward in a pediatric hospital	n = 13	♂n = 2 ♀n = 11	7-14 (mean of 10.7 y. o.)	DSM-5 criteria
Fadila Farag et al. (2022) UK[17]	Cross-sectional	Data collected prospectively from patients seen by the tertiary feeding department	Pediatric patients experiencing severe feeding difficulties referred to tertiary feeding clinic at Evelina London Children's Hospital between January 2013 and June 2019	Tertiary care pediatric feeding clinic	n = 263	♂n = 215 ♀n = 48	1-20 (mean of 6.8 y. o.)	DSM-5 criteria
Sarah E. Strandjord et al. (2015) Canada[18]	Retrospective chart review	Data was collected by reviewing medical records	Patients who were hospitalized for refeeding and met DSM-5 criteria for an eating disorder, at an academic medical center between 2008 and 2014	Academic medical center	n = 41	♂n = 6 ♀n = 35	14-18 (mean of 16.0 y. o.)	DSM-5 criteria

(Continues)

Table 1. Characteristics of the included studies *(continued)*

Author, year, and country	Design	Method	Sample description	Sample setting	Sample size	Sample gender	Sample age	How was the ARFID diagnosis made?
Laura Cañas et al. (2020) Spain[19]	Descriptive observational and comparative study	Data collection was conducted through assessments of children and adolescents, along with their families, within a 15-day period starting from their first visit to the eating disorders unit of Hospital Sant Joan de Déu in Barcelona	Eating disorder patients seeking treatment from October 2015 to May 2018 at the eating disorders unit of Hospital Sant Joan de Déu in Barcelona, Spain	Eating disorders unit	n = 33 (outpatients n = 29, partial	♂n = 20 ♀n = 13	7-17 (mean of 10.8 y. o.)	DSM-5 criteria
Martin M. Fisher et al. (2013) USA & Canada[10]	Cross-sectional	Retrospective chart review	New patients who presented to seven adolescent medicine eating disorder programs in the US and Canada between January and December 2010	Adolescent medicine-based ED programs	n = 98	♂n = 28 ♀n = 70	8-18 (mean of 12.9 y. o.)	DSM-5 criteria
Melissa Lieberman et al. (2018) Canada[28]	Observational study	Data was collected through clinical interviews, psychometric questionnaires, and chart reviews	In- and outpatients who met the DSM-5 criteria for AN and ARFID, between May 2013 and January 2017, that were part of the specialized COPE program at the Hospital for Sick Children in Toronto	Specialized program for children under 13 years of age	n = 29	♂n = 7 ♀n = 22	8-13 (mean of 10.8 y. o.)	DSM-5 criteria
Megan Cooney et al. (2018) Canada[12]	Cross-sectional	Retrospective chart review	Patients referred for a comprehensive eating disorder assessment at a tertiary care pediatric hospital between May 2013 and April 2016	Pediatric tertiary care ED program	n = 28	♂n = 10 ♀n = 18	9-18 (mean of 13.2 y. o.)	DSM-5 criteria
Evelyna Kambanis et al. (2022) USA, Switzerland & UK[20]	Comparative observational study	Data was collected through structured interviews	Female participants diagnosed with ED; part of larger studies on the neurobiology of eating disorders	Within the context of broader research projects at an academic institution, focusing on the neurobiology of eating disorders	n = 51	♂n = 0 ♀n = 51	10-23 (mean of 16.6 y. o.)	DSM-5 criteria
Dominik Düplois et al. (2023) Germany[21]	Comparative observational study	Data was collected with semi-structured clinical interviews	Patients seeking in- or outpatient treatment for a restrictive feeding or eating disorder, at Leipzig University Medical Center between February 2018 and October 2021	Leipzig University Medical Center	n = 19	♂n = 7 ♀n = 12	0-17 (mean of 10.6 y. o.)	DSM-5 criteria

(Continues)

Table 1. Characteristics of the included studies *(continued)*

Author, year, and country	Design	Method	Sample description	Sample setting	Sample size	Sample gender	Sample age	How was the ARFID diagnosis made?
Mark L. Norris et al. (2014) Canada[11]	Cross-sectional	Retrospective chart review of patients diagnosed with food avoidant emotional disorder, childhood AN, selective eating, eating disorder not otherwise specified (EDNOS), or EDNOS restrictive subtype, or those that were discharged without diagnosis	Patients who received an ED initial assessment between 2000 and 2011	Pediatric ED treatment program	n = 34	♂n = 7 ♀n = 27	(mean of 13.7 y. o.)	DSM-5 criteria
Anna Aulinas et al. (2021) USA, Spain & Switzerland[22]	Cross-sectional	Data was collected from studies investigating the neurobiology of restrictive EDs	Low-weight females diagnosed with an ED	Pediatric Endocrinology Unit	n = 20	♂n = 0 ♀n = 20	10-22 (mean of 14.3 y. o.)	No reference
Katelynn E Boerner et al. (2021) Canada[23]	Retrospective chart review	Data was collected through a retrospective review of medical records	Patients diagnosed with ARFID or a GI-related Somatic Symptom and Related Disorder (SSRD), between January 2014 and January 2019	Specialized ED program	n = 62	♂n = 19 ♀n = 43	5-18 (mean of 14.0 y. o.)	No reference
Terri A Nicely et al. (2014) USA[13]	Cross-sectional	Retrospective chart review	Patients admitted to a day program for children and adolescents with EDs between August 2008 and May 2012	Day program for EDs	n = 39	♂n = 8 ♀n = 31	7-17 (mean of 11.1 y. o.)	DSM-5 criteria
Evelyna Kambanis et al. (2019) USA & Switzerland[24]	Cross-sectional	Data was collected through structured interviews	Children and adolescents with full and subthreshold ARFID	Within the context of broader research projects at an academic institution, focusing on the neurobiology of eating disorders	n = 74	♂n = 38 ♀n = 36	9-22 (mean of 15.0 y. o.)	DSM-5 criteria
Takeshi Inoue et al. (2021) Japan[25]	Cross-sectional	Multicenter cohort study	Children with Feeding and Eating Disorders (FEDs) recruited as part of the Japanese Pediatric EDs Outcome: a Prospective Multicenter Cohort Study (J-PED) study	Multiple medical institutions throughout Japan	n = 32	♂n = 7 ♀n = 25	5-15 (mean of 11.8 y. o.)	No reference
Kamryn T. Eddy et al. (2015) USA[26]	Cross-sectional	Retrospective chart review	Patients who presented for an initial evaluation at one of the 19 Boston area pediatric gastroenterology clinics affiliated with Massachusetts General Hospital, comprising a teaching hospital and community settings, between January 2008 and December 2008	Pediatric gastroenterology clinics	n = 33	♂n = 22 ♀n = 11	8-18 (mean of 11.4 y. o.)	DSM-5 criteria
Mark L. Norris et al. (2021) Canada[27]	Longitudinal study	Retrospective chart review	Patients meeting criteria for ARFID who were admitted to a specialized pilot clinic within a tertiary care children's hospital in Ontario, from December 2014 to June 2016	Specialized pilot clinic	n = 26	♂n = 10 ♀n = 16	9-18 (mean of 13.9 y. o.)	DSM-5 criteria

ARFID: Avoidant/Restrictive Food Intake Disorder; ED: eating disorder; AN: Anorexia Nervosa; EDNOS: eating disorder not otherwise specified; GI: gastrointestinal.

Table 2. Results from the included studies

Author, year, and country	Medical comorbidities	Psychiatric comorbidities	Other findings
Hana F. Zickgraf et al. (2019) USA[9]	Gastrointestinal (GI) symptoms (gastroesophageal reflux, early satiety, nausea, gastroparesis, and abdominal pain) n = 26 (31.3%) Asthma n = 4 Cerebral palsy/ambulatory dysfunction n = 3 Amplified musculoskeletal pain syndrome n = 2 Seizure history n = 2 Eczema n = 1 Juvenile rheumatoid arthritis n = 1 Lyme disease n = 1 Ehlers-Danlos syndrome n = 1 Tetralogy of Fallot n = 1 Interstitial cystitis n = 1 Scoliosis n = 1	Anxiety disorder n = 61 Mood disorder n = 17 Obsessive-compulsive disorder (OCD) n = 17 Attention-deficit/hyperactivity disorder (ADHD) n = 10 Developmental delay n = 6	The criteria A symptoms of DSM-5 A1 (weight loss) n = 67 A1 (faltering growth) n = 11 A2 (nutritional deficiency) n = 78 A3 (dependence on supplements) n = 28
Valeria Zanna et al. (2020) Italy[14]	No reference	Anxiety disorder n = 33 Mood disorder n = 15	
Helene Keery et al. (2019) USA[15]	No reference	Anxiety disorder n = 61 (57.5%) ADHD n = 25 (23.6%) Depressive disorder n = 20 (18.9%) Autistic spectrum disorder (ASD) n = 6 (5.7%) History of eating disorders n = 40 Use of psychotropic medication n = 38	Signs of medical instability: Orthostatic instability, (> 20 beats per minute (bpm), > 10 mmHg) n = 57 (53.8%) Amenorrhea n = 7 (11.1%) Bradycardia (< 50 bpm) n = 5 (4.7%) Hypotension (systolic pressure < 90 mmHg) n = 2 (1.9%)
Isaku Kurotori et al. (2019) Japan[16]	No reference	Developmental disorders n = 6	Family history of mental disorders n = 6
Fadila Farag et al. (2022) UK[17]	No reference	ASD n = 144	
Sarah E. Strandjord et al. (2015) Canada[18]	No reference	Unspecified psychiatric comorbidity n = 5	Family history: Eating disorder n = 3 Other psychiatric disorder n = 9
Laura Cañas et al. (2020) Spain[19]	No reference	Anxiety disorders n = 16 (59.3%) ADHD n = 7 (25.9%) OCD n = 2 (7.4%) Behavioral disorders n = 2 (7.4%) Depressive disorders n = 0 (0.0%)	The criteria A symptoms of DSM-5: A1 (significant weight loss or faltering growth) n = 20 A2 (significant nutritional deficiency) n = 24 A3 (dependence on oral nutritional supplements) n = 12 A4 (marked interference with psychosocial functioning) n = 16
Martin M. Fisher et al. (2013) USA & Canada[10]	Unspecified medical condition related to the disorder n = 34 unrelated to the disorder n = 16 *mentions that patients had GI symptoms and food allergies but does not have any specific numbers/data	Anxiety disorder: Generalized anxiety disorder (GAD) n = 28 Other n = 23 Mood disorder: Major depressive disorder (MDD)/ Dysthymia n = 7 Other n = 11 OCD n = 6	

(Continues)

Table 2. Results from the included studies *(continued)*

Author, year, and country	Medical comorbidities	Psychiatric comorbidities	Other findings
Melissa Lieberman et al. (2018) Canada[28]	Food allergies n = 4 Abdominal pain n = 9	GAD n = 7 OCD n = 6 Unspecified neurodevelopmental disorder n = 3 ADHD n = 1 ASD n = 1 Mood disorder n = 1 Other specified dissociative disorder (OSDD) n = 1	Infection prior to onset of ED n = 32 (37.9%)
Megan Cooney et al. (2018) Canada[12]	No reference	Anxiety disorder n = 10 ADHD n = 4 MDD n = 2 Other unspecified psychiatric comorbidity n = 5	The criteria A symptoms of DSM-5: A1 (significant weight loss or faltering growth) n = 27 A2 (significant nutritional deficiency) n = 0 A3 (dependence on oral nutritional supplements) n = 1 A4 (marked interference with psychosocial functioning) n = 0 Trigger for their eating disturbance: Abdominal pain n = 5 Bullying n = 3 Death of a family member/ friend n = 2 Starting a medication n = 2 Having emesis n = 2 or witnessing emesis n = 1 Concern for food allergy n = 2 Concern for animal rights n = 1
Evelyna Kambanis et al. (2022) USA, Switzerland & UK[20]	No reference	GAD n = 18 (35.0%) MDD n = 15 (29.0%) Panic disorder n = 7 (14.0%) Specific phobia n = 5 (10.0%) Social anxiety disorder n = 5 (10.0%) Suicidality n = 5 (10.0%) ADHD n = 4 (8.0%) Post-traumatic stress disorder (PTSD) n = 4 (8.0%) Other specified depressive disorder n = 3 (6.0%) OCD n = 3 (6.0%) Other specified ADHD n = 2 (4.0%) Other specified anxiety disorder n = 1 (2.0%) ASD n = 1 (2.0%) Persistent depressive disorder n = 1 (2.0%) Separation anxiety disorder n = 0 (0.0%)	
Dominik Düplois et al. (2023) Germany[21]	GI diseases n = 7 (36.8%) Metabolic disorders n = 3 (15.8%) Congenital anomalies n = 2 (10.5%)	Affective disorders n = 8 (42.1%) ADHD n = 2 (10.5%) OCD n = 1 (5.3%)	
Mark L. Norris et al. (2014) Canada[11]	No reference	GAD n = 17 MDD n = 4 *other diagnoses including panic disorder, OCD, and social phobia were present but there was no mention of values	Immediate family member with a diagnosed psychiatric disorder n = 5

(Continues)

Table 2. Results from the included studies *(continued)*

Author, year, and country	Medical comorbidities	Psychiatric comorbidities	Other findings
Anna Aulinas et al. (2021) USA, Spain & Switzerland[22]	Gastrointestinal system: History of GI symptoms n = 9 (45.0%) Acid reflux n = 8 (40.0%) Delayed gastric emptying n = 2 (10.0%) Irritable bowel syndrome n = 1 (5.0%) Immune system: Drug allergies n = 6 (30.0%) Asthma n = 5 (25.0%) Food allergies n = 4 (20.0%)	History of depression n = 3 History of anxiety n = 13 History of OCD n = 0 Current psychiatric medication: Total n = 12 (60.0%) Antidepressants n = 5 (25.0%) Anxiolytics n = 3 (15.0%) Psychostimulants n = 3 (15.0%) Antihistamines n = 3 (15.0%)	Family history of eating disorders n = 2 Family history of psychiatric disorders n = 9
Katelynn E Boerner et al. (2021) Canada[23]	Co-occurring medical diagnosis: Total n = 14 (22.6%) GI conditions (chronic abdominal pain and inflammatory conditions) n = 6 (9.7%) Chronic (non-abdominal) pain n = 2 (3.2%) Endocrine conditions n = 2 (3.2%) Neurological conditions n = 1 (1.6%) Oncological conditions n = 1 (1.6%) Physical symptoms (reported at assessment) Total n = 58 (93.5%) GI n = 52 (83.9%) Headache n = 21 (33.9%) Cognitive problems n = 17 (27.4%) Dizziness or fainting/syncope n = 15 (24.2%) Sensory problems n = 8 (12.9%) Perceptual disturbances n = 3 (4.8%) Movement problems n = 2 (3.2%) Other pain n = 12 (19.4%) Other symptoms n = 18 (29.0%)	Co-occurring psychiatric diagnosis: Total n = 33 (53.2%) Anxiety disorder n = 27 (43.5%) Neurodevelopmental disorder n = 8 (12.9%) OCD n = 7 (11.3%) Bipolar-related or depressive disorder n = 6 (9.7%) Disruptive, impulse-control, or conduct disorder n = 1 (1.6%) History of abuse Physical n = 4 (6.5%) Sexual n = 1 (1.6%) Self-harm and suicidality History of suicidal ideation n = 17 (27.4%) History of self-harm n = 8 (12.9%) History of suicide attempt n = 4 (6.5%) Substance use (historical and/or current): Total n = 8 (12.9%) Alcohol use n = 8 (12.9%) Illicit substance use n = 6 (9.7%) Prescription medication misuse n = 2 (3.2%)	This study compared characteristics of pediatric patients diagnosed with ARFID to those with GI-related SSRD. 16% of the total sample reported symptoms consistent with co-occurring diagnoses of ARFID and SSRD
Terri A Nicely et al. (2014) USA[13]	Symptoms and features Fear of choking or vomiting n = 17 (47.0%) Enteral supplement use n = 18 (46.0%) Recent medical specialist consult n = 18 (46.0%) Sensory issues n = 10 (26.0%) Food allergy n = 8 (20.0%) Excessive exercise n = 6 (15.0%) Purge-vomit n = 0 (0.0%)	Psychiatric comorbidities Anxiety disorder n = 28 (72.0%) Mood disorder n = 13 (33.0%) Cognitive impairment n = 10 (26.0%) ASD n = 5 (13.0%) Learning disorder n = 4 (10.0%) ADHD n = 2 (4.0%)	21% of participants exhibited body preoccupation with somatic concerns. For example, some children were fixated on fears of physical illness due to issues related to shape/weight, e.g., high cholesterol and/or obesity leading to heart disease, either because of personal experiences with relatives or information in their school curriculum
Evelyna Kambanis et al. (2019) USA & Switzerland[24]	No reference	Anxiety, OCD, and trauma-related disorders: Total: current (C) n = 26 (35.0%)/ lifetime (L) n = 30 (41.0%) GAD: C n = 18 (24.0%)/L n = 18 (24.0%) Panic disorder: C n = 7 (10.0%)/L n = 9 (12.0%) Social anxiety disorder: C n = 7 (10.0%)/L n = 9 (12.0%) Specific phobia: C n = 5 (7.0%)/L n = 5 (7.0%)	The sensory sensitivity profile (rated on a 0 – 6 scale) was associated with more than twice the odds of a current or lifetime comorbid neurodevelopmental, disruptive, or conduct disorder; The fear of aversive consequences profile was associated with more than twice the odds of a current

(Continues)

Table 2. Results from the included studies *(continued)*

Author, year, and country	Medical comorbidities	Psychiatric comorbidities	Other findings
		OCD: C n = 3 (4.0%)/L n = 3 (4.0%) Agoraphobia: C n = 1 (1.0%)/L n = 1 (1.0%) Separation anxiety disorder: C n = 0 (0.0%)/L n = 1 (1.0%) Other specified anxiety disorder: C n = 1 (1.0%)/L n = 1 (1.0%) PTSD: C n = 0 (0.0%)/L n = 1 (1.0%) Neurodevelopmental, disruptive, and conduct disorders: Total: C n = 12 (16.0%)/L n = 14 (19.0%) ADHD: C n = 6 (8.0%)/L n = 7 (10.0%) Other specified ADHD: C n = 5 (7.0%)/L n = 5 (7.0%) Oppositional defiant disorder: C n = 2 (3.0%)/L n = 2 (3.0%) ASD: C n = 2 (3.0%)/L n = 2 (3.0%) Suicidality: Total: C n = 6 (8.0%)/L n = 10 (14.0%) Depressive and bipolar-related disorders: Total: C n = 3 (4.0%)/L n = 15 (20.0%): MDD: C n = 2 (3.0%)/L n = 10 (14.0%) Other specified depressive disorder: C n = 1 (1.0%)/L n = 3 (4.0%) Persistent depressive disorder: C n = 0 (0.0%)/L n = 2 (3.0%) Eating disorders and substance-related disorders: Total: C n = 0 (0.0%)/L n = 1 (1.0%) Binge eating disorder: C n = 0 (0.0%)/L n = 1 (1.0%) Schizophrenia spectrum and other psychotic disorders: Total: C n = 0 (0.0%)/L n = 0 (0.0%)	comorbid anxiety, OCD, or trauma-related disorder; The ARFID sensory sensitivity profile was associated with nearly three times the odds of a current or lifetime comorbid anxiety, OCD, or trauma-related disorder; The sensory sensitivity profile was associated with more than twice the odds of a lifetime comorbid depressive or bipolar-related disorder; Severity in the sensory sensitivity profile contributed to both current and lifetime likelihood of neurodevelopmental, disruptive, and conduct disorders; and severity in the fear of aversive consequences profile contributed to current and lifetime anxiety, OCD, and trauma-related disorders
Takeshi Inoue et al. (2021) Japan[25]	No reference	ASD n = 4 (12.5%)	
Kamryn T. Eddy et al. (2015) USA[26]	Presenting GI complaint: Poor weight gain/growth n = 17 Low weight/underweight n = 10 Poor appetite n = 10 Abdominal pain n = 9 Weight loss n = 5 Reflux n = 5 Nausea n = 3 Diarrhea/loose stools n = 3 Food allergies n = 3	No reference	
Mark L. Norris et al. (2021) Canada[27]	No reference	Anxiety disorder: ARFID total n = 19 (73.1%) Aversive n = 6 (100.0%) Sensory n = 2 (100.0%) Low appetite, limited interest n = 4 (50.0%) ARFID-Mixed n = 7 (70.0%) ASD: ARFID total n = 16 (23.1%)	Patients with aversive presentations presented an abbreviated course of illnesses and were all diagnosed with anxiety. Patients with low appetite represented the highest proportion of single-symptom presentations

(Continues)

Table 2. Results from the included studies *(continued)*

Author, year, and country	Medical comorbidities	Psychiatric comorbidities	Other findings
		Aversive n = 1 (16.7%) Sensory n = 1 (50.0%) Low appetite, limited interest n = 0 (0.0%) ARFID-Mixed n = 4 (40.0%) Mood disorder: ARFID total n = 9 (34.60%) Aversive n = 3 (50.0%) Sensory n = 1 (50.0%) Low appetite, limited interest n = 2 (25.0%) ARFID-Mixed n = 3 (30.0%) Learning difficulties: ARFID total n = 8 (30.08%) Aversive n = 1 (16.7%) Sensory n = 0 (0.0%) Low appetite, limited interest n = 3 (37.5%) ARFID-Mixed n = 4 (40.0%) ADHD: ARFID total n = 6 (23.1%) Aversive n = 2 (33.3%) Sensory n = 1 (50.0%) Low appetite, limited interest n = 0 (0.0%) ARFID-Mixed n = 3 (30.0%) OCD: ARFID total n = 4 (15.4%) Aversive n = 2 (33.3%) Sensory n = 0 (0.0%) Low appetite, limited interest n = 0 (0.0%) ARFID-Mixed n = 2 (20.0%)	Patients with sensory-based food avoidance (i.e., extremely selective eaters) are less likely to present with markers of medical instability, and as such, would have been less likely to meet inclusion criteria for this pilot initiative

GI: gastrointestinal; OCD: obsessive-compulsive disorder; ADHD: attention-deficit/hyperactivity disorder; ASD: autistic spectrum disorder; GAD: generalized anxiety disorder; MDD: major depressive disorder; OSDD: other specified dissociative disorder; PTSD: post-traumatic stress disorder; ARFID: avoidant/restrictive food intake disorder; SSRD: somatic symptom and related disorder.

in their sample[9,12,19]. Due to the consistent methodology employed across the studies, the results were aggregated to provide a more robust body of evidence. The sample consisted of 144 participants, of whom 125 filled the A1 criteria (significant weight loss (or failure to achieve expected weight gain or faltering growth in children)), 102 the A2 criteria (significant nutritional deficiency), 41 the A3 criteria (dependence on enteral feeding or oral nutritional supplements), and 16 the A4 criteria (marked interference with psychosocial functioning).

Keery et al. reported signs of medical instability such as bradycardia, hypotension, orthostatic instability, and amenorrhea[15].

While Lieberman et al. found that some participants had an infection before the onset of the eating disorder, Cooney et al. investigated what the trigger for the eating disorder was in each participant (Table 2)[12,28].

Another interesting finding, according to Nicely et al., was that although individuals with ARFID do not have body distortion (as seen in anorexia nervosa), 21% of the participants from that study had a fear of physical illness[13].

Lastly, Kambanis et al. and Norris et al. presented some noteworthy conclusions when it comes to the different ARFID presentations[24,27]. Participants with a lack of interest in food are more likely to present one single symptom. Participants with an aversive phenotype have a shorter course of illness and are twice as likely as the other phenotypes to have comorbid anxiety, OCD, and trauma-related disorder. Participants with sensory sensitivity are three times as likely as the other phenotypes to have comorbid anxiety, OCD, and trauma-related disorder, and twice as likely as the other phenotypes to have comorbid mood, neurodevelopmental, and conduct disorders. However, this last phenotype is less likely to present with signs of medical instability.

Discussion

To our understanding, this is the first systematic literature review that specifically targets the most prevalent comorbidities in children and adolescents diagnosed with ARFID. Knowledge about comorbid conditions is fundamental to improving healthcare outcomes, as it shapes effective treatment, prognosis, and patient care. The findings from this review indicate that there are a significant number of comorbidities amongst young individuals with ARFID[10,19,21,28]. This is congruent with other literature that finds a greater medical and psychiatric comorbidity in this population, in comparison with other EDs[19].

When it comes to medical comorbidities, GI, neurological, and immune disorders are the most frequent. The high prevalence of GI symptoms and conditions among the participants suggests a connection between ARFID and digestive health, such as central sensitization and altered gut physiology, and also raises questions about the etiology of this disorder[23]. GI problems can cause discomfort during eating, potentially influencing food avoidance or restrictive behaviors[9,19,28]. This discomfort is often linked to high anxiety levels, commonly associated with symptoms like nausea and decreased appetite, leading individuals to adopt restrictive food intake as a maladaptive coping technique[11]. Regardless of their etiological value, GI symptoms often contribute to the continuation of the ED, so evaluating and addressing these issues should be a priority[23].

High levels of atopy were also found, such as food allergies and asthma, which raises suspicion for an immune-mediated disorder like eosinophilic esophagitis intensifying the symptomatology[22]. It is also important to note that young people with food allergies have high levels of anxiety associated with eating, which can be an underlying motive for the ED[28].

Regarding psychiatric comorbidities, the results converge across the different studies and also with the core literature in the field of psychiatry, which works to further enhance the reliability and validity of the findings[1]. Anxiety, neurodevelopmental disorders, mood disorders, and OCD were consistently the most prevalent comorbidities.

Children with anxiety may be more prone to developing particular phobias and avoidance behaviors, especially if they experience events such as choking or vomiting, which they might find more distressing due to their increased sensitivity to fear and anxiety-related responses[9]. This tendency is in line with the observed high prevalence of anxiety in various types of eating disorders[24]. In such cases, the tendency to avoid food can be attributed to underlying anxiety, or act as a coping mechanism to reduce such feelings, thereby negatively reinforcing these avoidance patterns[24]. Moreover, this overlap with anxiety disorders is evidenced by parental observations of ARFID patients, who often report separation anxiety. Supporting this link, research by Zanna et al. indicates that anxiety and worries during childhood can be predictors of eating disorders in adolescence[14]. The restrictive eating pattern can also increase the risk of suicide ideation and predict suicidality, although this has only been proven in females[20].

The elevated frequency of neurodevelopmental disorders can be explained by the cognitive rigidity and sensory sensitivity difficulties - hypersensitivity and exaggerated response to sensory stimuli present in ASD and ADHD[17,24]. ASD can influence and maintain ARFID, which suggests that this ED could be an indicator of ASD[17]. Zickgraf et al. also mention that the loss of appetite seen in some variations of this ED can be caused by the high rate of comorbidities. For example, stimulating medication for ADHD can cause appetite loss, as can depressive disorders[9].

ARFID patients also frequently experience nutritional deficiencies that lead to medical instability and consequently to a high rate of hospitalizations[10,11,13,17,19]. This should be tackled with early interventions and prompt diagnosis, which would ameliorate the effects of the food deprivation[12,17].

However, the highly heterogeneous presentation of the disorder, with its non-specific cadre of symptoms, can make this challenging[9,10,12,13,19,25,26,28]. To address these complexities, a multidisciplinary approach is paramount[17,23,27]. This should include a comprehensive assessment and care pathways encompassing medical nutrition, oral-motor skills, behavioral therapy, and sensory and environmental considerations[17]. Such a holistic intervention, tailored to each patient's needs, aims to improve resource planning, clinical management, and health outcomes[17]. Boerner et al. underscore the benefits of integrating physical and mental healthcare to address the mind-body connection in ARFID patients, highlighting the importance of multidisciplinary teams in managing the complex medical-psychosocial integration inherent in these disorders[23].

The impact of ARFID extends to the patients' families, causing psychological distress and interfering with parent-child relationships[10,19]. This stress is often heightened during mealtimes. Therefore, treatments should also include family involvement to support the patient's social and family interactions[27]. In view of ARFID's significant influence on the physical, sexual, and emotional development of patients, a holistic, family-inclusive approach is essential for a comprehensive treatment plan[17,23,28].

While this study presents compelling results, it is important to acknowledge its limitations. This systematic literature review predominantly includes studies conducted in North America and Europe, with a particular emphasis on specialized pediatric eating disorder clinics. This specificity in terms of geography and clinical setting, along with the exclusive emphasis on a pediatric population, raises concerns about the representativeness and applicability of the findings. Additionally, most of the studies included in the review are retrospective chart reviews, which may not capture the full spectrum of clinical experiences and can introduce bias due to their retrospective nature. This focus on specific regions, a particular age group, and limited settings suggests potential biases and limits the generalizability of the research to more diverse populations. Furthermore, the current literature reveals significant gaps, particularly in longitudinal perspectives and the exploration of various factors (biological, environmental, or otherwise) that contribute to ARFID. This narrow scope highlights the urgent need for more inclusive and diverse research methodologies to fully understand and address this complex disorder. From the risk of bias assessment, it is evident that while many studies exhibit a low risk of bias in certain domains, there is also a significant presence of moderate risk and areas lacking sufficient information to make a judgment. The prevalence of question marks across the matrix in figure 2 suggests that data for many domains was not adequately reported or was unclear, highlighting the need for more rigorous reporting standards in non-randomized studies. Conclusively, these visual tools collectively emphasize the varying levels of bias within the evaluated studies, underscoring the importance of thorough bias assessment in understanding the validity and reliability of study outcomes[29-31].

Future research on ARFID should strive for greater geographical diversity and varied methodological approaches to broaden our understanding and improve outcomes for those affected. Key areas for further investigation include conducting longitudinal studies to track ARFID's progression and long-term impacts, developing standardized assessment tools, and exploring its biological and environmental causes. Research should also focus on understanding ARFID's heterogeneity, examining its subtypes, and the high comorbidity with conditions like anxiety and GI and neurodevelopmental disorders. An integrated clinical approach involving various healthcare professionals is crucial, alongside personalized treatment strategies. Investigating the causal pathways between ARFID and its comorbidities, developing comprehensive screening tools, and conducting longitudinal studies on outcomes are also essential to enhance treatment and support for individuals with ARFID.

This systematic literature review, focusing on prevalent comorbidities in children and adolescents with ARFID, identified significant correlations between ARFID and GI, neurological, and immune disorders, as well as a range of psychiatric comorbidities like anxiety, neurodevelopmental disorders, OCD, and mood disorders. These findings align with existing literature and highlight a greater medical risk in this population compared to other eating disorders. The review emphasizes the need for early intervention and a multidisciplinary treatment approach due to ARFID's heterogeneous symptomatology. Given the complexity of ARFID, effective management extends beyond psychiatric care to involve pediatricians, gastroenterologists, endocrinologists, and other relevant medical specialists. This collaborative approach is crucial for comprehensive care, addressing the multifaceted nature of ARFID. Moreover, there is an urgent need to increase awareness and knowledge about ARFID among those who regularly interact with children and adolescents, such as educators and school health personnel. Training these individuals to recognize the early signs of ARFID can facilitate timely referrals and interventions, thus playing a pivotal role in improving outcomes for affected individuals. The impact of the disorder extends beyond the individual, affecting family dynamics and necessitating family-inclusive treatment plans.

Author contributions

F. Gomes Neves: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. D. Ferreira: Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. P.C. Correia: Conception and design of the study, report, review or other type of work or paper; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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

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

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REVIEW ARTICLE

Postnatal corticosteroids to prevent bronchopulmonary dysplasia: balancing benefits and risks. A narrative review

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Abstract

This review analyzes the beneficial and adverse effects of corticosteroids used in the prevention and treatment of bronchopulmonary dysplasia, aiming to provide clinicians with evidence-based information.

Keywords: Bronchopulmonary dysplasia. Budesonide. Corticosteroids. Dexamethasone. Hydrocortisone.

Corticosteroides pós-natais para prevenir a displasia broncopulmonar: equilibrando benefícios e riscos. Uma revisão narrativa

Resumo

Esta revisão analisa os efeitos benéficos e adversos dos corticosteróides utilizados na prevenção e tratamento da displasia broncopulmonar do grande prétermo, de forma a poder fornecer ao clínico informações úteis baseadas em evidências.

Palavras-chave: Budesonide. Corticosteroides. Dexametasona. Displasia broncopulmonar. Hidrocortisona.

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Keypoints

What is known

- Postnatal corticosteroids have been used in neonatology to prevent and treat bronchopulmonary dysplasia in preterm infants.
- Clinical trials have examined various corticosteroids, including dexamethasone and hydrocortisone used systemically, and several others used by the inhalation route.
- The use of corticosteroids in preterm infants has shown benefits but also significant risks, such as cerebral palsy.

What is added

- This review summarizes current evidence on the use of postnatal corticosteroids in preterm infants.
- The role of corticosteroids in the prevention and treatment of bronchopulmonary dysplasia is not yet a completely resolved issue.
- Systemic corticosteroids are indicated after the first week of life in ventilator-dependent preterm infants with the aim of enabling extubation.

Introduction

Bronchopulmonary dysplasia (BPD) remains a significant chronic morbidity for preterm infants, posing as a potentially devastating condition with lasting negative impacts on pulmonary function and neurodevelopmental outcomes[1]. Despite advances in obstetric and neonatal care over the last few decades, BPD still affects approximately 50% of preterm infants born before 28 weeks of gestation[2]. The disease, which has a multifactorial etiology and complex pathophysiology, is marked by inflammation in immature lungs and airways[1,3]. Due to their potent anti-inflammatory effects, corticosteroids were introduced around 50 years ago to treat breathing problems in preterm infants[4]. Enthusiasm for the use of corticosteroids to prevent and treat BPD emerged in the 1980s. Since then, more than 80 randomized controlled trials (RCTs) have been conducted, making corticosteroids one of the most researched medications and also one of the most controversial interventions in neonatal medicine[5,6].

Initially, corticosteroids were administered systemically, and the inhalation route was developed later[7]. Clinical trials have examined various corticosteroids, including dexamethasone and hydrocortisone administered systemically, as well as several others administered via the inhalation route[7].

The objective of this review is to summarize the results of the most recent literature on the use of corticosteroids in the prevention and treatment of BPD, with a focus on highlighting the risks versus the benefits. The aim is to provide clinicians with safe and practical information for their decision-making processes.

Methods

A literature search was conducted in the PubMed database for review articles on corticosteroids for preventing and treating bronchopulmonary dysplasia, written in English and published from 2010 onwards. The search included the following keywords: corticosteroids, dexamethasone, hydrocortisone, budesonide, bronchopulmonary dysplasia, surfactant, inhaled, systemic, intratracheal, adverse effects, neurodevelopment and cerebral palsy.

The information from the review articles was analyzed and compiled in this manuscript.

Systemic corticosteroids

The primary corticosteroids administered systemically to prevent or treat BPD are dexamethasone and hydrocortisone[8,9]. Dexamethasone has no affinity for mineralocorticoid receptors; it only exerts glucocorticoid effects. It is approximately 25 times more potent than hydrocortisone and is considered a long-acting agent, with a duration of action exceeding 36 hours[10,11]. The glucocorticoid activity reduces inflammation, suppresses immune function, influences nutrient metabolism and aids in the normal response to stress[12]. Hydrocortisone is the synthetic analog of endogenous cortisol and can exert both mineralocorticoid and glucocorticoid effects, depending on the dose and the patient's state of stress. It exhibits greater glucocorticoid binding in states of high stress and greater mineralocorticoid binding in states of low stress[12-14]. Hydrocortisone is absorbed rapidly through the enteral route and is short-acting, with a duration of action typically ranging from eight to 12 hours[14]. Mineralocorticoid activity enhances sodium absorption and potassium excretion in the nephrons, resulting in passive water retention, increased intravascular volume and elevated blood pressure[12].

Synthetic glucocorticoids with a long biological action and little or no mineralocorticoid activity, such as dexamethasone, can suppress natural cortisol secretion and may leave mineralocorticoid receptors unoccupied for prolonged periods of time. This can lead to neuronal

apoptosis in the developing brain[15,16]. This may explain the neurodevelopmental deficits observed in preterm infants treated with dexamethasone but not with hydrocortisone[9]. A recent systematic review by Jenkinson et al., aimed at determining the cardiopulmonary and cognitive effects during childhood and adolescence of dexamethasone systemically administered to preterm infants during neonatal intensive care, found impaired respiratory and cognitive outcomes[17].

Meta-analyses of RCTs that assessed risks and benefits of systemic corticosteroids to prevent or treat BPD have divided the trials based on the timing of treatment initiation into early (< 7 days after birth) and late (≥ 7 days after birth).

Early (< 7 days after birth) systemic corticosteroids

The administration of systemic corticosteroids during the first six days of life has beneficial effects as it minimizes relative cortisol insufficiency and lung inflammation caused by factors such as ventilation, surfactant deficiency, oxygen toxicity, hypoxemia, chorioamnionitis and early-onset sepsis[7].

The most recent Cochrane systematic review, conducted by Doyle et al., published in 2021, included 32 trials (21 with dexamethasone and 11 with hydrocortisone) with a total of 4,393 participants[9]. In these trials, systemic corticosteroids were compared with a placebo or no intervention. The characteristics of the individual trials varied significantly, particularly in terms of treatment durations and cumulative doses of corticosteroids. The analysis of the results demonstrated that early systemic corticosteroids reduced the rates of BPD at 36 weeks, combined mortality or BPD at 36 weeks, but not mortality alone at 36 weeks (Table 1). Most of the reduction in BPD arises from studies using dexamethasone rather than hydrocortisone. Both dexamethasone and hydrocortisone contribute to a reduction in combined mortality or BPD at 36 weeks. There is also evidence that hydrocortisone reduces mortality at the latest reported age, but dexamethasone does not. Unfortunately, early administration of dexamethasone increases the rate of cerebral palsy and the combined outcome of cerebral palsy or mortality, whereas hydrocortisone does not have the same effect.

One of the studies that yielded interesting results regarding the early use of hydrocortisone is the PREMILOC trial[18]. In this double-blind, placebo-controlled RCT conducted at 21 French tertiary centers, 521 preterm infants ranging from 24 to 27 weeks' gestation were enrolled. Hydrocortisone was administered starting from the first day of life at a dose of 8.5 mg/kg over 10 days. The study found that hydrocortisone reduced the rate of the primary endpoint of BPD or mortality at 36 weeks (hydrocortisone 40%; control 49%, RR 0.82; 95% CI 0.67-0.99; p = 0.04). At the follow-up at 22 months' corrected age, the rates of cerebral palsy were similar in both groups (hydrocortisone 6%; control 5%)[19]. The five-year neurocognitive outcomes of 83 surviving children at one center showed that hydrocortisone treatment was significantly associated with a greater chance of survival at five years of age with a full-scale IQ equal to or greater than 90 compared to the placebo (adjusted odds ratio = 4.26, 95% CI = 1.47-12.36, p = 0.008)[20]. However, the results of the PREMILOC trial require confirmation through additional studies. Therefore, most authors do not yet recommend its routine use.

Other benefits of early systemic corticosteroids include increased rates of successful extubation and lower rates of patent ductus arteriosus and retinopathy of prematurity[9]. However, there are also adverse effects, such as gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy and growth failure[9]. These reported benefits and adverse effects are mostly associated with dexamethasone, with the exception of intestinal perforation, which was more common with both hydrocortisone and dexamethasone.

A major limitation of early systemic corticosteroid studies is their lack of sampling power to assess neurodevelopment in childhood. This limitation means they do not allow the risks and benefits to be assessed with certainty[5].

Balancing the risks and benefits of early systemic corticosteroids in the prevention of BPD, it is currently accepted that they should not be used routinely in clinical practice[5]. Due to the encouraging results of the PREMILOC study, more RCTs with early hydrocortisone are needed to assess survival without neurodevelopmental disability. Before the routine use of hydrocortisone can be recommended, further evidence from these trials is needed[5].

Late (≥ 7 days after birth) systemic corticosteroids

The most recent review on late systemic corticosteroids includes 23 trials (21 with dexamethasone and two with hydrocortisone), recruiting a total of 1,817 infants[8]. Most infants were ventilator-dependent at enrolment, and regimens varied significantly in duration and cumulative dose.

Table 1. Summary effects of early (< 7 days after birth) systemic corticosteroids in the various Cochrane reviews

	Dexamethasone	Hydrocortisone	Combined
BPD at 36 weeks	0.72 [0.63, 0.82] **p < 0.001** ns = 17 np = 2,791	0.92 [0.81, 1.06] p = 0.25 ns = 9 np = 1,376	0.80 [0.73, 0.88] **p < 0.001** ns = 26 np = 4,167
Mortality by 36 weeks	1.08 [0.94, 1.23] p = 0.29 ns = 17 np = 2,791	0.85 [0.67, 1.06] p = 0.15 ns = 10 np = 1,385	1.01 [0.90, 1.13] p = 0.92 ns = 27 np = 4,167
Mortality or BPD by 36 weeks	0.88 [0.81, 0.95] **p < 0.001** ns = 17 np = 2,791	0.90 [0.82, 0.99] **p = 0.04** ns = 9 np = 1,376	0.89 [0.83, 0.94] **p < 0.001** ns = 26 np = 4,167
Mortality at latest age report	1.02 [0.90, 1.16] p = 0.73 ns = 20 np = 2,940	0.80 [0.65, 0.99] **p = 0.04** ns = 11 np = 1,433	0.95 [0.85, 1.06] p = 0.38 ns = 31 np = 4,373
Cerebral palsy	1.77 [1.21, 2.58] **p = 0.003** ns = 7 np = 921	1.05 [0.66, 1.66] p = 0.84 ns = 6 np = 1,052	1.43 [1.07, 1.92] **p = 0.02** ns = 13 np = 1,973
Mortality before follow-up	0.99 [0.81, 1.21] p = 0.93 ns = 7 np = 921	0.81 [0.64, 1.02] p = 0.08 ns = 6 np = 1,052	0.90 [0.78, 1.05] p = 0.19 ns = 13 np = 1,973
Mortality or cerebral palsy	1.18 [1.01, 1.37] **p = 0.04** ns = 7 np = 921	0.86 [0.71, 1.05] p = 0.15 ns = 6 np = 1,052	0.03 [0.91, 1.16] p = 0.63 ns = 13 np = 1,973

Data are RR [95% confidence interval].
RR: risk ratio; BPD: bronchopulmonary dysplasia; ns: number of studies; np: number of participants; **bold P:** statistically significant.
Adapted from reference 5.

Late systemic administration of corticosteroids reduced the rates of BPD at 36 weeks, mortality by 36 weeks, combined mortality or BPD by 36 weeks and mortality at the latest reported age (Table 2). All the effects on BPD arise from studies with dexamethasone rather than hydrocortisone. Although the reduction in mortality at the latest reported age seems to arise from studies with hydrocortisone, there is little heterogeneity between the dexamethasone and hydrocortisone subgroups (p = 0.42). There is little evidence that late corticosteroids increase cerebral palsy in later childhood, although there was only one study with hydrocortisone assessing this outcome (Table 2).

In 2022, the results of the hydrocortisone for BPD trial, conducted by the *National Institute of Child Health and Human Development (NICHD) Neonatal Research Network*, were published[21]. In this trial, 800 preterm infants with a gestational age below 30 weeks who had been intubated for at least seven days at 14 to 28 days were randomly assigned to receive either hydrocortisone (4 mg per kilogram of body weight per day tapered over a period of 10 days) or a placebo. Hydrocortisone increased the probability of extubation and reduced the duration of mechanical ventilation. However, hydrocortisone did not affect survival without BPD at 36 weeks nor survival without moderate-to-severe neurodevelopmental impairment or survival without cerebral palsy. The meta-analysis of data from this trial, combined with the other two trials with hydrocortisone included in the 2021 Cochrane review, did not show any differences in the rates of death, BPD or cerebral palsy[7].

In recent studies by Halbmeijer N et al.[22,23], systemic hydrocortisone started in the second week after birth in ventilator-dependent infants born very preterm was not found to be associated with significant differences in brain development or neurodevelopment at two years of corrected age, compared with placebo treatment.

Table 2. Summary effects of late (≥ 7 days after birth) systemic corticosteroids in the various Cochrane reviews

	Dexamethasone	Hydrocortisone	Combined
BPD at 36 weeks	0.76 [0.66, 0.87] **p < 0.001** ns = 12 np = 553	1.10 [0.92, 1.31] p < 0.29 ns = 2 np = 435	0.89 [0.80, 0.99] **p = 0.03** ns = 14 np = 988
Mortality by 36 weeks	0.68 [0.43, 1.08] p = 0.11 ns = 13 np = 594	0.71 [0.49, 1.04] p = 0.08 ns = 2 np = 435	0.69 [0.52, 0.93] **p = 0.02** ns = 15 np = 1,029
Mortality or BPD by 36 weeks	0.75 [0.67, 0.85] **p < 0.001** ns = 12 np = 553	0.98 [0.88, 1.09] p = 0.68 ns = 2 np = 435	0.85 [0.79, 0.92] p < 0.001 ns = 14 np = 988
Mortality at latest age report	0.85 [0.66, 1.11] p = 0.23 ns = 19 np = 993	0.72 [0.52, 1.00] p = 0.05 ns = 2 np = 435	0.80 [0.65, 0.98] **p = 0.03** ns = 21 np = 1,428
Cerebral palsy	1.12 [0.79, 1.60] p = 0.51 ns = 15 np = 855	3.19 [0.35, 29.1] p = 0.30 ns = 1 np = 64	1.16 [0.82, 1.64] p = 0.39 ns = 16 np = 919
Mortality before follow-up	0.82 [0.62, 1.10] p = 0.18 ns = 15 np = 855	0.80 [0.39, 1.63] p = 0.61 ns = 1 np = 64	0.82 [0.63, 1.07] p = 0.14 ns = 16 np = 919
Mortality or cerebral palsy	0.95 [0.77, 1.16] p = 0.58 ns = 15 np = 855	0.98 [0.53, 1.81] p = 0.96 ns = 1 np = 64	0.95 [0.78, 1.15] p = 0.59 ns = 16 np = 919

Data are RR [95% confidence interval].
RR: risk ratio; BPD: bronchopulmonary dysplasia; ns: number of studies; np: number of participants; **bold P:** statistically significant.
Adapted from reference 5.

It can be challenging to choose which corticosteroid to use and at what dose in infants with ongoing lung disease. Two trials examined low-dose late systemic corticosteroids[21,24]. The NICHD Neonatal Research Network Hydrocortisone for BPD Trial used a 24.5 mg/kg cumulative dose of hydrocortisone tapered over 10 days[21]. In this study, hydrocortisone increased the probability of successful extubation by day 10 (44.7% vs. 33.6%, NNT 9). However, it did not reduce the risk of BPD. In the second study, the DART trial[24], dexamethasone at a cumulative dose of 0.89 mg/kg, tapered over 10 days, significantly increased the chance of successful extubation (60.0% vs. 11.7%, NNT 2) without a significant reduction in the risk of BPD. This trial did not show significant neurological harm in survivors at two years' corrected age. However, unfortunately, it was not designed to evaluate neurodevelopmental outcomes. Other trials with late dexamethasone only showed a reduction in BPD when the cumulative dose was 2-4 mg/kg[25].

Other benefits of late systemic corticosteroids include faster extubation[8]. Adverse effects include hyperglycemia, glycosuria, systemic arterial hypertension, cardiomyopathy and severe retinopathy of prematurity[8].

As with trials on the early use of systemic corticosteroids, there are limitations in trials of late systemic corticosteroids. Most studies reporting long-term outcomes were not designed to detect clinically important neurodevelopmental deficits[5].

Based on the results of the trials with late systemic corticosteroids, they should be reserved for infants at high risk of developing BPD to maximize the risk-to-benefit profile. Researchers from the NICHD Neonatal Research Network conducted a propensity score-matched cohort study in 964 extremely preterm infants[26]. The results of this study suggested that corticosteroids were associated with a reduced risk of

death or disability at two years' corrected age in infants at moderate to high pretreatment risk of death or with grade 2 or 3 BPD, but they might pose harm in infants at lower risk[26].

Currently, late systemic corticosteroids are only indicated for ventilator-dependent infants, with the aim of extubating them and reducing the damage caused by prolonged ventilation[27,28].

Inhaled corticosteroids

Four different inhaled corticosteroids (budesonide, beclomethasone, fluticasone and flunisolide) have been studied[5]. Among these, budesonide is the most studied.

Early (≤ 14 days of life) inhaled corticosteroids

Early inhaled corticosteroids reduce the rates of BPD at 36 weeks and the combined outcome of mortality and BPD by 36 weeks (Table 3). Mortality before follow-up and the combined outcome of mortality and cerebral palsy are both higher in the corticosteroids group. The results of the meta-analyses are strongly influenced by the results of the NEUROSIS trial[29]. In this study, inhaled budesonide in preterm infants aged 23-27 weeks' gestational age under respiratory support reduced the primary outcome of death or BPD at 36 weeks. However, there was an increase in mortality by 36 weeks in the budesonide group, which had further increased by two years of age (p = 0.04)[29].

Due to being associated with increased mortality, early inhaled corticosteroids are not recommended[5].

Late (≥ 7 days after birth) inhaled corticosteroids

There is limited data on late inhaled corticosteroids. Only one trial contributed data on BPD at 36 weeks, and only three trials had data on mortality at 36 weeks. Additionally, none of the trials reported on long-term outcomes (Table 3). Based on this evidence, late inhaled corticosteroids are not recommended.

Inhaled versus systemic corticosteroids

The two Cochrane reviews that compare inhaled versus systemic corticosteroids include small numbers of studies and participants, with complex study designs and limited long-term data[30,31]. The lack of evidence of any benefit of inhaled over systemic corticosteroids and the increased mortality with early budesonide prevent their routine use in clinical practice (Table 4)[7].

Table 3. Summary effects of inhaled corticosteroids in the various Cochrane reviews

	≤ 14 days	≥ 7 days
BPD at 36 weeks	0.76 [0.83, 1.48] **p = 0.005** ns = 6 np = 1,285	1.00 [0.59, 1.70] p = 1.00 ns = 1 np = 30
Mortality by 36 weeks	1.09 [0.62, 0.92] p = 0.54 ns = 6 np = 1,285	3.00 [0.35, 25.8] p = 0.32 ns = 3 np = 61
Mortality or BPD by 36 weeks	0.86 [0.75, 0.99] **p = 0.04** ns = 6 np = 1,285	1.10 [0.74, 1.63] p = 0.66 ns = 1 np = 30
Mortality at latest age report	1.36 [1.02, 1.81] **p = 0.04** ns = 3 np = 1,127	3.00 [0.35, 25.8] p = 0.32 ns = 3 np = 53
Cerebral palsy	1.05 [0.67, 1.65] p = 0.83 ns = 3 np = 1,127	Not reported
Mortality before follow-up	1.36 [1.02, 1.81] **p = 0.04** ns = 3 np = 1,127	Not reported
Mortality or cerebral palsy	1.26 [1.00, 1.58] **p = 0.05** ns = 3 np = 1,127	Not reported

Data are RR [95% confidence interval]; RR: risk ratio; BPD: bronchopulmonary dysplasia; ns: number of studies; np: number of participants; **bold P:** statistically significant.
Adapted from reference 5.

Intratracheal corticosteroids administered with a surfactant

The results of a meta-analysis from 2022, including 12 trials and 1,377 ventilated preterm infants, suggested that the early combined utilization of budesonide and surfactant have a superior effect on BPD incidence (risk ratio [RR] = 0.62; 95% CI: 0.54-0.71, p < 0.001], mortality (RR = 0.64; 95% CI: 0.45-0.92, p = 0.016), the composite outcome of BPD and mortality (RR = 0.58; 95% CI: 0.50-0.68, p < 0.001), the additional doses of surfactant (RR = 0.53; 95% CI: 0.44-0.63, p < 0.001), the duration of assisted ventilation (standard mean difference [SMD] = 1.14; 95% CI: 1.58 to 0.70, p < 0.001),

Table 4. Summary effects of inhaled versus systemic corticosteroids in the Cochrane reviews

	≤ 7 days	> 7 days
BPD at 36 weeks	1.45 [0.99, 2.11] p = 0.06 ns = 1 np = 278	1.06 [0.88, 1.29] p = 0.53 ns = 3 np = 431
Mortality by 36 weeks	0.83 [0.56, 1.23] p = 0.36 ns = 2 np = 294	0.94 [0.62, 1.43] p = 0.77 ns = 3 np = 431
Mortality or BPD by 36 weeks	1.09 [0.88, 1.35] p = 0.43 ns = 1 np = 278	1.02 [0.84, 1.23] p = 0.86 ns = 3 np = 431
Mortality at latest age report	No data	No data
Cerebral palsy	1.87 [0.36, 9.72] p = 0.46 ns = 1 np = 91	1.00 [0.34, 2.92] p = 1.00 ns = 1 np = 118
Mortality before follow-up	0.94 [0.47, 1.86] p = 0.85 ns = 1 np = 91	0.83 [0.47, 1.49] p = 0.54 ns = 1 np = 118
Mortality or cerebral palsy	1.07 [0.59, 1.93] p = 0.82 ns = 1 np = 91	0.88 [0.55, 1.39] p = 0.57 ns = 1 np = 118

Data are RR [95% confidence interval]; RR: risk ratio; BPD: bronchopulmonary dysplasia; ns: number of studies; np: number of participants.
Adapted from reference 5.

duration of invasive ventilation (SMD = 1.77; 95% CI: 2.61 to 0.93, p < 0.001) and hospital stays (SMD = 1.11; 95% CI: 1.73 to 0.49, p = 0.001) in preterm infants with respiratory distress syndrome. Moreover, these benefits were not associated with increased adverse outcomes[32].

The intratracheal administration of a corticosteroid combined with surfactant looks promising, and several trials are ongoing.

Summary

The role of corticosteroids in the prevention and treatment of BPD is not yet a completely resolved issue, and further studies are still needed. The systemic route appears to be superior to the inhalation route. Systemic dexamethasone should not be used in the first week of life. Weighing the benefits against the risks, the use of corticosteroids should be considered after the first week of life. However, the benefits of low-dose systemic hydrocortisone used in the first 10 days of life deserve confirmation through further research. When used after the first week of life, corticosteroids should be reserved for high-risk BPD patients, particularly ventilator-dependent infants. Additionally, regardless of the drug used, its dose and duration should be minimized. The use of corticosteroids plus surfactant appears promising, but more research is needed before they can be recommended for routine use. Data on long-term follow-up, including motor and cognitive outcomes, are necessary for a comprehensive understanding of their effects.

Conclusion

Systemic corticosteroids are currently only indicated after the first week of life in ventilator-dependent preterm infants at high risk of developing BPD, with the aim of facilitating extubation. They should be used at the lowest possible dose and duration.

Author contributions

G. Rocha: Literature research, conception and review of the manuscript.

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

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CASE REPORT

Success in changing from intravenous to oral antibiotics in pediatric intracranial infections: report of three cases

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Abstract

Introduction: Acute bacterial rhinosinusitis is a common infection in children. Intracranial complications like subdural empyema or brain abscess are rare, albeit with significant morbidity and neurological sequelae. **Case report:** We present three clinical cases of intracranial suppurative complications secondary to sinus infection in which the transition to oral antibiotic therapy took place between day 14 and day 21 of intravenous treatment. In all, both neurosurgery and otorhinolaryngology surgery with empyema and sinus drainage were performed, the bacterial etiology was identified and clinical cure was achieved with no relapses. **Discussion:** Although the early transition to oral antimicrobials has been adopted in some countries, effectiveness and safety remain uncertain. The optimal timing for the transition to oral antibiotic therapy is not well established, but an early switch to oral treatment has been suggested to be equally effective and safe.

Keywords: Intracranial infections. Oral therapy. Levofloxacin. Chloramphenicol. Linezolid.

Sucesso na transição de terapêutica endovenosa para terapêutica oral em infeções intracranianas em idade pediátrica: relato de três casos

Resumo

Introdução: A sinusite aguda bacteriana é uma infeção frequente em idade pediátrica. As complicações intracranianas, como o empiema subdural ou o abscesso cerebral, são raras, mas apresentam significativa morbilidade com sequelas neurológicas graves. **Relato do caso:** Apresentamos três casos clínicos de complicações supurativas intracranianas secundárias a sinusite aguda bacteriana nos quais a transição para a antibioticoterapia oral foi realizada entre o 14° e o 21° dia de antibioticoterapia endovenosa. Em todos os casos, foi realizada drenagem dos seios perinasais e do empiema, o agente etiológico foi identificado e a resolução clínica foi alcançada sem recidivas. **Discussão:** Embora a transição precoce para antibioticoterapia oral tenha sido adotada em alguns países, a sua eficácia e segurança permanecem incertas. O momento ideal para esta transição não se encontra bem estabelecido, todavia tem sido sugerido que a transição precoce para a terapêutica oral seja igualmente eficaz e segura.

Palavras-chave: Infeções intracranianas. Terapêutica oral. Levofloxacina. Cloranfenicol. Linezolide.

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Keypoints

What is known
- Subdural empyema and brain abscess are rare complications of acute bacterial rhinosinusitis.
- The effectiveness and timing of the switch to oral antibiotics has been extensively debated, but no recommendations are offered.

What is added
- We present three clinical cases of intracranial suppurative infections in which early transition to oral antibiotic therapy was made.
- In all three cases described, the outcome was favorable with no recurrence of the infectious process.

Introduction

Acute bacterial rhinosinusitis (ABRS) is a common infection in children[1]. It is estimated that eight percent of viral upper respiratory infections may be complicated with secondary ABRS[2]. In children, sinusitis usually has a benign evolution with orbital complications being the most common, while intracranial complications, like subdural empyema, brain abscess, meningitis and cerebritis, occur less frequently, with an estimated incidence of 4–5.3/1,000,000[3,4].

Suppurative intracranial complications are often caused by *streptococci* but may also stem from *staphylococci* or be polymicrobial[5]. Besides the advances in cranial imaging, antibiotic therapy selection and surgery, they remain a significant source of neurological morbidity[3] and the mortality rate is still as high as 3.7–24%[4].

The total length of antibiotic treatment for intracranial suppurative infections ranges from four to eight weeks[4]. No recommendation is offered for early transition to oral antimicrobials because of a lack of data. The effectiveness and timing of the switch to oral antibiotics has been extensively debated[6]. This case series studies show successfully-treated patients who transitioned to oral treatment as early as one to two weeks after starting intravenous therapy[7,8].

Case description

We present three clinical cases of empyema and brain abscess secondary to sinus infection in which the switch to oral antibiotic therapy was performed successfully (Table 1).

Case 1

A 13-year-old female patient, with a history of asthma, was admitted to the pediatric emergency department with a one-week history of fever, rhinorrhea and headache. Brain Magnetic Resonance Imaging (MRI) showed pansinusopathy complicated by a right paramedian frontopolar empyema. The patient was subjected to a bilateral antrostomy and full frontoetmoidectomy with frontal sinus drainage followed by a right frontal craniotomy with subdural convexity, parafalcial empyema drainage and cranialization of the frontal sinus. She was started on empiric antibiotic therapy with ceftriaxone, vancomycin (two days) and metronidazole (nine days) initially, then moved to a single regimen with intravenous flucloxacillin (12 days) after identifying methicillin-sensitive *Staphylococcus aureus* from the pus culture. A switch to oral antibiotic linezolid took place on day 14 and a total of four weeks of antibiotic therapy was completed. The patient fully recovered and the control CT scan (Fig. 1) did not show any recurrence of the infection at the 12 week follow-up visit.

Case 2

An 11-year-old female patient, with a history of allergic rhinitis and a recent hospital admission from pansinusitis complicated with postseptal cellulitis. She was readmitted one month later, with a nine-day clinical history of fever, headache and vomiting. The examination showed a decrease in left-sided muscle strength of 4/5 and marked left-sided facial palsy. The initial CT scan revealed pansinusopathy with right-sided extra-axial frontopolar collections. The patient underwent a bilateral antrostomy and frontal sinusotomy followed by a right frontal craniotomy and drainage of the empyema. Empirical antibiotic treatment with ceftriaxone, vancomycin and metronidazole was started. The latter two were discontinued after identifying *Streptococcus intermedius* from the pus culture. On day 10 after surgery, she presented with a progressively worsening headache. A brain MRI was performed, which showed recurrence of the empyema and a worsening mass effect. She was then taken back to the operative room to enlarge the craniotomy and re-drain the empyema; the antibiotic therapy was upscaled to meropenem and vancomycin. Due to the resurgence of fever, eighteen days later, another brain MRI (Fig. 2) was performed, revealing a left frontobasal intraparenchymal abscess. Intravenous chloramphenicol was added. Three weeks after initial treatment, she was transitioned to oral chloramphenicol. Due to slight pancytopenia and increased lactates,

Table 1. Summary of the three clinical cases

	Case 1	Case 2	Case 3
Age	13	11	14
Duration symptoms (days)	7	9	14
Symptoms	Fever; Headache; Rhinorrhea	Fever; Headache Vomiting; Slight left-sided hemiparesis	Fever; Headache; Vomiting
Imaging	MRI: pansinusopathy; right paramedian frontopolar epidural empyema	CT-scan: pansinusopathy; right frontopolar empyema. MRI day 10 and day 18: Subdural empyema and left frontobasal abscess	MRI: pansinusopathy; left frontal epidural empyema
Microbiology (pus)	*S. aureus*	*S. intermedius*	*S. constellatus*
ENT surgery	Antrostomy; full frontoethmoidectomy; frontal sinus drainage	Antrostomy; frontal sinusotomy; frontal sinus drainage	Antrostomy; bilateral anteroposterior ethmoidectomy
Neurosurgery	Empyema drainage and cranialization of the frontal sinus	Empyema drainage (two step surgery)	Empyema drainage
Empiric antibiotics	Ceftriaxone, vancomycin and metronidazole		
Oral antibiotics	Linezolid	Chloramphenicol/Levofloxacin	Levofloxacin
Transition to oral	Day 14	Day 21	Day 21
Total treatment	Four weeks	Nine weeks	Four weeks
Follow-up	Full recovery; no evidence of active infection on control CT scan at 12 weeks	At eight weeks: full recovery; control MRI with no evidence of active infection	Full recovery; no evidence of active infection on control CT scan at four weeks

chloramphenicol was discontinued and oral levofloxacin was initiated until she had completed nine weeks post-operative antibiotic therapy. There was a rapid recovery of pancytopenia and neurological deficits. Two months after being discharged from the hospital, the patient was asymptomatic and the MRI did not show any recurrence of the infectious process.

Case 3

A 14-year-old female patient, with no relevant medical history, was admitted to the pediatric emergency department with a 14 day history of fever, headache and vomiting. The MRI showed pansinusopathy complicated by left frontal intracranial empyema. Empirical antibiotic therapy was initiated with ceftriaxone, vancomycin and metronidazole. Upon admission, the patient was submitted to antrostomy and bilateral anteroposterior ethmoidectomy. Due to a worsening headache, a CT scan was performed on the fifth day of hospitalization, which showed bilateral anterior frontal subdural empyema. The patient underwent a frontal craniotomy and empyema drainage. *Streptococcus constellatus* was identified from the pus culture and antibiotic therapy was changed to cefotaxime and clindamycin. In the third week of treatment, she was transitioned to oral antibiotics with chloramphenicol. The patient developed an erythematous maculopapular rash which could not be definitively attributed to any of the antibiotics. The antibiotic therapy was switched to levofloxacin. She completed a total of four weeks of antibiotic therapy. Three months later, she remained asymptomatic, with no evidence of recurrence of the infectious process in the brain CT scan.

Discussion

In our short series, we used three different oral antibiotics in the transition strategy, as early as two weeks after surgery, with clinical cure and no relapses.

Chloramphenicol is a broad-spectrum antibiotic effective against gram-positive, gram-negative and anaerobic

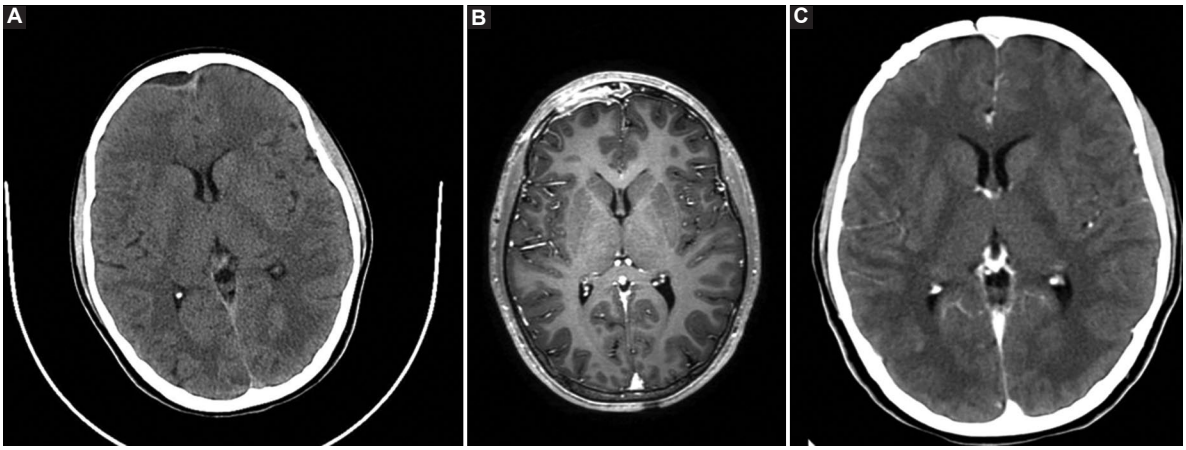

Figure 1. Epidural empyema in a 13-year-old girl (case 1). **(A)** axial CT scan showing a right-sided extra-axial frontal infectious collection; **(B)** axial T1 MRI with gadolinium on day 24 of antibiotic therapy (day 10 of linezolid) and **(C)** axial CT scan with contrast, eight weeks after completing the antibiotic therapy regimen with prior empyema surgical drainage.

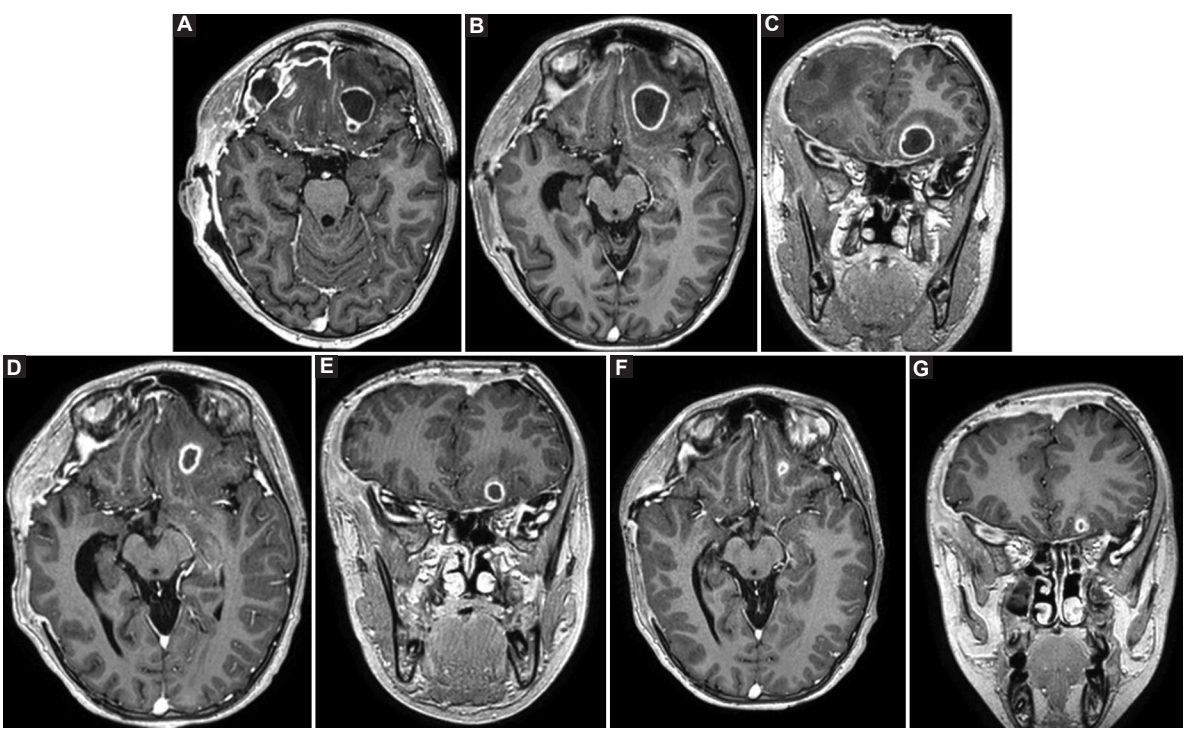

Figure 2. Subdural empyema complicated by intraparenchymal abscess in an 11-year-old girl (case 2). **(A)** axial T1 MRI with gadolinium; **(B, C)** axial and coronal T1 MRI on the ninth day of chloramphenicol (total of two days of oral therapy); **(D, E)** axial and coronal T1 MRI on day 12 of levofloxacin (total of 14 days of oral therapy); **(F, G)** axial and coronal T1 MRI, two weeks after completing the antibiotic regimen, showing regression of the intraparenchymal abscess.

bacteria with a good diffusion capacity in the central nervous system (CNS)[7]. Higher doses and longer treatments (over 14 days) are risk factors for hematological toxicity that is usually reversible, as observed in case 2[9].

Levofloxacin has proved to be effective and well tolerated as an oral regimen[7]. Its high oral absorption and lipophilic characteristics promote CNS penetration, bolstering efficacy in treating CNS infections,

Table 2. Summary of literature review for switching from intravenous to oral antibiotics for pediatric intracranial infections

Review	Summary
Bodilsen et al. / Clinical Microbiology and Infection 30 (2024) 66e89	No recommendation. For early transition to oral antimicrobials in patients with a brain abscess, there is insufficient evidence at the time of writing to provide a recommendation.
Dodson D et al. / Oral Antibiotics for Intracranial Infections, OFID (2022)	Levofloxacin-based oral regimens were effective. Criteria for transitioning patients to oral antibiotics for intracranial infections should be established.
Lauda-Maillen et al. / Eur J Clin Microbiol Infect Dis (2020)	Switch to oral antibiotic therapy during the first 14 days of brain abscess treatment for patients with a favorable clinical evolution may reduce the hospital stay and the risk of parenteral catheter-related adverse events.

including those that are deep-seated or intraparenchymal[10,11].

Systemic absorption of linezolid approaches 100% following oral administration. Linezolid binds poorly to serum proteins, penetrating well into most body compartments, and is used in treating gram-positive bacterial CNS infections[12]. Oral therapy allows for a quicker hospital discharge and eliminates the risks of a central venous catheter.

Extended intravenous treatment has been considered essential for managing patients with a brain abscess and intracranial infections. However, in recent years, some experts recommended early transition to an appropriate oral regimen after one or two weeks of intravenous treatment in patients with a good clinical response[6,7]. Gilchrist et al. conducted a retrospective, observational study of 42 children with intracranial empyema admitted to a pediatric neurosurgical center. The median total antibiotic duration was 47 days and in 16 cases, after a course of intravenous therapy, antibiotics were switched to an oral agent. They selected children for the switch to oral agents where there was adequate source control, down-trending or normalized inflammatory markers and no clinical features suggestive of disease recurrence. The oral agent was most commonly amoxicillin/clavulanic acid with a transition at a median of 33 days[13]. As in the cases we described above, the outcome was favorable with no recurrence of the infectious process. Bodilsen et al. summarized the current evidence for early transition to oral antimicrobials in children and adults with a brain abscess. Although there is insufficient evidence to provide a recommendation, in a 2023 narrative review, the authors concluded that early transition to oral antimicrobials in patients with an uncomplicated brain abscess may be beneficial due to the convenience of the treatment and potential decreased risks associated with prolonged hospitalization and intravenous lines[6].

Although the early transition to oral antimicrobials has been adopted in some countries, effectiveness and safety remain uncertain[6,7,14]. The optimal timing for a transition to oral antibiotic therapy is not well established (Table 2), but an early switch to oral treatment has been suggested to be equally effective and safe and should be considered in patients with controlled infection, after effective surgical drainage and with confirmed tolerability to suitable oral antibiotics.

Author contributions

R. Sousa: Conceptualization, literature search, draft writing and preparation, approval of the final version. M. Andrade, J. Jonet: Conceptualization, literature search, approval of the final version. S. Lemos, F. Prata, V. Oliveira, M.M. Santos, J.G. Marques: Review and editing, approval of the final version.

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Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The 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.

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CASE REPORT

Central hyperthermia control after propranolol therapy in an infant with septo-optic dysplasia

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Abstract

Introduction: Septo-optic dysplasia (SOD) is a congenital midline brain malformation syndrome involving the hypothalamus-pituitary axis with hypopituitarism and thermal instability. The treatment of central hyperthermia in children with propranolol has already been described. **Case report:** We report the case of a nine-month-old boy with SOD with prolonged fever and increased urinary output. The physical examination was unremarkable, and a thorough etiological investigation was inconclusive. After adjusting the desmopressin dosage to control the central diabetes insipidus and ruling out infectious, inflammatory, and neoplastic etiologies, the diagnosis of central hyperthermia was established and therapy with propranolol was initiated, with sustained normothermia. **Discussion:** Although a definite causal relationship could not be proven, this paper is the first to report the successful management of central hyperthermia in an infant with SOD using propranolol. Further trials are needed to evaluate its efficacy and safety in the management of central hyperthermia in children with SOD.

Keywords: Central hyperthermia. Propranolol. Septo-optic dysplasia plus.

Utilização de propranolol num caso de hipertermia de causa central num lactante com displasia septo-óptica

Resumo

Introdução: A displasia septo-óptica (DSO) corresponde a uma malformação congénita do eixo hipotálamo-hipofisário, conduzindo a hipopituitarismo e instabilidade térmica. Já foi descrito o tratamento da hipertermia central em crianças com propranolol. **Relato do caso:** Lactente do sexo masculino, 9 meses, seguido por DSO. Recorre ao hospital por febre prolongada e aumento da diurese. Exame objetivo não apresentava alterações. Após ajuste da dose de desmopressina para melhorar o controlo da diabetes insipidus e exclusão de causas infeciosas, inflamatórias e neoplásicas, foi assumido o diagnóstico de hipertermia central e iniciada terapêutica com propranolol, verificando-se normotermia nos meses subsequentes. **Discussão:** Ainda que uma relação causal definitiva não possa ser comprovada, este é o primeiro caso reportado de controlo com sucesso de hipertermia utilizando propranolol em lactente com malformações da linha média. São necessários mais estudos para avaliar a sua eficácia e segurança na hipertermia central em crianças com DSO.

Palavras-chave: Hipertermia de causa central. Propranolol. Displasia septo-óptica plus.

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Keypoints

What is known

- Septo-optic dysplasia is a congenital midline brain malformation syndrome associated with hypopituitarism and thermal instability.
- Central hyperthermia should not be overlooked in the pediatric population, especially after ruling out more common causes.
- There are no evidence-based guidelines on the management of central hyperthermia in patients with midline brain malformations.

What is added

- This is the first report of the successful management of central hyperthermia in a SOD infant patient using propranolol.
- In this case, the administration of propranolol was associated with thermic regulation.
- Close monitoring is required during propranolol therapy due to its potential side effects, namely hypothermia, hypoglycemia, and bradycardia.

Introduction

Septo-optic dysplasia (SOD) is a rare congenital midline brain malformation syndrome, originally described by Georges de Morsier in 1956[1]. A diagnosis of SOD requires the presence of at least two features from the triad: optic nerve hypoplasia, agenesis of midline structures, and hypoplasia of hypothalamus-pituitary axis with hypopituitarism[2,3]. SOD "plus" also encompasses associated malformations of cortical development[2,4]. The spectrum of clinical manifestations is broad and only 30-47% of patients display all the elements of the triad[5]. The etiology of SOD is diverse and its estimated prevalence among European countries is 1.9-2.5/100,000 births[6].

Central hyperthermia is characterized by an elevation in body temperature secondary to a thermoregulation defect, devoid of any infectious or inflammatory cause. It is often linked with intracranial injury such as traumatic brain injury (TBI), subarachnoid hemorrhage, and hypothalamic damage as the hypothalamus plays a pivotal role in body temperature regulation[7,8]. Central hyperthermia is frequently resistant to typical antipyretic drugs such as paracetamol, requiring non-pharmacological interventions or drugs with notable side effects, such as bromocriptine[9]. Propranolol has also been utilized in treating central hyperthermia in adults due to its comparatively milder side-effect profile, although its precise mechanism of action is not fully understood[10].

Midline brain malformations are most commonly associated with hypothermia[11]. SOD induces dysfunction in the hypothalamus-pituitary axis with hypopituitarism and thermal instability. The cause of thermal instability in SOD is still not fully understood but is presumed manifold.

We report a case of persistent central hyperthermia in a nine-month-old male patient with SOD plus and its management using propranolol. This case report describes a potential new indication for an extensively-studied drug and, to our knowledge, is the first paper describing the use of propranolol and the successful management of central hyperthermia possibly caused by hypothalamic dysfunction in a pediatric patient with SOD.

Case report

Following the onset of hypoglycemia, bilateral nystagmus, and axial hypotonia during the first days of life, along with laboratory findings consistent with panhypopituitarism encompassing central hypothyroidism, adrenal insufficiency, and diabetes insipidus, a diagnosis of SOD was suggested. The brain MRI confirmed the diagnosis of SOD "plus" as a broad spectrum of abnormalities of the midline structures and associated malformations of cortical development were present. The brain MRI abnormalities included complete agenesis of the pituitary stalk, involving both the anterior and posterior pituitary and olfactory bulbs, optic nerve hypoplasia, bilateral subependymal heterotopia, and perisylvian polymicrogyria. Genetic testing yielded negative results for pathogenic mutations. After the neonatal diagnosis of SOD, a multidisciplinary follow-up was established. He was prescribed levothyroxine, hydrocortisone, and desmopressin. The patient was admitted to the pediatric emergency department (PED) with fever and increased urinary output, with no other symptoms.

The fever had started 19 days before admission to the PED. Before being admitted to our hospital, he was observed twice at a regional hospital and discharged home with conservative measures. The temperature rise, measured by a digital thermometer, occurred two to three times a day, reaching 39.7°C in the evening and was associated with polyuria (daily urine output estimated at 7-8 mL/Kg/h), with no other associated symptoms. No recent respiratory or gastrointestinal disorders were reported, nor had the patient travelled to any rural or exotic areas, been in contact with sick people or animals, or had any other notable exposures.

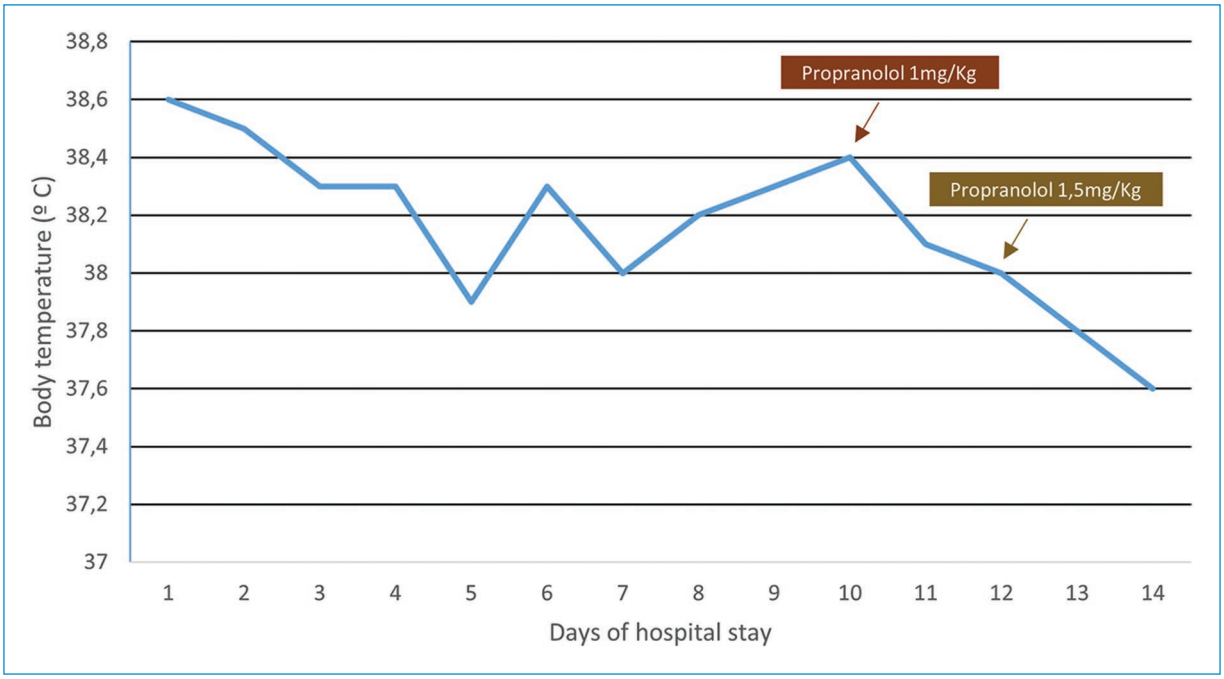

Figure 1. Evolution of the highest daily body temperature during the hospital stay. Propranolol therapy was initiated on day 10 (red) at 1 mg/Kg/day and adjusted to 1.5 mg/kg/day 48 hours later (yellow) as hyperthermia persisted.

Involuntary weight loss, night sweats, or other constitutional symptoms were also not present. The patient had had no prior episodes of fever of unknown origin. Air temperature during this period peaked at 24°C, with average daily values of 14°C, and there was no family history of autoimmune disorders.

The physical examination was unremarkable except for the high body temperature measured in the tympanic membrane. The patient was admitted. Initial laboratory results revealed the presence of hypernatremia (Na^+ 158 mEq/L), with no other electrolyte disturbances. Both C-reactive protein and procalcitonin were negative, and all other laboratory results were unremarkable. Blood and urine cultures showed no pathogen growth. The desmopressin dosage was increased to correct the high urinary output and hypernatremia, and the hydrocortisone dosage was adjusted to the stress dose (40 mg/m2). A watchful waiting approach was adopted, and no broad-spectrum empiric antibiotic therapy was initiated as all the inflammatory markers were within the normal range and the patient did not appear septic.

During the hospital stay, a thorough etiological investigation was performed, including blood, urine, and stool cultures, IGRA and SARS-CoV-2 RT-PCR tests, all of which were consistently negative. Other serological tests for infectious agents, including the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) were also negative. Inflammatory markers were repeated and remained within the normal range throughout. Imaging tests were also performed: the chest radiograph was normal, as was the abdominal, renal, and bladder ultrasound. A record of the infant's daily body temperature during his hospital stay is shown in figure 1.

A neoplastic etiology was also considered but deemed unlikely, as the patient showed no cytopenia and had normal blood levels of uric acid and lactate dehydrogenase and a normal erythrocyte sedimentation rate. Moreover, imaging studies did not support this diagnosis.

As an infectious cause was excluded and recurrent hyperthermia (on average, two to three times a day, in a predominant evening pattern) persisted despite the normalization of serum sodium levels and urinary output achieved after increasing the daily doses of desmopressin and the use of paracetamol, the hypothesis of central hyperthermia was considered.

In view of this hypothesis, an electrocardiogram was performed and, as no cardiac contraindications were present, a trial therapy with propranolol was initiated on day 10, followed by an improvement in body temperature regulation. The initial propranolol dose of 1 mg/Kg/day was adjusted to 1.5 mg/Kg/day after 48 hours of therapy as hyperthermia persisted, albeit at

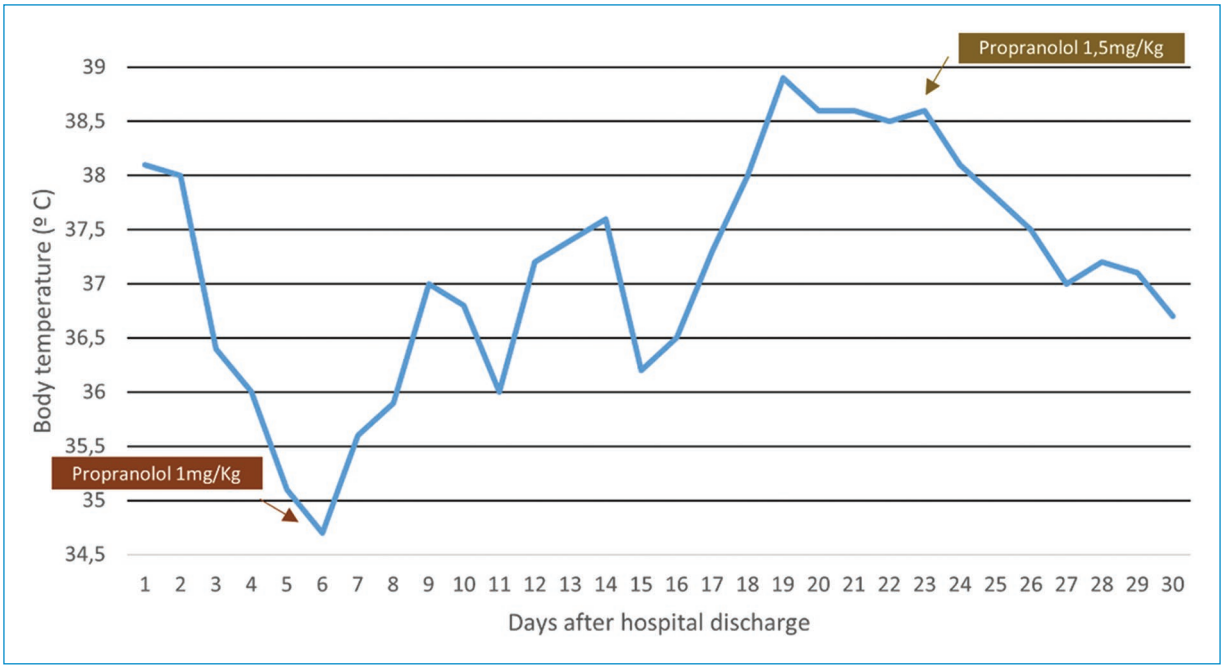

Figure 2. Evolution of body temperature in the first 30 days after hospital discharge. The propranolol dose was reduced to 1 mg/Kg/day on day 5 (red) as the patient presented with hypothermia. A second dose increase was performed on day 23 after hospital discharge hyperthermia reappeared (yellow).

lower levels (Fig. 1). Verbal informed consent was given by the mother for the off-label use of propranolol.

During the infant's hospital stay, no side effects of the propranolol therapy were observed, namely hypothermia, hypoglycemia, hypotension, or bradycardia, and no other electrolyte disturbances were observed. The patient became afebrile on day 12 and was discharged on day 14.

After discharge, the mother continued to monitor body temperature daily with a tympanic membrane device. In the days following discharge, a descending pattern in the body temperature curve was noted with hypothermia, as body temperature reached its nadir at 34.7°C. As a result, the daily doses of propranolol were reduced to 1 mg/Kg/day five days after discharge and there were no further instances of hypothermia during follow-up.

Hyperthermia recurred on day 18 post discharge and a new adjustment of the propranolol dose was needed on day 23. Following this adjustment, a stable temperature within the normal range was maintained, even in the warmer months of summer.

The variation in daily body temperature and propranolol daily doses during the first month is represented in figure 2.

Over the remaining follow-up period of 10 months, no other periods of persistent fever were present, with normothermia, except for short self-limited episodes of acute infection. Since no other periods of hyperthermia were present, therapy was gradually reduced and stopped after 22 months. No further episodes of hyperthermia have occurred since then.

Discussion

Fever is one of the leading reasons for emergency department admissions among the pediatric population, particularly in infants. In most instances, the etiology is an infectious disease, often from the gastrointestinal or upper respiratory tract presenting as a self-limited benign condition[12]. Diagnosis can often be established through a meticulous clinical examination and no further etiological investigation is usually required[12]. Nevertheless, in a minority of cases, the cause of the fever remains uncertain, even after performing a comprehensive medical history, a thorough physical examination, and an initial laboratory assessment. In this case, after ruling out other infections by atypical agents, less prevalent causes such as inflammatory or neoplastic etiologies were considered[13].

Central hyperthermia is rare among the pediatric population and is usually considered a diagnosis of exclusion after ruling out more common infectious or neoplastic causes[14]. This diagnosis should not be overlooked, especially in a patient with midline brain malformations involving the hypothalamus and its temperature-regulating nuclei[14]. Central hyperthermia is primarily associated with TBI, brain neoplasms, and disturbances of the hypothalamic-pituitary axis with thermal instability[15]. Rarely, the use of certain medications, such as halogenated volatile anesthetics and succinylcholine, may trigger a life-threatening temperature rise secondary to a hypermetabolic state known as malignant hyperthermia[15,16].

The use of propranolol is widespread in children, namely in migraine prophylaxis, congenital heart disorders, and infantile hemangiomas, where it is regarded as first-line therapy due to its vasoconstriction, inhibition of angiogenesis, and stimulation of apoptosis effects[17]. Notwithstanding the use of propranolol being considered generally safe, hypothermia is one of its side effects. The explanation behind the thermal instability secondary to its use is thought to be twofold: the nonspecific blockage of β2 and β3 receptors in the central nervous system given its high lipophilicity and capacity to cross the brain-blood barrier and the lowering of the thermogenic effect of brown adipose tissue by inhibiting its β2 adrenergic receptors[18].

There are no evidence-based guidelines on the management of central hyperthermia in infants since there is insufficient data to provide solid recommendations and the use of available therapeutic drugs in the pediatric population is generally an extrapolation from adult trials, with little to no expertise among pediatric teams[9,19].

The use of propranolol for the treatment of central hyperthermia has already been documented in pediatric patients and, on a larger scale, in adults, namely in intracranial hemorrhage secondary to TBI[20-21]. The proposed hypothesis is that the non-specific beta-adrenergic blockage of propranolol within the CNS leads to a reduction of the hyperadrenergic tone, thereby lowering body temperature in cases of a hyperadrenergic state following acute brain injury[22].

In this particular case, the exact pathophysiological mechanism for the persistent fever remains unknown, although dysfunction of the hypothalamus-pituitary axis is presumed to play a leading role. The use of propranolol to treat central hyperthermia in SOD in pediatric patients is considered "off-label" since there is currently insufficient evidence to support its use. Even though a definite causal relationship cannot be proven, this is the first report of the successful management of central hyperthermia in a SOD infant patient using propranolol. Further trials are warranted to assess the efficacy and safety of this therapy, thus providing high-quality evidence that will allow for the successful management of central hyperthermia in pediatric patients.

Previous presentations

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Author contributions

A. Sousa: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analyisis or interpretation of data either from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. M. João Lage: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analyisis or interpretation 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. L. Lopes: Acquisition of data either from patients, research studies, or literature; Analyisis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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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.

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Brain manganese deposition: potential effects of long-term parenteral nutrition

Deposição cerebral de manganésio: efeitos da nutrição parentérica a longo prazo

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Keypoints

What is known

– Manganese serves as a cofactor for numerous enzymes, and its inclusion in parenteral nutrition (PN) admixtures is recommended across various clinical scenarios.

What is added

– Brain manganese deposition represents a rare consequence of long-term PN and may manifest in patients with pauci-symptomatic neurological conditions.

Manganese is a cofactor for several enzymes and its administration in parenteral nutrition (PN) admixtures is recommended[1,2]. Nevertheless, exposure to manganese through PN has been associated with acute and long-term toxicity manifestations[3,4].

We report a 15 year-old boy with a previous medical history of short bowel syndrome due to complicated gastroschisis. He underwent two transverse enteroplasty procedures and was submitted to intestinal transplant at five years old. He was on continuous PN until the transplant and intermittent supplementation afterwards, for a total period of eight years. He was referred to neurological consultation due to mild and intermittent episodes of headache and a gait imbalance. Symptoms began during the period he was on PN supplementation and persisted for several months, with progressive improvement over time. Neurological examination revealed preserved cranial nerve function, motor strength, sensation, and coordination. He presented no movement abnormalities, dystonia, or parkinsonism. A brain magnetic resonance angiography revealed a symmetrical hyperintensity signal of basal ganglia in T1-weighted images, normal signal in T2-weighted images and no vascular abnormalities (Fig. 1). The features of this imaging are characteristic of paramagnetic properties, which are observed in manganism, due to manganese overexposure. During the following two years, he did not show additional neurological complaints or deficits. Given that the patient had discontinued PN by the time of the initial neurological evaluation, no follow-up MRI was conducted. Nevertheless, prior studies have reported an improvement of T1 hyperintensities in the basal ganglia following the discontinuation of PN[5].

This case reports a child who underwent long-term PN and presents pauci-symptomatic neurological manifestations which seem unrelated to brain manganese deposition. The authors would like to highlight the clinical and neuroimaging features of this uncommon entity.

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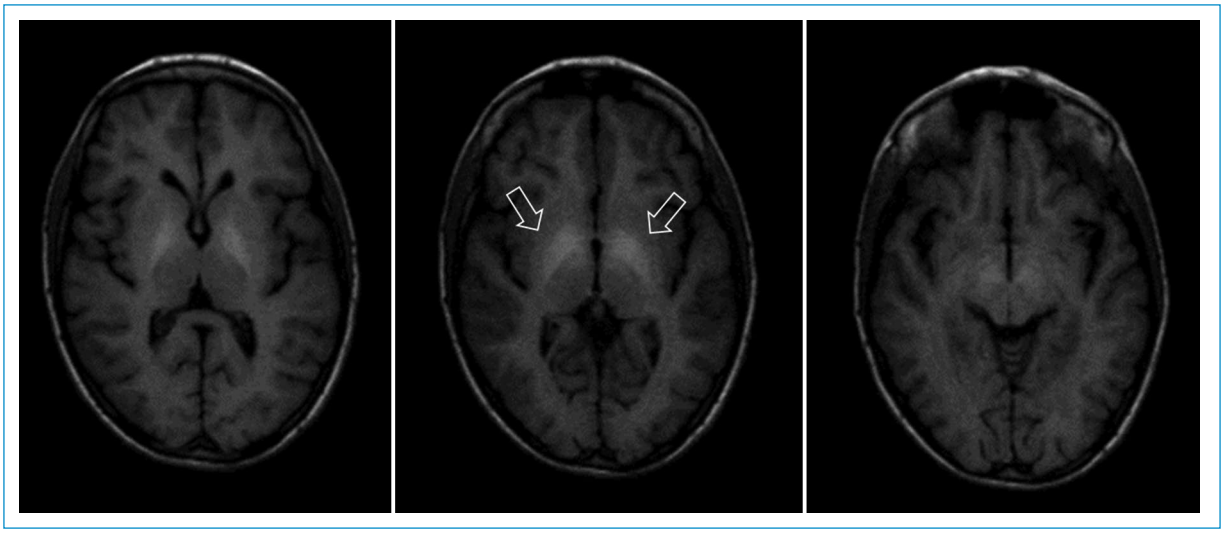

Figure 1. Cerebral MRI depicting bilateral basal ganglia hyperintensity (white arrows) in T1-weighted image as a result of manganese deposition in a child with long term parenteral nutrition.

Author contributions

J. Fonseca: Conception and design of the study, report, review or other type of work or paper. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. R. Sousa: Conception and design of the study, report, review or other type of work or paper. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. C. Melo: Conception and design of the study, report, review or other type of work or paper. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work.

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Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

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.

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LETTER TO THE EDITOR

Neonates in intensive care units: the healing harmony of pediatric recovery

Recém-nascidos em unidades de cuidados intensivos: a harmonia curativa da recuperação pediátrica

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Dear Editor,

After carefully reading Dr. Areiras' article[1], it has come to our attention that the pleasant, gentle background music in neonatal Intensive Care Units (ICU) plays a far more significant role than mere relaxation in aiding babies to fall asleep. As outlined in Dr. Areiras' inspiring article, there is scientific evidence that supports a robust correlation between music and the neurophysiological behavior and development of neonates and children, as well as a measurable enhancement in their recovery. Incorporating music therapy in the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) and neurodevelopment-centered care programs usually provides both the benefits of music therapy and it facilitates vocal parental interaction with their preterm babies, which nurtures parent-baby bonding, especially amidst the challenging circumstances surrounding preterm births.

Due to the sterile and technology-dependent nature of intensive care units, they may lack elements that support the emotional and physiological well-being of their young patients. Music has the potential to fill this gap with its capacity to influence emotions and physiology. It is worth reflecting on the fact that from as early as 20-25 weeks of gestation, a fetus begins to respond to a mother's voice, heartbeat, and movements. Preterm infants are deprived of these enriching intrauterine experiences, revealing a gap that music therapy could help bridge. The influence of early auditory experiences on brain development cannot be overstated, presenting a compelling case for the inclusion of music therapy in neonatal care.

Several studies have shown that exposure to music can trigger physiological responses in the body. For instance, Thoma et al.[2] discovered that listening to music can reduce the cortisol response, the primary stress hormone in the body. These observations have been affirmed by further research conducted in neonatal ICUs[3,4]. This reduction in stress can be particularly beneficial in a hospital setting, where stress and anxiety are common for both patients and their families.

Most studies find positive outcomes when employing music, promoting more stable sleep patterns[5] while diminishing agitation, crying, stress, and pain-related behavior. Similarly, research concurs on the fact that music encourages feeding[6], thereby impacting weight gain and reducing hospital stay duration. This is particularly significant for premature infants, who cannot be discharged until they reach a minimum weight and are able to self-feed.

Music also has the potential to influence patient homeostasis. In neonatal intensive care units, music

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has been beneficial in stabilizing neonates' vital signs[7]. The choice of calming music, especially lullabies, can contribute towards regulating heart rates and breathing[8] in neonates. The timing of music therapy, especially in relation to the newborn's sleep stages, should be taken into account so as to maximize its benefits. Music therapy can be effectively combined with other methods, such as kangaroo mother care, non-nutritive sucking, or exposure to the smell of breast milk, thereby involving the family in the care process and enhancing the therapeutic outcomes.

However, while lullabies are a popular choice, we should also consider cultural diversity and individual preferences when selecting music. Different cultures have their own soothing songs that can be equally effective. Integrating music choice with the patient's cultural environment can enhance the effectiveness of musical intervention.

Beyond the physiological effects, music can also play a role in patients' emotional recovery. In pediatrics, where children may face traumatic situations, music can offer a means to express and process emotions. Thus, while soft music may be suitable for neonates, older children can benefit from a wider range of musical stimuli, including songs with lyrics they can identify with and relate to[9]. Music therapy serves as a tool for both relaxation and physiological regulation, and a medium for emotional expression and recovery. The multiple benefits of its usage underscore its value as an integral component of comprehensive pediatric care.

Moreover, the family, who are often the primary support system for pediatric patients, can also benefit from musical interventions, far beyond mere entertainment. Shared musical sessions can facilitate bonding, offer a reprieve from the stress of hospitalization, and promote a positive environment conducive to healing[10].

Unfortunately, most of the published studies cover very small sample groups, leading to substantial statistical variability between them (potentially exacerbated by different intervention and data collection methods); so, caution must be exercised when extrapolating their promising results.

Incorporating music in the ICU offers a non-invasive and therapeutic means to support both physiological and emotional patient recovery. In view of the fact that music therapy is a cost-effective, low-risk intervention, we can expect that comprehensive, well-designed, larger-scale studies will be undertaken to evaluate these parameters in a precise and evidence-based way, offering clinicians insights into the application of music therapy in neonatal and pediatric intensive care units.

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Author contributions

R. Tenajas: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. D. Miraut: Conception and design of the study, report, review or other type of work or paper; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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