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

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EDITORIAL

# Training in adolescent medicine in the pediatric residency program: are we on the right path?

*Helena Fonseca*[1]*, *Maria Ravara*[2], *and Katia Mauricio*[3]

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The Convention on the Rights of the Child was adopted by the United Nations General Assembly on November 20, 1989 and ratified by Portugal on September 21, 1990. Article 1 defines a child as "every human being under the age of eighteen years". The age range for pediatric care in Portugal was initially established as up to 14 years and 364 days for consultations, and emergency and inpatient care by order of the Directorate-General for Hospitals on February 24, 1987. However, in 2010 the age range for pediatric care was officially extended to 17 years and 364 days, nationally[1]. Pediatric departments had to gradually adapt to this new reality.

Current evidence shows the importance of investing in adolescent health and well-being[2,3]. Disease prevention and health promotion have gained increasing importance over disease management, even though human and financial resources are still very much focused on hospital care and emergency services. Adolescents have specific health needs inherent to their stage of development. There is evidence of the health gains that come from a bio-psycho-social approach to adolescents, carried out by trained professionals and in conditions of privacy. Training in the field of adolescent medicine includes acquiring specific practical skills. For instance, assessing patients' autonomous decision-making capacity, adopting effective communication skills and tackling sensitive issues such as sexual behavior or substance use[4]. In the past decade, there has been a growing international endeavor to find appropriate responses when it comes to providing health care for adolescents, as well as training competent professionals in this area[5-7].

Adolescent medicine should have been given a prominent place in pediatric residents' training from the moment pediatric care was extended to 18 years of age in Portugal. However, this has not happened[8]. The skills and knowledge that a pediatric resident must acquire in adolescent medicine are supposedly obtained during the first three years of training, which comprise the basic pediatric training. In other words, a newly-trained pediatrician should be competent in approaching adolescents in the various contexts of medical practice: outpatient, emergency and inpatient care. This is especially true when young pediatric specialists are part of teams together with older pediatricians who have not had any specific training in adolescent medicine during their residency experience.

The emergency department is often the "gateway" for adolescent medicine consultation referrals (70% of referrals to the adolescent medicine division at ULSSM's pediatrics department come from the pediatric emergency department). A pediatric resident must be able to systematically conduct the clinical history and physical examination of an adolescent, be trained in the challenges of crisis care and be aware of the criteria for referral. Hospitalization is a time of increased vulnerability for adolescents who are admitted due to an acute illness or as a result of chronic conditions. This period should also be seen and used as an opportunity

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for prevention and health promotion. In an outpatient setting, pediatric residents are initially exposed to adolescent medicine consultations and the specific factors involved in these through observation, then with increasing autonomy. This occurs both in the hospital context and during the primary health care internship.

According to the 2013 National Child and Adolescent Health Program, pediatric monitoring is recommended at key ages. In Portugal, adolescents are expected to have three consultations in a primary care center, at 10, 12-13 and 15-18 years of age. It is therefore essential that pediatric residents undertake their primary health care internship after completing their training in adolescent medicine. This training could (and, in our opinion, should) be done beforehand in an adolescent medicine internship, included in the period of basic pediatric training, to optimize the provision of care to adolescents during the primary health care internship.

The Specialized Training Program in Pediatrics was initially approved by *Ministerial Order No. Article 616/96 of October 30* and recently updated by *Ministerial Order No. 52/2023*, published in *Diário da República No. 38/2023*. All residents who start their residency in pediatrics after 2023 are covered by the new internship program, while those who started in 2022 may or may not have opted to join the new program[9].

With the new training program, residents in pediatrics may come into contact with adolescent medicine at specific points during their five-year internship: (i) in an optional internship during the 2nd or 3rd year of training, lasting one to two months; and/or (ii) in an optional internship during the 4th year, lasting three months; and/or (iii) in an optional internship in the 5th year of training, lasting one month if grouped with two other outpatient medicine internships or lasting three to 12 months, depending on the resident's personalized plan.

In other words, comparing the two extremes, by the end of their residency, a pediatric resident could have completed a total of 17 months of internship in adolescent medicine (2 + 3 + 12), or none. This flexibility gives residents the obvious advantage of being able to direct the years of training in specialized areas towards a subspecialty of their interest, without giving up the opportunity for more generalist training. But, given the risk of finishing five years of pediatric training without having had any specific contact with adolescent medicine, should not a one-month internship in the first three years of basic pediatric training be compulsory?

It would appear vital to ensure cross-sectional training in adolescent medicine for every pediatrician. If only a few residents choose adolescent medicine as an optional internship, it is essential to ensure a training period in adolescent medicine of at least one month, ideally two, for all the rest. One potential concern might be whether there are sufficient training centers available to provide this training. In our view, the current nine available pediatric departments in Portugal with a training capacity in adolescent medicine[10] should join efforts to ensure the necessary conditions to guarantee this training.

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ORIGINAL ARTICLE

# Congenital lobar emphysema: a 10-year case series review

*André Assunção[1,3]*, Pedro Miragaia[1,3], Filipa Flôr-de-Lima[2,3], Susana Guimarães[4,5,6], Gustavo Rocha[2], Catarina Ferraz[1,3], and Inês Azevedo[1,3,7]*

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## Abstract

**Introduction and Objectives:** Congenital lobar emphysema (CLE) is a rare congenital lung malformation that causes one or more pulmonary lobes to overinflate as a result of an air trapping-like mechanism and it may cause progressive respiratory distress. It is diagnosed in one in every 20,000 - 30,000 neonates. Diagnosis is usually made postnatally, with most cases identified in the first six months of life, but advances in ultrasound technology have allowed for some prenatal diagnosis. We report on the presentation, diagnostic methods, and management of a series of cases of CLE. **Methods:** Review of electronic files of patients diagnosed with CLE, over the past 10 years. **Results:** We identified four patients diagnosed with CLE: three female and one male. Two of these patients were diagnosed with CLE prenatally and remained asymptomatic for the entire recorded period, and the other two developed symptoms soon after birth. Chest radiographic imaging was performed in all four patients and a CT scan was carried out in three cases. The symptomatic cases required lobectomy and follow-up showed a slight decrease in residual volumes, total lung capacity, and forced expiratory volume, with no long-term pulmonary dysfunction. **Discussion:** Prenatal diagnosis of CLE is becoming more feasible with advances in imaging technology. In our population, we observed an inverted male-to-female ratio. Patients may remain asymptomatic and conservative management is advocated for such cases. When patients start to develop symptoms, there are progressive signs of increasing respiratory distress and, for these cases, surgery is recommended, with open thoracotomy being the preferred approach. Post-surgical complications are minimal and long-term pulmonary function remains stable.

***Keywords:*** Congenital lobar emphysema. Congenital lung disease. Lung overinflation. Pulmonary emphysema.

## *Enfisema pulmonar congénito: uma revisão de casos de 10 anos*

## Resumo

**Introduçã e Objetivos:** O Enfisema Lobular Congénito (CLE) é uma malformação pulmonar congénita rara com consequente hiperinsuflação de um ou mais lobos pulmonares, devido à retenção de ar no seu interior e que pode conduzir a progressiva dificuldade respiratória. Ocorre em 1 em cada 20.000-30.000 recém-nascidos. Frequentemente, diagnostica-se no pós-natal, em particular nos primeiros seis meses de vida, embora o desenvolvimento da ecografia tenha permitido diagnósticos pré-natais. Apresentamos a clínica, os métodos diagnósticos e a orientação numa série de casos de CLE. **Métodos:** Revisão de todos os processos de doentes com o diagnóstico de CLE no nosso centro, nos últimos 10 anos.

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**Resultados:** Identificamos 4 doentes diagnosticados com CLE: 3 do sexo feminino e 1 masculino. Dois tiveram diagnóstico pré-natal e mantiveram-se assintomáticos durante o seguimento, enquanto que os outros dois desenvolveram sintomas pouco após o nascimento. Todos realizaram radiografias de tórax e três realizaram tomografia computadorizada. Os casos sintomáticos necessitaram de lobectomia, tendo-se verificado, durante o seguimento, ligeira diminuição dos volumes residuais, capacidade pulmonar total e volume expiratório forçado, mas sem disfunção pulmonar a longo prazo. **Discussão:** O diagnóstico pré-natal de CLE tem sido mais frequente, particularmente com o desenvolvimento da ecografia. Constatámos uma inversão da relação entre sexos no nosso grupo de doentes. Para os doentes assintomáticos preconiza-se atitude expectante e vigilância. Para os doentes que desenvolvem sintomas, como aumento gradual de dificuldade respiratória, recomenda-se a abordagem cirúrgica por toracotomia aberta; as complicações pós-cirúrgicas são mínimas, e a função pulmonar permanece estável a longo prazo.

***Palavras-chave:*** Enfisema pulmonar congénito. Doença pulmonar congénita. Sobredistensão pulmonar. Enfisema pulmonar.

## Keypoints

**What is known**
- CLE is a congenital malformation with overinflation of pulmonary lobes and progressive respiratory distress.
- Symptoms usually develop in the first six months of life.

**What is added**
- Asymptomatic patients can be managed conservatively.
- Follow-up studies have shown no long-term pulmonary dysfunction.

## Introduction

Congenital lobar emphysema (CLE) is a rare type of congenital lung malformation (CLM). It was first described in 1932 by Nelson[1,2] and its incidence is estimated to be about one in every 20,000 to 30,000 live births. CLE is more common among Caucasians, with a male-to-female ratio of 1:3[3-6].

CLE is characterized by the overexpansion of one or more pulmonary lobes[6] due to partial bronchial obstruction that creates a “ball-valve” mechanism, leading to air trapping in the affected lobe[2,4,5]. Symptoms are present at birth in up to 33% of cases and almost all infants will develop symptoms within the first six months of life if there is continued lobar overdistension and depending on how fast it develops[2-5,7,8]. Infants typically present with tachypnea, shortness of breath, wheezing, cyanosis, and difficulty in feeding. An important aspect to take into consideration is the possible association of CLE with other congenital malformations: cardiac (the most common types, e.g. patent ductus arteriosus, pulmonary stenosis or valve atresia, and aortic coarctation), vascular (e.g. double superior vena cava), renal (aplastic kidney), gastrointestinal (e.g. omphalocele), and syndromes (e.g. Williams-Beuren syndrome and Niemann-Pick disease)[2,5,9-11].

## Methods

We identified all patients with a diagnosis of CLE in our center, since 2010, and reviewed the electronic files to describe clinical presentation, diagnostic methods, imaging techniques used, management options, and development during follow-up.

## Results

The patients were all term neonates and Caucasian, one male and three female; three were inborn and one was outborn. One patient presented to the emergency department and another, at two months old, was transferred from another hospital following diagnosis. The demographics and clinical characteristics are presented in table 1.

Neonates (patients 2 and 3 in Table 1) had a prenatal diagnosis and were asymptomatic at birth. Another neonate (patient 1, in Table 1) developed symptoms on day 14. The fourth patient displayed mild symptoms from birth, but was mistakenly diagnosed with transient tachypnea of the newborn and correct diagnosis was not made until two months of age. Presenting features included sleepiness, refusal to feed, inadequate weight gain, and shortness of breath.

Management and follow-up details are provided in table 2. All patients had chest x-rays (Figs. 1, 3, 4 and 5) compatible with CLE in the left upper lobe and one had a (CT) scan (Figs. 1, 3 and 4) for diagnostic purposes. The two patients with a prenatal diagnosis are closely followed up at the outpatient department. The two cases with moderate-to-severe symptoms underwent left upper lobectomy via thoracotomy and, in both cases, the histopathology study (Fig. 2 and 5) revealed diffused emphysematous lesions with no parenchymal destruction.

**Table 1.** Demographics and clinical characteristics

| Patient | Gender | Caucasian | Prenatal diagnosis | Age at diagnosis | Start of symptoms | Symptoms |
|---|---|---|---|---|---|---|
| 1 | Female | Yes | No | 14 days | 14 days | Sleepiness, refusal to feed, perioral cyanosis, and subsequent shortness of breath |
| 2 | Female | Yes | Yes. Ultrasound at 22 weeks of gestation and MRI at 25 weeks | NA | NA | Asymptomatic |
| 3 | Female | Yes | Yes. Ultrasound at 22 weeks of gestation, MRI at 24 weeks | NA | NA | Asymptomatic |
| 4 | Male | Yes | No | 2 months | Day 1 | Poor weight gain, irritability, wheezing, costal retraction, groaning |

NA: not applicable; MRI: magnetic resonance imaging.

In all four patients, whether during their initial admission or follow-up, an ultrasound examination (including abdominal and renal) and echocardiogram were performed to identify potential associated congenital malformations, but none were found.

## Discussion

This series of four clinical cases of CLE recorded over a 10-year period, at a level III hospital with about 2,500 deliveries per year, highlights the rarity of this pathology. CLE is a rare disease, with an unknown cause in 50% of cases. It is believed that a partial obstruction of the lobar bronchi leads to air trapping and the consequent overinflation and compression of adjacent structures as the affected lobe continues to grow and herniates leading to a deviation of the mediastinum and compression of the structures on the opposite lung. This lobar involvement is most commonly found in the left upper lobe (43%), followed by the right middle lobe (32%) and the right upper lobe (21%), while lower lobe involvement is less common and the rarest form is polylobar involvement[5,6].

Diagnosis can be made using chest X-rays showing a hyperlucent lobe, that may herniate and cause ipsi- and even contralateral atelectasis and mediastinal shift[3-5,9]. Although CT scans are considered the gold standard for diagnosing CLE, they may not be always necessary, especially when symptoms and a chest X-ray clearly point to the condition. CT scans are valuable in confirming a suspected diagnosis and provide a more detailed characterization of lung involvement[2,5]. Bronchoscopy was once commonly performed to exclude intraluminal causes for obstruction but it is no longer routinely performed[5,9].

Histologically, there are overgrown alveoli and the acinar structure is preserved with no lung tissue destruction or other parenchymal abnormalities[2,5,6]. While the etiology is unknown in about half of cases, a quarter have absent, hypoplasic, or dysplasic bronchial cartilage and, in rare cases, there may be intrinsic or extrinsic causes for the airway obstruction[5,6]. In this series, the two patients that underwent lobectomy had histopathology reports that described emphysematous-like lesions, with multifocal ruptured septa, which was associated with the surgery itself rather than the pathology. Dysplasic or absent cartilage was not observed, which is in line with the literature[5].

Some studies have recently described the prenatal diagnosis of CLE using ultrasound and confirming it with magnetic resonance imaging (MRI)[2,6,8,10]. In some cases, a regression of the lesion is described, avoiding the need for fetal or postnatal intervention[2,6,8,10].

Contrary to previous literature, our series presents a male-to-female inverted ratio, but all our patients were Caucasian, as usually reported. Traditionally, diagnosis is made postnatally, with most cases identified in the first six months of life. However, with advances in ultrasound technology and awareness, prenatal diagnosis has been described by some authors[2,6,10]. In our series, two cases were diagnosed prenatally and were asymptomatic, one presented with symptoms at 14 days of life, and the fourth was only diagnosed at two months of age, despite symptom progression from birth.

All patients had a chest X-ray, which enabled diagnosis; three had a CT scan, but only in one case

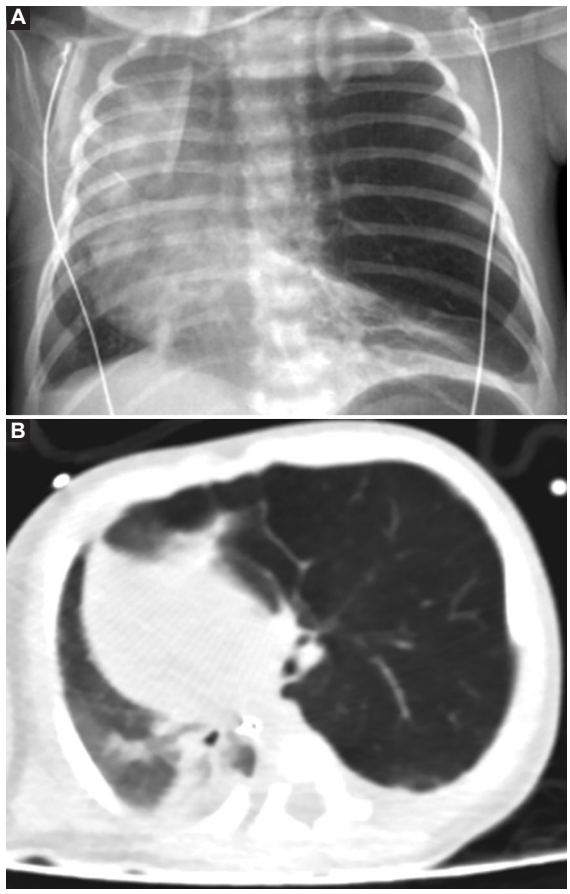


**Figure 1. A:** chest X-ray: hyperlucent LUL, mediastinum shift and atelectasis. **B:** CT scan: large-volume CLE, pushing the mediastinum to the opposite side.

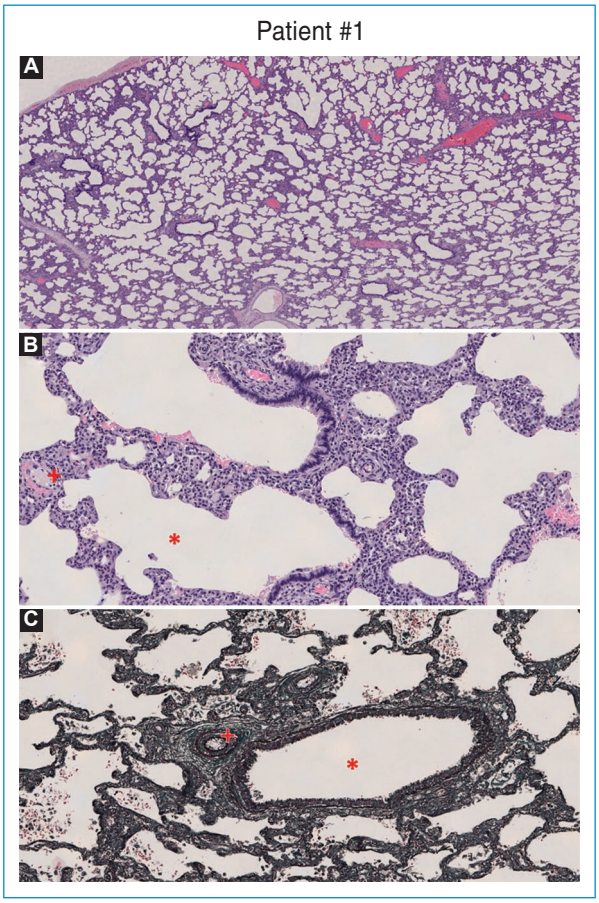


**Figure 2.** Histopathology images. **A:** H&E, x1.25: alveolar spaces are enlarged, but the global architecture is structurally normal; there is also lung immaturity (there were no periodic acid-Schiff positive cells or exudates). **B:** and **C:** H&E, x100; elastic fiber stain, x100 respectively: not only are alveolar spaces markedly enlarged, but also the bronchioles (*) are wider than matching arterioles (+).

(patient 4) was it necessary for diagnosis, since the image on the chest X-ray was not specific enough. The left upper lobe was affected in each case, which is in line with the literature. None of our patients underwent a bronchoscopy, as this exam is no longer routinely performed since the advent of CT[9]. Most patients who underwent a CT scan did so in order to better characterize the extension of lobar involvement, the number of lobes affected, and to evaluate the compromise of the surrounding structures[2,6,7,10]. An echocardiographic evaluation was also performed to rule out a congenital heart defect associated with CLE and no major abnormalities were found.

According to recent reports, patients with few or no symptoms can be managed conservatively, which involves close follow-up[2,5-7,10]. However, once there is any deterioration of the clinical condition with development or worsening of the symptoms, surgery is the best option. This approach has been described more frequently and shows no different outcomes compared to the normal population[2,8,10].

There are two surgical approaches available: open thoracotomy and thoracoscopy surgery. In our series, the two patients who were operated upon underwent an open thoracotomy as it is currently the preferred method. Typically, the surgery is well tolerated and recovery is fast, with a good prognosis. In our series, one patient (number 1, in Table 2) developed post-operative anemia and a red blood cell transfusion was needed, and the same patient developed an opioid withdrawal syndrome. To date, no other complications have been recorded. No other post-operative complications were reported, and no respiratory symptoms have been observed in the follow-up appointments. Without

**Table 2.** Study, management, and outcome

| Patient | Imaging study | Affected lobe | Histopathology | Cardiology evaluation | Lobectomy | Compli-cations | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | Chest X-Ray (D14) –hyperlucent LUL, mediastinum shift, and atelectasis | LUL | Global structure preserved, but there are enlarged alveolar spaces; bronchioles are wider than matching arterioles | PFO at 1 month | Yes (17 days) | Anemia; Opioid withdrawal syndrome | Asymptomatic |
| 2 | Chest X-Ray (D2) –hyperlucent LUL CT scan (2 months): single CLE with small parathymic atelectasis; no mediastinal shift | LUL | NA | Mesocardia; minimal VSD | No | NA | Asymptomatic |
| 3 | Chest X-Ray (D1) –hyperlucent LUL CT scan (6 months): minor CLE; no atelectasis or mediastinum shift | LUL | NA | Normal | No | NA | Asymptomatic |
| 4 | Chest X-Ray (2 months) – hyperlucent LUL and mediastinum shift; no atelectasis CT scan (2 months) – left CLE; right lobe atelectasis and right mediastinum shift | LUL | Global structure preserved, but there are enlarged alveolar spaces | Normal | Yes (2 months) | No | Asymptomatic |

CLE: congenital lobar emphysema; CT: computed tomography; VSD: ventricular septal defect; NA: not applicable; PFO: patent foramen ovale; LUL: left upper lobe.

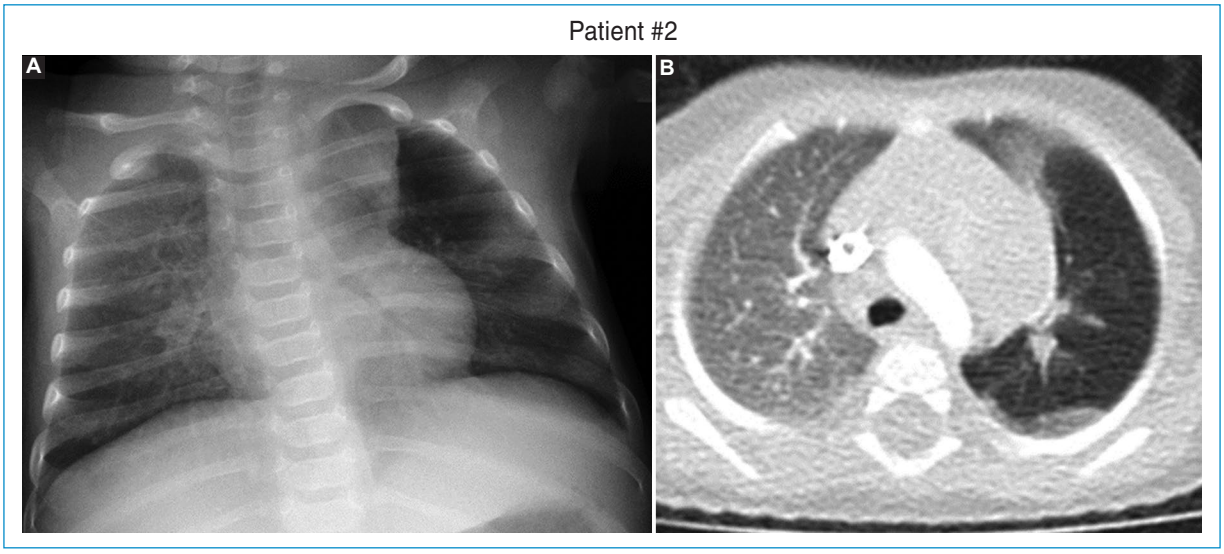


**Figure 3.** **A:** chest X-ray: hyperlucent LUL, with no mediastinum shift. **B:** CT scan: single CLE with small parathymic atelectasis; no mediastinal shift.

Patient #3

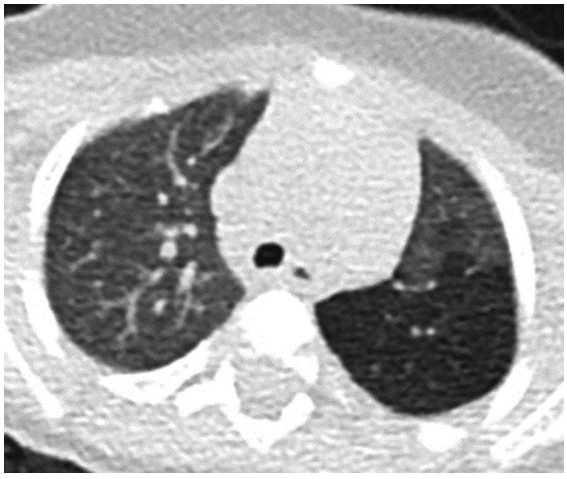

**Figure 4.** CT scan at 6 months of age: minor right posterior CLE; no atelectasis or mediastinum shift.

Patient #4

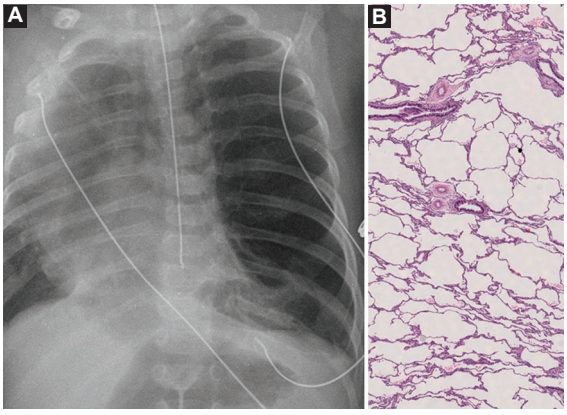


**Figure 5. A:** chest X-ray at 2 months of age: hyperlucent LUL and mediastinum shift; no atelectasis.
**B:** histopathology image (H&E, x1.25): alveolar spaces are enlarged, in this case markedly, but the global architecture is structurally normal.

surgery, the natural history of CLE is eventual progressive cardiorespiratory failure due to the compression effect over ipsi- and contralateral lung tissue as well as over the venous drainage from the pulmonary and systemic bed leading to heart failure[2,5,10].

Follow-up studies on patients who underwent surgery as well as on those who were managed conservatively showed slight decreases in residual volumes, total lung capacity, and forced expiratory volume, but no long-term pulmonary dysfunction was noted.

More recently, some authors have claimed a probable genetic predisposition, with an apparent autosomal dominant transmission[4,5], but more studies are needed in order to confirm this hypothesis.

In conclusion, CLE is a rare disease with unknown etiology in 50% of cases. The diagnosis of CLE can be made prenatally or postnatally. Imaging techniques, such as chest X-ray, in some specific cases, and CT scans are useful for diagnosis, and echocardiographic evaluation is recommended to identify any associated malformations. Conservative treatment of CLE should be preferred in mild and moderate cases, while lobectomy should be considered in severe disease cases. As more cases are diagnosed prenatally, conservative treatment seems to be increasing when intrauterine regression of CLE is observed. Histologically, broncho-alveolar involvement with over-distension of the affected lobe and no destruction of surrounding pulmonary parenchyma, is typically described. Follow-up studies have shown that there is no long-term pulmonary dysfunction and the prognosis is generally good with surgery or conservative management.

Although CLE is rare, a high index of clinical and radiological suspicion is required to diagnose this rare anomaly which may mimic other causes of respiratory distress. Therefore, in order to provide the best care for affected patients, it is important that clinicians are aware of this entity.

## Authors' contribution

A. Assunção, P. Miragaia, F. Flôr-de-Lima, G. Rocha, C. Ferraz and I. Azevedo: 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; Anayisis 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. Susana Guimarães: 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.

## Funding

None.

## Conflicts of interest

None.

## Ethical disclosures

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

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

# Alpha-1-antitrypsin deficiency in children: a 10-year case study from a tertiary hospital

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## Abstract

**Introduction and Objectives:** Alpha-1-anti-trypsin (A1AT) is a glycoprotein mainly produced in the hepatocyte. A1AT deficiency is one of the most prevalent genetic disorders and the spectrum of it related diseases is quite wide. Severe A1AT deficiency predisposes individuals to Chronic Obstructive Pulmonary Disease (COPD) and liver disease. Our aim was to characterize clinically, biochemically and phenotypically a sample of pediatric A1AT-deficient (A1ATD) patients and to investigate whether there was any lifestyle change after diagnosis. Additionally, it was our goal to promote awareness to A1ATD among the medical community and to encourage the creation of a national pediatric registry and collaboration in the European registry. **Methods:** An observational retrospective study with analysis of the clinical records of all pediatric patients that had AAT measurement in our tertiary center between January 2010 and December 2019 and revealed levels < 93 mg/dl. **Results:** We enrolled 203 patients, 125 (61.6%) males. Median age at diagnosis was 2.93 years (IQR: 0.73-6.31). There was a family history in 18 patients (8.9%). The assessment of serum A1AT levels was motivated by: respiratory disease (121/203; 59.6%), liver disease (39/203; 19.2%), and family screening (6/203, 3%). The median serum A1AT concentration was 79 mg/dl (IQR: 68-85.4). Phenotyping in 47 patients (23.2%) revealed: MZ (12; 28.6%), MS (10; 23.8%) and ZZ (7; 16.7%). The prevalence of smoking exposure before and after diagnosis was 23.6% and 20.1%, respectively. Only 33% of patients underwent influenza vaccination after diagnosis. **Discussion:** In our sample, there was no significant change in the smoking exposure before and after diagnosis. It would be important to evaluate the impact of early diagnosis and the lifestyle changes on the long-term prognosis, as well as the creation of follow-up protocols in pediatric age. Larger, multicentric studies are needed to determine the real prevalence, the frequency of the main associated mutations, as well as the clinical consequences and follow-up approach required.

***Keywords:*** Alpha-1-antitripsin deficiency. Pediatric age. Familiar history.

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## *Défice de alfa-1-antitripsina na população pediátrica: casuística de 10 anos de um hospital de nível III*


## Resumo

**Introdução e Objetivos:** O défice de A1AT apresenta um espetro clínico variável e a sua prevalência está subestimada, estando um curso um registo nacional. Caracterizar clínica, bioquímica e fenotipicamente uma amostra de doentes com défice de A1AT em idade pediátrica, promover a participação no registo nacional, e averiguar se houve alteração do estilo de vida após o diagnóstico. **Métodos:** Análise retrospetiva de todos os doentes pediátricos que realizaram doseamento sérico de A1AT no CHUP no período de janeiro/2010 a dezembro/2019 e que revelaram uma concentração < 93 mg/dl. **Resultados:** Incluídos 203 doentes, sendo 125 (61,6%) do sexo masculino. A idade mediana ao diagnóstico foi 2,93 anos (IQR: 0,73-6,31). Havia história familiar de défice de A1AT em 18 doentes (8,9%). O doseamento de A1AT foi motivado por: doença respiratória (121/203; 59,6%), doença hepática (39/203; 19,2%), e rastreio familiar (6/203, 3%). A concentração sérica mediana de A1AT foi 79 mg/dl (IQR: 68-85,4). A fenotipagem em 47 doentes (23,2%) revelou: MZ (12; 28,6%), MS (10; 23,8%) e ZZ (7; 16,7%). Em quatro doentes foi efetuada biópsia hepática e um foi submetido a transplante hepático. A prevalência de exposição tabágica antes e depois do diagnóstico foi de 23,6% e 20,1%, respetivamente. Apenas 33% dos doentes realizaram vacina antigripal após o diagnóstico. **Discussão:** A incidência de diagnóstico por rastreio familiar foi baixa e o genótipo foi avaliado numa minoria dos doentes. Destaca-se ainda a baixa redução da exposição tabágica após o diagnóstico. Seria importante avaliar o impacto do diagnóstico precoce e alteração do estilo de vida no prognóstico a longo prazo, bem como a criação de protocolos de seguimento em idade pediátrica.


***Palavras-chave:*** Défice de alfa-1-antitripsina. Idade pediátrica. História familiar.

## Keypoints

**What is known**

- A1AT deficiency is one of the most prevalent genetic disorders and the spectrum of it related diseases are quite wide, but it seems to be underdiagnosed in pediatric age.
- Severe A1AT deficiency predisposes individuals to Chronic Obstructive Pulmonary Disease (COPD) and liver disease.
- Lifestyle changes appear to have an important influence on the prognosis of the disease.

**What is added**

- Family screening accounted for only 3% of diagnoses, which contrasts with the expected prevalence and highlights significant underdiagnosis, even among families with a positive history of A1AT deficiency.
- The PiMZ phenotype was the most prevalent (28.6%) in this cohort, differing from previous studies in the Iberian Peninsula that identified PiMS as the most frequent phenotype.
- To encourage diagnosis and inclusion in the European register of the disease.

## Introduction

Alpha-1-antitrypsin (A1AT) is a glycoprotein from the serine protease inhibitor superfamily. It is encoded in the PI locus of the *SERPINA1* gene on the long arm of chromosome 14 (14q31.32)[1,2,3]. A1AT is mainly produced in the hepatocytes, but is also synthetized by neutrophils, mononuclear phagocytes, lung epithelial cells and intestinal cells[1,4,5]. Under normal conditions the liver is capable of secreting 34 mg/kg of A1AT in 24 hours, but that may increase two- to five-fold in response to inflammatory, tumoral or infectious conditions[1].

The highly polymorphic A1AT gene is passed by simple mendelian inheritance in an autosomal codominant pattern through two alleles, meaning that affected individuals have inherited an abnormal A1AT gene from each parent[1,8]. More than 150 alleles of A1AT have been identified by isoelectrofocusing (IEF) and each has a letter code (A and Z)[1,5,8]. The set of variants is called the PI (protease inhibitor) system, and most have no clinical significance[1]. Normal alleles are present in more than 85 – 90% of individuals and are Pi*M. The most prevalent deficient alleles are designated PiS and PiZ[1,5,9].

A1AT deficiency is one of the most prevalent genetic disorders, and is most common in the adult population[5]. The estimated prevalence is around 1:2000 – 4000 people in Europe, but it seems to be underdiagnosed mainly in the pediatric age range[5,10]. Despite several studies having been carried out in the past decade, more epidemiological studies are needed to determine the real prevalence of this condition[10]. In 2018, Ruiz et al., reported a prevalence of 8.1% of the Z allele and 81.9% of the PiZZ phenotype in an adult

population of the Portuguese island of Madeira[22]. Nevertheless, to the best of our knowledge there are no epidemiological studies conducted in the Portuguese pediatric population.

The A1AT deficiency, together with other genetic characteristics, as well as certain environmental factors, predispose these individuals to a greater risk of developing disease (tobacco smoke to lung disease and alcohol to liver disease)[1,5]. Also, obesity was described in association with a higher risk of liver disease progressing to fibrosis and cirrhosis in adults with A1AT deficiency[23]. The spectrum of A1AT deficiency-related diseases is quite wide, and depends on the age at presentation. It is currently considered a systemic condition, with the lungs and liver being the most affected organs, and less commonly, the skin[5,9,13,14]. The main clinical manifestations of severe A1AT deficiency include severe liver disease in infancy and childhood, caused by polymer toxicity, and pulmonary emphysema occurring in adulthood, due to low serum A1AT concentration[1,5].

The accumulation of A1AT polymers in hepatocytes can lead to their injury and progression to cirrhosis may occur[2]. Although hepatic involvement is more frequent with advancing age, cholestatic jaundice or hepatitis may be seen in infants and young children[13,19]. Only 3% of cases are diagnosed due to hepatic manifestations, such as elevated transaminases[12]. Skin involvement is rare, although panniculitis and vasculitis may appear[5].

The diagnosis of A1AT deficiency is confirmed by laboratory tests that quantify serum A1AT levels[1]. Several tests are currently available, both quantitative and qualitative: serum A1AT assay is a quantitative test that quantifies the amount of protein circulating in the blood; A1AT phenotyping is a qualitative test that detects circulating variants; A1AT genotyping and *SERPINA1* gene sequencing are considered the ideal method for identifying specific mutations associated with A1AT deficiency[1,5]. In the event of clinical suspicion, the quantification of serum A1AT levels is recommended. The consensus of the American Thoracic Society and European Respiratory Society suggests the combination of a quantitative test and phenotyping as the gold standard for diagnosis[5,15]. If blood levels are lower than 110 mg/dL phenotyping should be performed to confirm the diagnosis[15].

According to the American Thoracic Society/European Respiratory Society, and extrapolating for the pediatric age range, the indications for serum A1AT levels are: early onset emphysema; emphysema in the absence of exposure to known risk factors; confirmed cases of A1AT deficit in the family; family history of respiratory pathology, such as emphysema, dyspnea, cough or bronchiectasis; family history of liver disease or panniculitis; individuals with chronic obstructive pulmonary disease (COPD); asthmatics whose respiratory function tests do not normalize after adequate treatment; or in the presence of liver disease of unknown origin[12,20].

After diagnosis, the initial approach should include a thorough clinical history and examination, focusing on the aforementioned organ systems that are most affected. Other auxiliary diagnostic tests should be performed depending on the clinical findings, as well as the age of the patient[5]. Respiratory function tests, such as spirometry, plethysmography and carbon dioxide diffusion capacity should be performed in the case of older children or adolescents[15]. Other examinations, such as arterial blood gas analysis, respiratory effort tests, chest x-ray and a computed tomography (CT) scan, can also be considered depending on the clinical setting[16]. Liver function tests and abdominal ultrasounds should be considered[1,5,10]. Serum liver assessment should include transaminases, as well as alkaline phosphatase, gamaglutamiltransferase (GGT), bilirubin, albumin, coagulation tests, platelets count, fat soluble enzymes, and alpha-fetoprotein[17]. Abdominal ultrasound identifies indirect signs suggestive of steatosis and cirrhosis, clarifying the need for further investigation[5]. Liver biopsy is not recommended as an initial test, but may be performed when there is an established liver lesion to better assess diagnosis and prognosis[17].

In regard to the management of these patients, the primary focus should be on promoting lifestyle modifications, including avoidance of tobacco exposure, adherence to a healthy diet, daily exercise and immunizations. In patients with respiratory symptoms, symptomatic treatment and respiratory kinesiotherapy should also be provided[1,5,10]. In patients with end-stage liver disease, liver transplantation is an option[23].

The follow-up depends largely on the clinical presentation and evolution. Individuals diagnosed during childhood may never show manifestations if they have never been exposed to tobacco, for example[5]. Respiratory function tests should be considered in late adolescence, as well as every two to three years. Liver evaluation with abdominal ultrasound and laboratory testing should also be performed at similar intervals[5,10].

Our aim was to characterize clinically, biochemically and phenotypically a sample of pediatric A1AT-deficient patients and to investigate whether there was any change in lifestyle after diagnosis. It was also our goal to promote awareness and to encourage the creation of a national pediatric registry and collaboration in the European registry.

**Table 1.** Sample baseline characterization

| Total | 203 |
|---|---|
| Gender | |
| Male | 125 (61.6%) |
| Female | 78 (38.4%) |
| Age at diagnosis (years) | 2.93 (0.75-6.31) |
| Time until diagnosis | 2 (0-13) months |
| County of residence | |
| Porto | 48 (23.6%) |
| Gondomar | 35 (17.2%) |
| Vila Nova de Gaia | 15 (7.24%) |
| Valongo | 14 (6.9%) |
| Matosinhos | 11 (5.4%) |
| Other | 80 (39%) |
| Positive family history of A1AT deficiency | 18 (23.4%) |
| Reason for A1AT measurement | |
| Respiratory disease | 121 (59.6%) |
| Hepatic disease | 39 (19.2%) |
| Family screening | 6 (3.0%) |
| Unknown | 37 (17.9%) |
| Serum A1AT levels (mg/dL) | 79 (68.0-85.4) |
| Phenotype | 47 (23.2%) |
| MZ | 12 (28.6%) |
| MS | 10 (23.8%) |
| ZZ | 7 (16.7%) |
| SZ | 6 (14.3%) |
| SS | 1 (2.4%) |
| Other | 6 (14.3%) |

Data is presented as n, n (percentage) or median (IQR), as appropriate.
A1AT: alpha-1-antitrypsin.

**Table 2.** Auxiliary exams and therapeutic approach

| Total | 203 |
|---|---|
| Serum measurements performed at diagnosis | |
| BT - Abnormal values (n = 84) | 29 (14.3%) |
| GGT - Abnormal values (n = 120) | 36 (17.7%) |
| ALT - Abnormal values (n = 128) | 28 (13.9%) |
| Liver biopsy (total) | 4 (2.0%) |
| Nuclear inclusions | 1 (25%) |
| Spirometry (total) | 24 (11.8%) |
| Abnormal | 15 (62.5%) |
| Abdominal ultrasound | 50 (24.6%) |
| Abnormal | 15 (29.4%) |
| Supportive therapy | 14 (6.9%) |
| UDCA | 9 (64.3%) |
| Vitamins and UDCA | 5 (35.7%) |
| Smoke exposure | |
| Prior to diagnosis | 41 (23.6%) |
| After diagnosis | 34 (20.1%) |
| Immunizations | |
| Influenza | 61 (33.0%) |
| Pneumococcal | 127 (62.6%) |

Data is presented as n, n (percentage) or median (IQR), as appropriate.
BT: bilirubin; GGT: gamma-glutamyl transferase; ALT: alanine aminotransferase; UDCA: ursodeoxycholic acid.

## Methods

### *Study design and sample*

We conducted a retrospective study of patients under 18 years of age, diagnosed with A1AT deficiency in the biochemical laboratory of Centro Hospitalar Universitário de Santo António, between January 2010 and December 2019. We first analysed the laboratory records, and then we analysed the patients' clinical records.

### *Inclusion and exclusion criteria*

All pediatric patients who underwent serum A1AT measurements by immunoturbidimetry in the aforementioned period were screened. The inclusion criterion was a A1AT serum level lower than 93 mg/dL. Patients who did not undergo a clinical observation and follow-up in our institution were excluded.

### *Definition of variables and data collection*

Data were collected by assessing the electronic clinical files.

Demographic data (age at referral and diagnosis, sex and county of residence) and clinical variables (family history of A1AT deficiency; personal and family history of liver or respiratory disease; smoke exposure prior to and after diagnosis; and influenza and pneumococcal immunization) were collected. The reason behind the referral for consultation and the A1AT measurement (liver or respiratory disease, family screening, other or unknown) were also reviewed.

Regarding auxiliary examinations performed during follow-up time, we evaluated minimum and maximum serum levels of A1AT and, when performed, blood levels of bilirubin, gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT) at diagnosis, spirometry, abdominal ultrasound, liver biopsy and genotype/phenotype studies.

We also reviewed the need for support treatment (nutritional, vitamins and trace elements and ursodeoxycholic acid (UDCA)) and liver transplantation.

### Ethics

This research complies with all the relevant national regulations, institutional policies and is in line with the tenets of the Helsinki Declaration. The study was approved by the Ethics Committee of Centro Hospitalar Universitário de Santo António and Instituto de Ciências Biomédicas Abel Salazar.

### Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics 25.0. Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as median and percentiles 25 and 75.

## Results

The sample baseline characterization is described in table 1. A total of 203 patients were included, of whom 61.6% were male and 38.4% were female. The median age at diagnosis was 2.93 years (Interquartil range (IQR): 0.75 - 6.31). Most patients lived in Porto (23.6%) and were referred for a pediatric appointment by primary care facilities (26.8%). There was a family history of A1AT deficiency in 23.4% of patients, but this was not the reason for A1AT measurement in all. Serum A1AT measurement in the context of family screening was carried out in only 3.0% of patients. Other reasons included respiratory symptoms (59.6%), such as repeated airway infections, recurrent wheezing and asthma, and liver abnormalities (19.2%), such as unexplained elevation of transaminases and jaundice of unknown cause. The median serum A1AT levels in our sample was 79 (IQR: 68.0 - 85.4; minimum 6, maximum 89.8) mg/dL.

Table 2 describes the investigation and clinical approach in our sample during a median follow-up time of three years (IQR: 2 - 7). The median time until diagnosis was two months (IQR: 0 - 13). Serum measurements of BT, GGT and ALT were performed at diagnosis in 41.6%, 59.7% and 63.7% of patients, and were abnormal in 34.5%, 30.0% and 21.9% of cases, respectively. Spirometry was performed in 12%, with abnormal results in 63% of these. Concerning the liver study, abdominal ultrasound was carried out in 25% of patients, with abnormal results in 29%. Four patients underwent a liver biopsy and A1AT inclusions were found in one. Phenotype studies were conducted in 23.2% patients, with MZ, MS and ZZ being the most prevalent types (28.6%, 23.8% and 16.7%, respectively).

Fourteen (6.9%) patients needed supportive therapy with vitamins and/or UDCA. One patient had liver cirrhosis and underwent liver transplantation. The majority (62.6%) of patients were vaccinated against pneumococcal infection and approximately one third against influenza virus.

## Discussion

A1AT deficiency is underdiagnosed in the pediatric age, thus although it is assumed to be common, its real prevalence is not known[10]. The clinical implications of this deficiency are not yet fully understood, especially in heterozygotic individuals. Underdiagnosis is likely to be a major limitation in the study of the disease impact in the pediatric age group[12]. Nevertheless, several countries have already taken the first step with the creation of national A1AT registries and Portugal has recently joined this group of countries. Although still at the early stages of implementation, it has been growing. However, data regarding the pediatric population are still scarce.

During the study period of ten years, 203 pediatric patients were diagnosed with this condition in one tertiary hospital located in northern Portugal. This reinforces the need to carry out epidemiological studies, especially in this age group. The distribution by municipalities is linked to our hospital's area of intervention. As expected, the municipality of Porto had the highest number of cases, 48 (23.6%), since it is the largest municipality in our hospital's area of influence, with the largest population and the easiest access to health care.

With regard to phenotype, the Pi*MZ was the most common, present in 28.6% of cases. These results differ from previous studies carried out in the Iberian Peninsula, which indicate that the Pi*MS phenotype is the most common[11,13,21]. This difference may stem from the fact that the study was carried out in the general population, including adults.

According to the literature, the Pi*ZZ phenotype is associated with a higher prevalence of pulmonary disease and, in these patients, A1AT values below 50 mg/dL are more common[20]. This phenotype was found in 16.7% of our sample. Despite the percentage being lower than expected[2], it was found that all of these patients had A1AT values lower than 50 mg/dL, with the highest levels in this group being 45 mg/dL.

The identification of individuals at risk may be performed by the presence of clinical manifestations or through family screening[5,11]. Furthermore, asthma is a very common finding amongst these individuals, although there is no well-established relationship between A1AT deficiency and asthma[17]. Likewise, serum levels of A1AT should be measured during the etiologic

study of bronchiectasis, although no causal relationship has been made so far[18]. A1AT deficiency predisposes individuals to the early appearance of chronic obstructive pulmonary disease, such as emphysema, and severe and prolonged exacerbations are common in these individuals[5,16]. The pediatric population is a very particular group since the vast majority of patients are identified during investigations for respiratory symptoms, mainly recurrent infections or chronic cough[5].

In our population, 59.6% of cases had respiratory symptoms, including repeated airway infections, recurrent wheezing and asthma. This is in line with the literature, as the most common consequence of A1AT deficiency is lung injury consequent to a lower protection against the action of the electrophilic protease in the lung tissue[1,7]. Since the hepatocyte is the main site of production of this protein, its lower activity will lead to the accumulation of the abnormal alpha-1-anti-trypsin in the hepatocyte, with consequent injury[5,12]. As expected, hepatic manifestations were the second most frequent reason for A1AT measurement (19.2% of cases), mainly due to the unexplained elevation of transaminases and jaundice of unknown cause. Despite this, in our sample, initial measurements of serum BT, GGT and ALT were carried out in only around 60% of patients. The fact that this was a retrospective study is an important limitation of this study. Furthermore, the lack of determination of the prevalence of obesity in our population is also an important limitation, as it may be overestimating the echographic alterations found (hepatic steatosis).

A positive family history is to be expected, since it is a genetic disease passed by autosomal codominant mendelian inheritance[1,8]. Nevertheless, a positive family history of A1AT deficiency was described in only 23.4% of our sample, a much lower percentage than that described in the literature[1,5]. Moreover, diagnosis by family screening was performed in only 3.0% of patients. These data, in conjunction with the high prevalence that appears to exist and the presence of disease even in heterozygotes, raises the question of whether A1AT measurement should be performed in asymptomatic children with a positive family history. Furthermore, since the presence or absence of disease manifestations also depends on environmental factors, early diagnosis can promote lifestyle changes to minimize some important risk factors. Although there are no clear recommendations in the pediatric age range, it is known that in the adult population, a positive family history is a criterion for AAT measurement.

There are no established protocols regarding the initial approach and follow-up for these patients. As such, a patient's clinical management should be individualized, according to their age, clinical manifestations and complementary test findings. In our sample, the median follow-up time was three years. Serum levels of bilirubin, GGT and ALT were measured at diagnosis in the majority of cases. The frequency of laboratory check-ups were also determined individually and according to previous findings and clinical evaluation. Spirometry and abdominal ultrasound tests were performed in 11.8% and 24.6% of our sample, respectively. Clinical presentation, progress and the individual clinician's experience, is therefore shown to be the principal impetus behind the follow-up of these patients, since there are no defined national or international protocols.

Smoking avoidance and the implementation of healthy lifestyle habits were reinforced in all newly-diagnosed children[1,10]. It has been proven that these measures can delay and minimize the impact of the disease on the quality of life of affected individuals[12]. In our sample, there was a non-significant decrease in smoke exposure after diagnosis. Similarly, these patients were also advised to have the annual influenza vaccine and anti-pneumococcal vaccine. However, the vaccination rate in our sample was only 33.0% and 62.6%, respectively. In our view, it would be interesting to run awareness campaigns in schools, primary health care facilities and even the media regarding the importance of these preventive measures, integrated in a broader prevention of OCPD.

We acknowledge a number of important limitations to our study. First, the retrospective nature of this study, the short follow-up period, and the fact that we report a single center's experience. Furthermore, our sample included only children living in northern Portugal. Despite these limitations, to our knowledge this is one of the first Portuguese studies that tried to characterize a sample clinically, biochemically and phenotypically, although there may have been a selection bias with the inclusion of more severe cases.

Larger, multicentric studies are needed to determine the real prevalence of this condition in Portugal, the frequency of the main associated mutations, as well as the clinical phenotypes and follow-up approach required for these patients. Furthermore, prospective studies would be essential to evaluate the impact of an early diagnosis on the prevention of complications and on the quality of life of these patients. The creation of a national register is essential for a better understanding of this condition and consequently an improvement of healthcare. In Portugal, it is hoped that this is a step in the process of integration into the European register.

## Authors' contribution

J. Carvalho: Conceptualization, bibliographic research, writing-original draft, writing-review and editing. R. Gomes: Conceptualization, writing-original draft, writing-review and editing. B. Sousa: Conceptualization, writing-original draft, writing-review and editing. J. Vasconcelos: Validation, writing-review and editing. E. Santos-Silva: Patient's follow-up, validation, writing-review and editing. M. Guilhermina-Reis: Conceptualization, Patient's follow-up, validation, writing-review and editing.

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## Conflicts of interest

None.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

# Self-harm and suicidality in child and adolescent psychiatric emergencies

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## Abstract

**Introduction and Objectives:** Suicidal ideation (SI), suicide attempts (SA) and non-suicidal self-injuries (NSSI) are frequent causes of admissions to pediatric emergency departments (ED). We aim to evaluate the trends of self-harm and suicidality in children and adolescents in a mental health ED between 2019 and 2021 and compare it with similar data extracted from two previous studies carried out in our department in 2008 and 2016. We also analyze the impact of the COVID-19 pandemic in admissions for these causes. **Methods:** We performed a retrospective, descriptive analysis of all patients admitted to our ED for NSSI, SI and SA during 2008, 2016 and from March 2019 to May 2021. To analyze the impact of the COVID-19 pandemic, we compared the number of admissions between March and May 2021 (post-pandemic) with the same period in 2019 (pre-pandemic). **Results:** The number of SA was significantly higher in 2008 (18.7%, p = 0.038), SI (6.4%, p = 0.001) and NSSI (7%, p = 0.001) were higher between March 2019 and February 2020. We observed an increase of almost double (98.43%, p < 0.001) the number of episodes in March-May 2021 (compared to the pre-pandemic period), with higher SA (p < 0.001), SI (p = 0.008) and NSSI (p < 0.001). **Discussion:** We found a rise in self-harm-related ED admissions in recent years due to an increase of NSSI and SI. We did not find an increase in SA. After the initial period of the COVID-19 pandemic, there was an increase of self-harm admissions. Our findings are in line with trends reported in the literature.

***Keywords:*** Self-injurious behavior. Suicide. Attempted. Suicidal ideation. Adolescent psychiatry. Pediatric emergency medicine.

## *Comportamentos auto-lesivos e ideação suicida nas urgências pedopsiquiátricas*

## Resumo

**Introdução e Objetivos:** A ideação suicida (IS), tentativas de suicídio (TS) e comportamentos auto-lesivos não suicidários (CALNS) são causas comuns de admissões em urgências pediátricas. Este estudo pretende avaliar as tendências das admissões por IS, TS e CALNS numa urgência pedopsiquiátrica entre 2019 e 2021 e compará-las com dados semelhantes de dois estudos realizados no nosso departamento em 2008 e 2016. Pretendemos ainda analisar o impacto da pandemia COVID-19 nas admissões por estas causas. **Métodos:** Realizámos uma análise retrospetiva e descritiva dos doentes admitidos em urgência pedopsiquiátrica por CALNS, IS e TS em 2008, 2016 e março de 2019 a maio de 2021. Para analisar o impacto da pandemia COVID-19, comparámos as admissões entre março e maio de 2021 (pós-pandemia) com o mesmo período em 2019 (pré-pandemia). **Resultados:** O número de TS foi significativamente maior em 2008 (18.7%, p = 0.038). IS (6.4%, p = 0,001) e CALNS (7%, p = 0,001) foram mais frequentes entre março de 2019 e fevereiro de 2020. Houve um

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aumento de quase o dobro de episódios (98.43%, p < 0.001) em março-maio 2021 (comparativamente ao período pré-pandémico) com um maior número de TS (p < 0.001), IS (p = 0.008) e CALNS (p < 0.001). **Discussão:** Nos últimos anos, verificámos um aumento nas admissões relacionadas com ideação/comportamentos auto-lesivos no serviço de urgência devido a um aumento de admissões por CALNS e IS. Não verificámos um aumento de TS. Após o período inicial da pandemia COVID-19, verificámos um aumento acentuado das admissões relacionadas com comportamentos auto-lesivos e IS. Estes resultados vão de encontro ao reportado na literatura.

***Palavras-chave:*** Comportamentos auto-lesivos. Tentativas de suicídio. Ideação suicida. Psiquiatria da adolescência. Urgência pediátrica.

## Keypoints

**What is known**
- Suicidal ideation and self-harm behavior are frequent causes of admissions to child and adolescent psychiatry emergency departments.
- There has been an increase in the number of cases of self-harm in children and adolescents.
- During the COVID-19 pandemic, children and adolescents experienced high levels of anxiety and depression, along with an increase in self-harm and suicidal thoughts.

**What is added**
- In recent years, there was an increase in NSSI and SI without suicidal behavior in pediatric mental health ED. However, we did not find an increase in admissions for SA.
- There was a steep increase in self-harm-related ED admissions in children and adolescents after the acute period of the COVID-19 pandemic.

## Introduction and objectives

Suicidal ideation (SI) and self-harm behavior are frequent causes of admissions to child and adolescent psychiatry emergency departments (ED)[1]. Non-suicidal self-injury (NSSI) is defined as deliberate, intentional self-harm without suicidal intent, using methods that are not socially sanctioned[1-4]. There has been an increase in the number of cases of self-harm in children and adolescents in the general population[5]. NSSI is more frequently observed in adolescents and young adults, with a prevalence ranging from 18 to 30%, and it is reported to be more common in female adolescents[1,6-12]. In clinical populations, its prevalence can rise as high as 80%[13]. NSSI is often associated with a broad spectrum of mental health problems, with psychiatric comorbidities being present in up to 80% of individuals who self-harm[9,14,15]. NSSI is associated with future suicide attempts and is considered the strongest predictor of suicide in adolescents[16,17]. Patients who sought care in ED after engaging in NSSI faced a recurrence risk of 16.3% and a 1.6% risk of suicide within the following year[18]. By examining the records of patients who died by suicide, a study showed that 15% of individuals had been admitted to the ED within one year prior to their death as a result of NSSI[19].

Pediatric ED are often the initial interface for many children and adolescents showing self-injury behavior, making it an important setting for assessing and managing this behavior[20-23]. There has been a steep increase in admissions to pediatric ED related to self-harm in children and adolescents, but an increase in the number of young people seeking assistance for self-harm within primary care settings has also been reported[24,25].

Admissions to ED for NSSI and suicidal attempts (SA) are linked to prior exposure to adverse life experiences and risk factors such as a history of childhood sexual abuse, interpersonal and intrafamilial conflicts, impulsivity and feelings of isolation and loneliness[12,26].

During the COVID-19 pandemic, adolescents went through several periods of forced isolation at home, school closures and bans from social activities, which limited their interaction with peers and increased their screen time and social media dependence[27]. There was a disruption to their normative seeking of independence from caregivers, impacting peer integration due to lockdown measures and social restrictions. Increased family pressures and mandatory confinement simultaneously exacerbated conflicts between parents and adolescents, contributing to negative moods and worsening the mental health of both parties[27-29]. Overall, deprived from social relationships and interactions, many adolescents were prevented from relying on their usual coping strategies and had to rely solely on their internal coping mechanisms, in a developmental stage where this should not be the norm. This contributed to increased difficulties in emotional regulation[30]. With restriction measures sustained over several months, the psychological burden among children and adolescents

was considerably aggravated. Research indicates that adolescents experienced high levels of anxiety and depression during the pandemic, along with a higher frequency of maladaptive behaviors, such as deliberate self-harm, which often represents an attempt to manage emotional arousal and reduce emotional distress[30-32].

In our research, we aim to evaluate the trends of self-harm and suicidality in children and adolescents in a pediatric mental health ED in Portugal between 2019 and 2021 and compare it with similar data extracted from two previous studies carried out in the same department in 2008 and 2016[33,34]. We also aim to analyze the impact of the COVID-19 pandemic in the number of admissions to this pediatric mental health ED for SA, NSSI and SI, comparing the number of admissions for these same causes between March and May 2021 (post-pandemic) with the same period in 2019 (pre-pandemic).

## Methods

Our study was conducted in a pediatric mental health ED in Oporto, Portugal. It is the only ED for pediatric mental health care in the north of Portugal. It provides 12-hour psychiatric care for children and adolescents, seven days a week, and all cases are admitted only after a medical referral. Our sample was restricted to children and adolescents under the age of 18 who were admitted to our pediatric mental health ED for NSSI, SA and SI. NSSI was defined as the deliberate, intentional behavior of harming one's own body without suicidal intent, using methods that are not socially sanctioned. SI was defined as patients who have thoughts about death but do not engage in suicidal behaviors. SA was defined as a condition in which body organs and tissues are deliberately damaged with the intention of causing death. In this study, drug intoxications were considered as SA.

We performed a clinical-based, retrospective and descriptive analysis of all children and adolescents aged up to 18 who were admitted to our pediatric mental health ED for NSSI, SI and SA (drug intoxications or other methods) from March 2019 to May 2021 and then we extracted similar data from two previous studies carried out in our department in 2008 and 2016[33,34]. The data were collected from the clinical patient records. We collected demographic data regarding gender and age (under and above 12 years of age). To analyze the impact of the COVID-19 pandemic in the number of admissions to our ED for SA, NSSI and SI, we compared the number of admissions for these causes between March and May 2021 (post-pandemic) with the same period in 2019 (pre-pandemic).

For comparison purposes, we analyzed our data by dividing it into five different periods:

1. From July 2007 to June 2008 (12 months, data from Queirós[33])
2. From January 2016 to December 2016 (12 months, data from Rodrigues et al.[34])
3. From March 2019 to February 2020 (12 months)
4. From March 2020 to February 2021 (12 months)
5. From March 2021 to May 2021 (3 months)

The data analysis was conducted using the SPSS program, version 27.0. Absolute frequencies (n) and percentages (%) were presented in the description of variables. The assessment of the association among categorical variables was performed using the chi-square test or Fisher's exact test, if Cochran's rules were not met. The distribution of categorical variables was assessed using the chi-square goodness-of-fit test. The significance level considered was 5%.

## Results

The total number of episodes for all causes by year, gender and age are described in table 1. The total number of episodes in our ED was higher in 2016 ($p < 0.001$). In every period of our study, there was a statistically significant higher number of females ($p = 0.037$) and adolescents ($p < 0.001$) assessed in our ED. In 2007/2008 there was a higher prevalence than expected of males (47.2%) [ri = 2.7] and children below 12 years of age (24.0%) [ri = 4.8].

Table 2 describes the prevalence of admissions for SA, SI and NSSI in four separate 12-month periods. The number of SA with drug intoxication was significantly higher in the 2007-2008 period (18.7%, $p = 0.038$). SI (6.4%, $p = 0.001$) and NSSI (7%, $p = 0.001$). Admissions were higher between March 2019 and February 2020. Table 3 describes each cause of the admissions by year, gender and age. Statistically significant differences were only found regarding gender in cases of SI, with a higher number of females in every period ($p = 0.006$).

To study the impact of the COVID-19 pandemic on the number of admissions to our ED for SA, NSSI and SI, we compared the period from March to May 2019 with the same three months in 2021, which corresponds to the time when the second lockdown measures were lifted in Portugal. These results are described in table 4. We observed an increase of almost double (98.43%, $p < 0.001$) the number of emergency episodes in March-May 2021 compared to the same period in 2019. In March-May 2021, there was a higher number of

**Table 1.** Distribution of admissions to our emergency department by gender and age

| | July 2007-June 2008 (12 months) | 2016 (12 months) | March 2019-February 2020 (12 months) | March 2020-February 2021 (12 months) | p |
|---|---|---|---|---|---|
| Total number of admissions to ED | 975 | 1136 | 1032 | 916 | p < 0.001 (a) |
| Female | 515 (52.8%) [–2.7] | 649 (57.1%) [0.5] | 587 (56.9%) [0.3] | 543 (59.3%) [2.0] | p = 0.037* (a)† |
| Male | 460 (47.2%) [2.7] | 487 (42.9%) [–0.5] | 445 (43.1%) [–0.3] | 373 (40.7%) [–2.0] | |
| < 12 years | 234 (24.0%) [4.8] | 215 (18.9%) [0.2] | 193 (18.7%) [0.0] | 119 (13.0%) [–5.1] | p < 0.001* |
| > 12 years | 741 (76.0%) [–4.8] | 921 (81.1%) [–0.2] | 839 (81.3%) [0.0] | 797 (87.0%) [5.1] | |

*p < 0.05; p-value calculated using either (a)† chi-square goodness-of-fit test, (a) Chi-square test of association, or Fisher's exact test; with p < 0.05, the [adjusted standardized residual] is provided, which assesses the differences between observed and expected frequencies and is considered statistically significant when it is < 1.96 or > 1.96.

**Table 2.** Distribution of admissions for suicide attempts, suicidal ideation without suicidal behavior and non-suicidal self-injury to our emergency department

| | July 2007-June 2008 (12 months) | 2016 (12 months) | March 2019-February 2020 (12 months) | March 2020-February 2021 (12 months) | p |
|---|---|---|---|---|---|
| SA with drug intoxication | 183 (18.7%) | 171 (15.1%) | 147 (14.2%) | 137 (15.0%) | p = 0.038 (a)† |
| SA with other suicidal behavior | 11 (1.1%) | 12 (1.1%) | 14 (1.4%) | 20 (2.2%) | p = 0.331 (a)† |
| SI without suicidal behavior | 31 (3.2%) | 41 (3.6%) | 66 (6.4%) | 60 (6.6%) | p = 0.001 (a)† |
| NSSI | 25 (2.56%) | 68 (6%) | 72 (7%) | 65 (7.1%) | p < 0.001 (a)† |

*p < 0.05; p-value calculated using either (a)† chi-square goodness-of-fit test, (a) Chi-square test of association, or Fisher's exact test; with p < 0.05, the [adjusted standardized residual] is provided, which assesses the differences between observed and expected frequencies and is considered statistically significant when it is < 1.96 or > 1.96.
SA: suicide attempt; SI: suicide intent; NSSI: non-suicidal self-injury.

admissions for SA with drug intoxication (p < 0.001), SI (p = 0.008) and NSSI (p < 0.001). We found a higher prevalence than expected of females with NSSI (86.4%) (RI = 2.7) from March to May of 2021.

## Discussion

We compared admissions to a pediatric mental health ED for NSSI, SI and SA in five different time periods between 2007 and 2021. We may assume that there was no increase in admissions for SA over the span of our study, with the most admissions for SA with drug intoxications being reported in 2007/2008 (18.7%). In the other periods included in our study, the number of admissions for SA with drug intoxications remained relatively stable, with a prevalence of around 15%. Our findings are in line with the literature. Evidence from recent decades concerning temporal trends of SA in pediatric age is limited and mainly based on the high school Youth Risk Behavior Survey by the U.S. Centers of Disease Control and Prevention[35]. It reports that the overall prevalence of SA in 2017 (7.4%) was almost the same as in 1991 (7.3%). A study from Xiao et al. also reports stable trends in non-fatal SA in recent decades[36]. A Dutch study reported a decrease in SA over a 5-year period from 2010 to 2015[37].

However, we found an increase in emergency admissions for NSSI when comparing admission numbers between 2007/2008 (2.56%) with the other periods (6-7%). Recently, there has been a notable rise in ED visits worldwide due to self-harm among adolescents[38,39]. Our results point to an increase of NSSI in adolescents over recent years, in line with what is described in the literature. A study performed in Turkey, that analyzed admissions to a pediatric mental health ED between 2012 and 2017, reported similar numbers of admissions for NSSI (10.7%) to our study (between 6 and 7%)[9]. McCluskey et al. characterized admissions for NSSI in a pediatric ED between 2009 and 2013 and found a greater prevalence of NSSI in females and in older adolescents, which is in line with our results[40]. Contrary to our findings, they found a decrease in

**Table 3.** Distribution of admissions for suicide attempts, suicidal ideation without suicidal behavior and non-suicidal self-injury to our emergency department by gender and age

| | July 2007-June 2008 (12 months) | 2016 (12 months) | March 2019-February 2020 (12 months) | March 2020-February 2021 (12 months) | p |
|---|---|---|---|---|---|
| SA with drug intoxication | 183 (18.7%) | 171 (15.1%) | 147 (14.2%) | 137 (15.0%) | p = 0.038 (a)† |
| Male | Not assessed | 33 (19.3%) | 25 (17.0%) | 27 (19.7%) | p = 0.836 (a) |
| Female | Not assessed | 138 (80.7%) | 122 (83.0%) | 110 (80.3%) | |
| < 12 years | Not assessed | 3 (1.8%) | 2 (1.4%) | 3 (2.2%) | p = 0.908 (b) |
| > 12 years | Not assessed | 168 (98.2%) | 145 (98.6%) | 134 (97.8%) | |
| SA with other suicidal behaviors | 11 (1.1%) | 12 (1.1%) | 14 (1.4%) | 20 (2.2%) | p = 0.331 (a)† |
| Male | Not assessed | 5 (41.7%) | 3 (21.5%) | 11 (55.0%) | p = 0.147 (a) |
| Female | Not assessed | 7 (58.3%) | 11 (78.6%) | 9 (45.9%) | |
| < 12 years | Not assessed | 0 (0%) | 2 (14.3%) | 2 (10.0%) | p = 0.557 (b) |
| > 12 years | Not assessed | 12 (100%) | 12 (85.7%) | 18 (90.0%) | |
| SI without suicidal behavior | 31 (3.2%) | 41 (3.6%) | 66 (6.4%) | 60 (6.6%) | p = 0.001 (a)† |
| Male | 3 (9.7%) [–3.1] | 17 (41.5%) [1.2] | 29 (43.9%) [2.1] | 18 (30.0%) [–0.8] | p = 0.006* (a) |
| Female | 28 (90.3%) [3.1] | 24 (58.5%) [–1.2] | 37 (56.1%) [–2.1] | 42 (70.0%) [0.8] | |
| < 12 years | Not assessed | 1 (2.4%) | 4 (6.1%) | 5 (8.3%) | p = 0.549 (b) |
| > 12 years | Not assessed | 40 (97.6%) | 62 (93.9%) | 55 (91.7%) | |
| NSSI | 25 (2.56%) | 68 (6%) | 72 (7%) | 65 (7.1%) | p < 0.001 (a)† |
| Male | 2 (8.0%) [–2.3] | 18 (26.5%) [–0.2] | 24 (33.3%) [1.4] | 19 (29.2%) [0.4] | p = 0.105 (a) |
| Female | 23 (92.0%) [2.3] | 50 (73.5%) [0.2] | 48 (66.7%) [–1.4] | 46 (70.8%) [–0.4] | |
| < 12 years | Not assessed | 2 (2.9%) | 6 (8.3%) | 1 (1.5%) | p = 0.155 (b) |
| > 12 years | Not assessed | 66 (97.1%) | 66 (91.7%) | 64 (98.5%) | |

*p < 0.05; p-value calculated using either (a)† chi-square goodness-of-fit test, (a) Chi-square test of association, or (b) Fisher's exact test; with p < 0.05, the [adjusted standardized residual] is provided, which assesses the differences between observed and expected frequencies and is considered statistically significant when it is < 1.96 or > 1.96.
SA: suicide attempt; SI: suicide intent; NSSI: non-suicidal self-injury.

**Table 4.** Comparison of admissions for suicide attempts, suicidal ideation without suicidal behavior and non-suicidal self-injury to our emergency department by gender and age in the pre and post-pandemic period

| | March-May 2019 | March-May 2021 | p |
|---|---|---|---|
| Total number of episodes in ED | 254 | 504 | p < 0.001 (a)† |
| Female | 147 (57.9%) [–3.1] | 348 (69.0%) [3.1] | p = 0.002* (a) |
| Male | 107 (42.1%) [3.1] | 156 (31.0%) [–3.1] | |
| < 12 years | 45 (17.7%) [2.2] | 60 (11.9%) [–2.2] | p = 0.029* (a) |
| > 12 years | 209 (82.3%) [–2.2] | 444 (88.1%) [2.2] | |
| SA with drug intoxication | 40 | 88 | p < 0.001 (a)† |
| Male | 5 (12.5%) | 11 (12.5%) | p > 0.990 (b) |
| Female | 35 (87.5%) | 77 (87.5%) | |
| < 12 years | 0 (0%) | 2 (2.3%) | p > 0.990 (b) |
| > 12 years | 40 (100%) | 86 (97.7%) | |
| SA with other suicidal behaviors | 4 | 2 | p = 0.414 |
| Male | 1 (25.0%) | 1 (50.0%) | p > 0.990 (b) |
| Female | 3 (75.0%) | 1 (50.0%) | |
| < 12 years | 1 (25.0%) | 1 (50.0%) | p > 0.990 (b) |
| > 12 years | 3 (75.0%) | 1 (50.0%) | |
| SI without suicidal behavior | 16 | 35 | p = 0.008 (a)† |
| Male | 7 (43.8%) | 8 (22.9%) | p = 0.187 (b) |
| Female | 9 (56.3%) | 27 (77.1%) | |
| < 12 years | 2 (12.5%) | 1 (2.9%) | p = 0.229 (b) |
| > 12 years | 14 (87.5%) | 34 (97.1%) | |
| NSSI | 25 | 59 | p < 0.001 (a)† |
| Male | 10 (40.0%) [2.7] | 8 (13.6%) [–2.7] | p = 0.007 (a) |
| Female | 15 (60.0%) [–2.7] | 51 (86.4%) [2.7] | |
| < 12 years | 2 (8.0%) | 1 (3.4%) | p = 0.591 (b) |
| > 12 years | 23 (92.0%) | 28 (96.6%) | |

*p < 0.05; p-value calculated using either (a)† chi-square goodness-of-fit test, (a) Chi-square test of association, or (b) Fisher's exact test; with p < 0.05, the [adjusted standardized residual] is provided, which assesses the differences between observed and expected frequencies and is considered statistically significant when it is < 1.96 or > 1.96.
SA: suicide attempt; SI: suicide intent; NSSI: non-suicidal self-injury.

admissions for NSSI in older adolescents during their study period, with an increase of NSSI and SA in children aged 11-12. A Spanish study reported that among 328 mental health emergencies in a pediatric ED, self-harm behavior, irrespective of the degree of suicidal intent, was the second most common reason for visits in females (29%)[41]. In a study conducted in Canada, 45% of the 468 cases involving young people who sought help for mental health emergencies reported engagement in NSSI within the preceding 24 hours[42].

Multiple systematic reviews and meta-analyses have documented an increase in anxiety, depression and post-traumatic symptoms among children and adolescents, with approximately 20% of adolescents reporting mental health difficulties[43,44]. A meta-analysis by Racine at al. reported a 25% prevalence of depressive symptoms in adolescents worldwide, with rates of anxiety symptoms doubling the pre-pandemic levels[44]. We contend that during the second year of the pandemic, the combined effects of stressors linked to school reopening culminated in heightened anxiety and depressive symptoms associated with reconnecting with peers and facing academic challenges. Consequently, this could potentially contribute to a rise in self-harm and suicidality among adolescents struggling with emotional regulation.

As verified in our research, several studies indicate a substantial increase in cases of pediatric psychiatric emergencies following the initial acute phase of the COVID-19 pandemic (at the start of 2021), including episodes of both suicidal and non-suicidal self-harm. Steeg et al. reported an increase of suicidal and non-suicidal self-harm behavior in adolescents admitted to a pediatric ED in Manchester between August 2020 and May 2021, compared to 2019[45]. Yard et al. found an increase in SA in adolescents between February and March 2021 in the United States[46]. During this difficult period, increased personal and social stress among adolescents and difficulties in regulating their emotions were associated with engagement in NSSI[47]. During the COVID-19 pandemic, considerable attention was directed towards loneliness and self-harm experiences among adolescents. The exacerbation of loneliness among young people during lockdown was associated with an increase in the odds of self-harm[48]. Cozzi et al. showed that pediatric ED admissions related to SA and eating disorders in adolescents had the most significant increase in the second year of the pandemic compared to both the first and the pre-pandemic years, with an increase of 72% in NSSI cases and 188% in admissions for SA[49]. A multicenter study conducted in Germany revealed a 2.84-fold increased risk of intensive care unit admission due to suicide attempts among adolescents aged 12 – 17 during the second year of the pandemic compared to preceding years[50]. Jung et al. showed an increase in SA in adolescents in Korea in 2021 (2.2%) and 2022 (2.5%), when compared to 2020 (1.9%)[51]. A study conducted in Spain reported increased ED admissions during the aftermath of the COVID-19 lockdown among adolescent females, with statistically significant increases in self-harm behavior and suicide attempts[52].

Our study has some limitations. Firstly, we compared five isolated periods of time across 14 years, based on previous studies performed in our department, as we did not have access to data regarding every year between 2007 and 2021. This may have influenced some of our assumptions. Secondly, it is not possible to infer the severity of the NSSI and suicidal behavior or their diagnostic framework, as the study of these did not fall within the scope of this paper.

However, our research has several strengths. To our knowledge, it is the first study to examine admissions for self-injury and suicidality in a Portuguese pediatric ED over a large period spanning more than a decade. Besides, due to its longitudinal nature, the study allowed for a more appropriate evaluation of trends and prevalence rates of self-injurious behaviors in childhood and adolescence over recent years.

In conclusion, in recent years, we found that NSSI and SI without suicidal behavior have increased in pediatric mental health ED. However, we did not find an increase in admissions for SA. Despite the limitations of our study, these findings are in line with trends reported in the literature. Moreover, according to recent studies, we found a steep increase in self-harm-related ED admissions in children and adolescents following the acute period of the COVID-19 pandemic.

## Authors' contribution

P. Carvalho-e-Marques: 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; Anayisis 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. O. Queirós: 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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## Conflicts of interest

None.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on publishing patient data.

**Right to privacy and informed consent.** The authors have obtained written informed consent from the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any kind of generative artificial intelligence for drafting this manuscript, nor for creating images, graphics, tables or their corresponding captions.

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ORIGINAL ARTICLE

# Burkitt lymphoma in children and adolescents: a single-center analysis over a 30-year period

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## Abstract

**Introduction and Objectives:** Burkitt lymphoma (BL) is a fast-growing and highly aggressive type of non-Hodgkin lymphoma. Nevertheless, 80-90% of patients on risk-adapted chemotherapy survive. The aim of this study was to characterize a pediatric population with BL in a center of reference, determine the 30-year incidence and calculate event-free and overall survival. **Methods:** We performed a retrospective and observational analysis of all patients diagnosed with BL between January 1993 and December 2022. Demographic and clinical data was collected. Patients were staged according to the St. Jude classification system and treated with different protocols according to risk stratification. A descriptive analysis, Portuguese central region incidence calculation and survival analysis were performed. **Results:** A total of 48 patients were included, 85% of which were male, with a mean age of 7.8 ± 3.7 years. Most cases (95.8%) were sporadic. The mean incidence rate was 0.34 cases per 100,000 person-years. Most (50%) patients were St. Jude stage III. A total of 41% were admitted to the pediatric intensive care unit (PICU), mostly due to tumor lysis syndrome (78.9%). The mortality rate was 6.3%. The mean follow-up was 87.8 ± 59.0 months with a 3-year event-free survival rate of 88.9% and overall survival rate of 93.2%. Subgroup analysis showed no differences between chemotherapy protocols. Higher uric acid was independently associated with PICU admission. **Discussion:** Our results regarding incidence and mortality are in line with previously-published literature. Notably, the last patient who died in our center was diagnosed 18 years ago. In conclusion, our results contribute to a better understanding of the epidemiology, clinical course and outcomes of BL in Portugal's pediatric population.

***Keywords:*** Burkitt lymphoma. Survival. Pediatric oncology.

## *Linfoma de Burkitt em idade pediátrica: 30 anos de experiência de um centro terciário*

## Resumo

**Introdução e Objetivos:** O linfoma de Burkitt (LB) é um linfoma não-Hodgkin agressivo mas 80-90% das crianças submetidas a quimioterapia adaptada sobrevivem. Este estudo pretendeu caraterizar a população pediátrica com LB seguida num centro de referência, determinar a incidência em 30 anos e calcular a sobrevida global/sem eventos. **Métodos:** Análise retrospetiva de doentes com diagnóstico de LB no período de janeiro 1993 a dezembro 2022. Foram colhidos dados demográficos e clínicos. Os pacientes foram estadiados de acordo com a classificação de St Jude e tratados com diferentes protocolos de acordo com a estratificação de risco. Foi realizada análise descritiva, cálculo de incidência na região Centro de Portugal e análise de sobrevida.

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**Resultados:** Incluídos 48 doentes, 85% do sexo masculino, idade média de 7,8 ± 3,7 anos. A maioria (95,8%) foi do tipo esporádico. A taxa média de incidência foi de 0,34 casos/100.000 pessoas-ano. A maioria (50%) estava no estágio III de St. Jude. Um total de 41% foram internados na Unidade de Cuidados Intensivos Pediátricos (UCIP), sobretudo por síndrome de lise tumoral (78,9%). A taxa de mortalidade foi de 6,3%. A duração média do follow-up foi de 87,8 ± 59,0 meses, com uma taxa de sobrevida livre de eventos aos 3 anos de 88,9% e uma taxa de sobrevida global de 93,2%. A análise de subgrupos não identificou diferenças entre protocolos de quimioterapia. Nível de ácido úrico elevado é um preditor independente de admissão na UCIP.
**Discussão:** Em conclusão, os nossos resultados contribuem para uma melhor compreensão da epidemiologia, evolução clínica e *outcomes* do LB na população pediátrica em Portugal.

***Palavras-chave:*** Linfoma de Burkitt. Sobrevida. Oncologia pediátrica.

## Keypoints

**What is known**
– BL is an aggressive neoplasia with significant morbimortality.

**What is added**
– Incidence and survival in Portugal is further characterized.
– With new protocols, survival is the norm.

## Introduction

Every year, around 400 children and adolescents are diagnosed with cancer in Portugal. Although it still is the leading cause of non-accidental death in this population, it is expected that more than 80% of these children and adolescents survive due to remarkable advancements in diagnosis and treatment. Leukemia, central nervous system malignancies and lymphoma are the most prevalent cancers[1,2].

Burkitt lymphoma (BL) is a rare, but highly aggressive, rapid-growing B-cell non-Hodgkin lymphoma. Three distinct subtypes of BL are recognized, with different epidemiology, risk factors and clinical presentations: endemic, sporadic and immunodeficiency-associated[3].

Sporadic BL occurs worldwide, with most cases in the United States and Western Europe. It is relatively more common in the pediatric population, accounting for 30% of pediatric lymphomas, with a peak incidence around the age of 10[4,5]. The most common site of involvement is intrabdominal, mainly the bowel[6]. The endemic subtype occurs in equatorial Africa and the most frequent presentation is a facial tumor that involves the mandible[6,7]. This subtype is closely associated with malaria and the Epstein-Barr virus. However, the underlying mechanisms and the relationship between the etiological factors and this subtype is still poorly understood[8]. Immunodeficiency-associated BL is most commonly seen in HIV-positive patients, but may also be seen in recipients of organ transplants and patients with congenital immunodeficiencies[4,6]. The most common sites of involvement include the lymph nodes, bone marrow and central nervous system[8].

Pathologically, BL is characterized by the translocation and deregulation of the MYC gene on chromosome 8, which encodes the c-myc protein transcription factor that regulates cell proliferation, differentiation and apoptosis, and therefore has the potential to involve multiple organ systems[4,9]. Overexpression of this c-myc protein leads to rapid B-cell proliferation, accounting for the rapid doubling time of BL tumor cells (between 24 and 48 hours)[10].

Histologically, BL has a “starry sky” appearance with benign histiocytes containing plentiful, clear cytoplasm dispersed among a background of basophilic tumor cells. High rates of proliferation and apoptotic cell death are generally observed (Ki-67+ fraction approaching 100 percent)[5,11].

Although a definitive diagnosis is confirmed through the histopathological evaluation of involved tissue (biological, immunophenotyping and genetic testing), imaging is essential throughout the entire clinical course of these patients: for diagnosis, staging and evaluating treatment response and potential therapy-related complications. The adoption of a multimodal approach is crucial in the management of BL with ultrasound, computed tomography, magnetic resonance imaging and positron emission tomography playing a role whenever necessary[12-15].

Chemotherapy is the mainstay of therapy in BL, with a similar approach regardless of the subtype. Given the effectiveness of chemotherapy regimens and often widespread disease at presentation, there is no role for radiation therapy. Current treatment options, with either a shorter or longer duration, employ intensive multiagent regimens[4,16].

Children and adolescents with BL require intensive treatments and prolonged hospitalization, which can have a negative impact on their quality of life[17]. Moreover, patients may experience several side effects from their treatments as well as the emotional distress associated with an oncological diagnosis[18].

Despite BL's aggressive behavior, 80 - 90% of patients on risk-adapted chemotherapy survive and reach adulthood in the developed world[19,20].

The primary aims of this study were to provide a demographic and clinical description of our population of BL patients and to calculate the overall, sex-specific and age-specific incidence rate of BL in the central region of Portugal. By way of secondary aims, we intended to evaluate prognostic factors and calculate overall survival and event-free survival.

## Materials and methods

### Study design and ethical approval

We performed a retrospective, observational and non-interventional study, based on the records of all children and adolescents with a diagnosis of BL, over a 30 year-period, at the Pediatric Oncology Department of the Centro Hospitalar e Universitário de Coimbra (CHUC). This unit provides care to all children and adolescents with cancer, diagnosed up to the age of 17 years old, in the central region of Portugal. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of CHUC.

### Study population and instrument

The study sample included all children and adolescents with BL from the Pediatric Oncology Department – CHUC, during the period between January 1993 and December 2022 (30 years).

### Data collection

All data was obtained from the patients' clinical and laboratory records. Analyzed variables included: age at diagnosis, sex, clinical presentation, St. Jude stage (stages I – IV), initial lactate dehydrogenase (LDH) and uric acid (UA), treatment protocol, therapeutic regimen and its duration, events (relapse/refractory disease, secondary cancer or death) and development. The resident population of the central region of Portugal by age and sex between 1993 and 2022 was provided by data collected from the Portuguese National Statistics Institute.

### Therapy and evaluation

Patients were stratified by stage as defined by Murphy at the St. Jude Children's Research Hospital. This staging system is primarily based on the clinicopathological features of childhood BL: the number and anatomical pattern of disease sites, their resectability and the involvement of bone marrow (BM) and the central nervous system (CNS). Patients with resected stage I and resected abdominal-only stage II disease are treated with the group A regimen. Patients with unresected stage I/II, III or CNS-negative stage IV disease with fewer than 25% of blasts in BM are treated with the group B regimen. Patients with ≥ 25% blasts in BM or with CNS involvement are treated with the group C regimen.

At diagnosis, risk groups were stratified as A, B (I or II) or C (1 or 3) according to the tumor stage, resectability (complete/incomplete) and initial LDH level (</≥ two times the upper limit of normal) with treatment intensity adjusted according to the risk group.

Favorable-risk patients were defined as patients with stage I, stage II and low LDH stage III. High-risk patients were defined as patients with high LDH stage III and stage IV disease.

In our institution, over the last three decades, patients were treated using the LMB84 protocol from 1991 to 1995, the LMB89 protocol from 1996 to 2000 and the FAB/LMB96 protocol from 2001 to 2017.

More recently, rituximab has been added in children and adolescents with disseminated (high-risk) mature B-NHL in the Inter-B-NHL ritux 2010 protocol since 2018.

After treatment, patients were followed up at 30-day intervals during the first year, three-month intervals for one semester and six-month intervals until they had completed three years out of treatment. Thereafter they had yearly follow-up appointments.

### Statistical analysis

Categorical variables were expressed as percentages and frequencies, while continuous variables were expressed as mean and standard deviation (SD).

We estimated incidence rates of BL (cases per 100,000 person-years) by sex (male and female), age group (0-4, 5-9, 10-14 and 15-19) and calendar-year (1993-2002, 2003-2012 and 2013-2022). We estimated the population at risk during the study period by extrapolating from the population of Portugal's central region, obtained in the national census. We calculated the incidence rates and their 95% confidence intervals.

Survival analysis was performed by plotting Kaplan-Meier survival curves. For the event-free survival

sub-analysis, the following factors were considered: relapse, progressive disease, secondary malignancy and death from any cause. Cox regression was used for subgroup survival analysis.

All potential risk factors for adverse events and death were investigated by univariate (chi square and Mann-Whitney, as appropriate) and multivariate analysis (logistic regression).

All p-values were two-tailed and considered significant if < 0.05. For statistical analysis, SPSS® Statistics version 29 was used.

## Results

### *Demographic and clinical patients' characteristics*

During the 30-year period, 48 children and adolescents were diagnosed with BL in our center. The distribution of new BL cases and the incidence rate (per 100,000) of BL in the central region of Portugal between 1993 and 2022 is shown in figure 1.

The new diagnosis mean was 1.6 cases per year and the mean age at diagnosis was 7.8 years (± 3.7). There was a predominance of the male sex (85%) and most cases were diagnosed in children aged five to nine (60%). All patients' demographic and clinical characteristics are summarized in table 1.

In terms of the clinical presentation of the disease, we registered two cases of immunodeficiency-associated BL (one case of AIDS and one of post-transplantation lymphoproliferative disease), while the rest were sporadic. There were no cases of endemic/African BL identified in our study.

The most common sites of involvement were the abdomen (54%) and jaw (25%). BL tumors arose on the nasopharynx and bone marrow (also called Burkitt cell leukemia) in 8.5% of cases and on the CNS in 4% of cases. During the initial investigation, infiltration of BM (39.6%), the kidney (39.6%) and the CNS (31.3%) was found.

Serum LDH levels at diagnosis were available for all patients with a mean serum LDH of 2321 IU/L (311-10730). Serum uric acid levels were available for 47 patients with a mean value of 455 μmol/L (71-1500).

Three patients (6%) received the LMB-84 protocol, 10 patients (21%) the LMB-89 protocol, 25 patients (52%) the FAB/LMB96 protocol and 10 (21%) the Inter-B-NHL ritux 2010 protocol. The mean treatment duration was 6.8 ± 2 months.

There were 19 (41%) admissions to the Pediatric Intensive Care Unit (PICU), most due to risk/tumor lysis syndrome (78.9%). There was no information regarding PICU admission for two patients diagnosed in 1993. All patients diagnosed with BL from 1993 to 2000 (n = 7) were admitted to the PICU. In contrast, since 2001 only 31% (n = 12) have undergone the same (p < 0.001).

The lethality rate was 6.3% (n = 3). The deaths were attributed to infection (n = 1, 1997), relapse (n = 1, 2005) and refractory disease (n = 1, 2005). In this 30-year period, two more events occurred, namely a relapse (1999) and secondary acute myeloblastic leukemia (2007). Both were subject to BM transplantation and are alive (out of treatment).

**Table 1.** Baseline demographic and clinical characteristics of children and adolescents with BL (n = 48)

| | n | % |
|---|---|---|
| Types of BL | | |
| Sporadic (non-African) | 46 | 96 |
| Immunodeficiency-associated | 2 | 4 |
| Sex | | |
| Male | 41 | 85 |
| Female | 7 | 15 |
| Age group (years) | | |
| (0-5) | 10 | 21 |
| (5-10) | 24 | 50 |
| (10-15) | 13 | 27 |
| (15-19) | 1 | 2 |
| Calendar year | | |
| (1993-2002) | 10 | 21 |
| (2003-2012) | 24 | 50 |
| (2013-2022) | 14 | 29 |
| Clinical presentation (site) | | |
| Abdomen | 26 | 54 |
| Jaw | 12 | 25 |
| Nasopharynx | 4 | 8.5 |
| Bone marrow | 4 | 8.5 |
| CNS | 2 | 4 |
| St. Jude staging | | |
| II | 1 | 2 |
| III | 24 | 50 |
| IV | 23 | 48 |
| Therapeutic scheme | | |
| B | 25 | 52 |
| C | 23 | 48 |
| Events | | |
| Relapse/refractory disease | 1 | 2 |
| Secondary cancer | 1 | 2 |
| Death | 3 | 6 |

### *Overall, age- and sex-specific BL incidence*

Overall BL incidence rates in Portugal's central region did not vary significantly by year (Fig. 1). The incidence

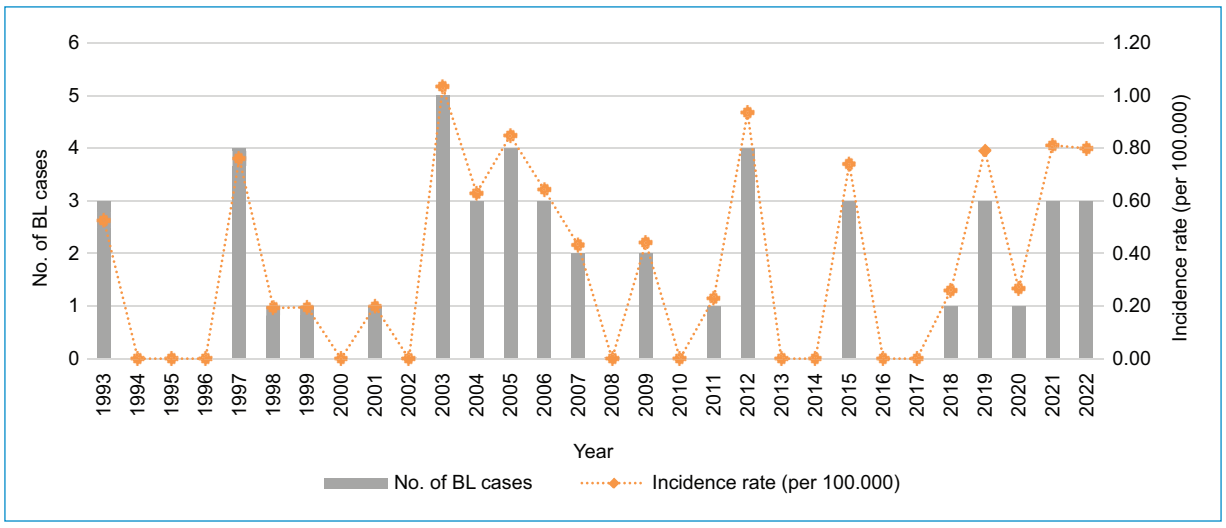


**Figure 1.** Distribution of BL cases per year in the central region of Portugal (n = 48).

rate was 0.34 cases per 100,000 person-years (95% CI 0.25-0.45) and was higher among boys than girls (0.55 vs. 0.11, respectively; p < 0.001), with this male predominance existing in all age groups (Fig. 2).

BL incidence rates increased rapidly with age from 0.34 cases per 100,000 person-years among children of age 0-4 years to 0.76 among those of age 5-9 years, then declined slightly among children aged 10-14 years before decreasing substantially at 15-19 years to the value of 0.03 cases per 100,000 person-years.

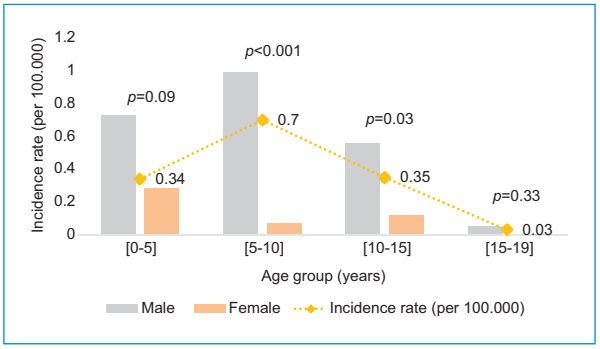


**Figure 2.** Age- and sex-specific incidence rates (per 100,000) of BL cases in the central region of Portugal (n = 45).

### *Survival analysis and prognostic factors*

Average patient follow-up was 87.8 ± 59.0 months, with a 3-year event-free survival rate of 88.9% and a 3-year overall survival rate of 93.2% (Fig. 3). By analyzing patients based on regimens used (B or C), we observed a 3-year event-free survival rate of 91.8% vs. 85.2% (p = 0.543) and a 3-year overall survival rate of 95.8% vs 89.8% (p = 0.533), respectively.

We found that increased uric acid levels were independently associated with PICU admission (p = 0.006; OR 1.004, 95% CI 1.001-1.006). However, the risk of adverse events and death was not independently associated with PICU admission, LDH and/or uric acid level, age at diagnosis, sex, the protocol used or the length of treatment.

## Discussion

Our results show an incidence rate of 0.34 BL cases per 100,000 person-years in the central region of Portugal, based on national data, which is in line with the published literature[21-23].

We also observed a slight increase in the incidence trend of BL in the last two decades compared to the first one, in keeping with previous reports[24]. The mechanisms underlying this trend are yet to be clarified.

The mean age at diagnosis and the mid-childhood peak incidence are in line with other studies conducted both in Portugal[25] and internationally[22,23,26-28].

A strong male predominance is a hallmark characteristic of this malignancy. These findings suggest that male sex itself may be an intrinsic risk factor for BL. This could be explained by the role of recessive genetic factors on sex chromosomes[29], such that a subset of X-chromosome genes can escape X-inactivation, protecting females from complete functional loss by a single mutation[30].

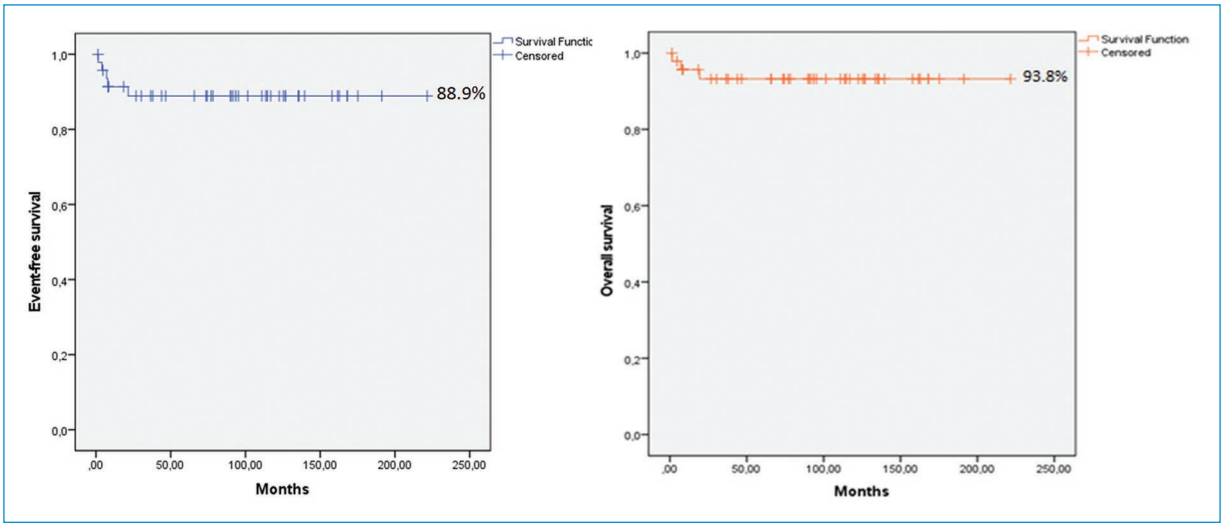


**Figure 3.** Kaplan-Meier event-free survival and overall survival curves of patients with BL (n = 48).

Most patients had a primary abdominal tumor. This is in line with it being the most frequent clinical presentation of the sporadic variant, which is the most prevalent type in Western Europe and the United States[5,6].

Serum LDH and UA levels seem to be important adverse prognostic factors. LDH levels in our study were higher when compared with previous studies from both European and non-European countries[26,31]. This could be explained by a larger tumor burden. However, there is insufficient available data to confirm this hypothesis. Our results support UA as a mark of poor prognosis, with higher levels being associated with a higher risk of admission to the PICU. However, we were not able to find a correlation between mortality and PICU admissions, LDH levels, UA levels, age at diagnosis, sex, the protocol used or the length of treatment. This may be justified by the low total number of adverse events and deaths in our population, limiting statistical inference.

Rasburicase, a recombinant urate oxidase, approved in February 2001, is recommended for the treatment and prophylaxis of acute hyperuricaemia[32]. In our study, tumor lysis syndrome or patients at a higher risk of tumor lysis syndrome were the most frequent cause of PICU admission. From 2001, admissions in this unit were significantly lower compared to the previous period. These findings suggest that rasburicase could be associated with a reduction in PICU admissions, since its use is now routine in BL treatment protocols in our center.

In the past few years, there has been substantial improvement in the prognosis of pediatric high-risk BL. Currently, the addition of dose-dense rituximab to FAB/LMB96 chemotherapy backbones is the main approach in children and adolescents with BL in Portugal, particularly in our center.

Overall and event-free survival were in line with the published literature, including two randomized trials for LMB96 and Inter-NHL ritux 2010 protocols[24,33,34]. Notably, the last patients who died were diagnosed with BL 18 years ago.

Chemotherapy-induced toxicity (mucositis, infection and myelosuppression) is a major endpoint but was not analyzed in our study, as this data was unavailable.

Our study is limited by the small sample, the fact that we only studied the population of a single center, the fact that it is retrospective and that cases are spread over a long period of time. Its strengths are that it was conducted in a center of reference, making the sample representative of the entire central region of Portugal.

Future studies relying on bigger samples and prospectively conducted, could result in a better evaluation and confirmation of our findings.

## Conclusion

Our study shows that BL in the central region of Portugal has a male predominance and a peak incidence in mid-childhood. Due to our low mortality rate, we could not determine a correlation between the prognostic factors, admissions to the PICU, age or sex and death, but we managed to prove an independent association between increased UA levels and PICU admission.

In conclusion, our results contribute to the understanding of BL epidemiology, clinical course and outcomes in Portugal's pediatric population.

### Authors' contribution

I. Pedrosa: 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; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. A.M. Figueiredo: 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; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. A.S. Simões: Conception and design of the study, report, review or other type of work or paper; Drafting the article; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. I. Luz, M. Jerónimo, S. Silva, and A. Carvalho: 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. Brito: 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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None.

### Conflicts of interest

None.

### Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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# Panniculitis in pediatric rheumatology practice: experience of a pediatric referral center

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## Abstract

**Introduction and Objectives:** Panniculitis is a group of disorders characterized by inflammation of the subcutaneous adipose tissue. We aim to characterize patients with panniculitis monitored in a Pediatric Rheumatology Unit. **Methods:** Descriptive, cross-sectional, retrospective study, from January 2004 to December 2020. Demography, clinical characteristics, laboratory tests, skin biopsy and treatment were evaluated. Patients were divided into two groups: erythema nodosum (EN) and non-erythema nodosum (non-EN). Non-EN panniculitis was confirmed by histology. Exclusion criteria: atypical EN without a biopsy. Laboratory and clinical characteristics were compared. **Results:** Twenty-seven patients were enrolled (girls: 70%; median age of onset: 11 years). The main etiologies of EN (n = 19) were undetermined (37%), streptococcal infection (32%) and Crohn's disease (11%). All patients with EN reported pain, 26% fever and 11% weight loss; 100% were treated with non-steroidal anti-inflammatory drugs (first-line therapy). Eight cases of non-EN panniculitis were included: lipoatrophic panniculitis (n = 3), lupus panniculitis (n = 2), cytophagic histiocytic panniculitis (n = 1 [CHP]), subcutaneous panniculitis-like T-cell lymphoma (n = 1; SPTCL), cutaneous polyarteritis nodosa (n = 1); 38% presented with nodules, 38% had fever and 38% had painful skin lesions. Seven non-EN panniculitis patients were initially treated with corticosteroids. The patients with CHP and SPTCL went into remission after immunosuppressive treatment and chemotherapy, respectively. The remaining patients were given immunomodulatory therapy. Patients with EN had more painful nodules and arthralgia/arthritis compared to non-EN patients. **Discussion:** New-onset constitutional symptoms during EN follow-up should prompt further investigation. Indurated and discolored nodules/plaques should evoke panniculitis. Histopathology can be helpful in non-EN panniculitis as it can guide towards specific diagnosis and appropriate treatment.

***Keywords:*** Panniculitis. Erythema nodosum. Pediatrics. Rheumatology. Subcutaneous adipose tissue.

## *Paniculites na prática de reumatologia pediátrica: experiência de um centro de referência pediátrica*

## Resumo

**Introdução e Objetivos:** As paniculites são caracterizadas por inflamação do tecido celular subcutâneo. Objetivo de estudo: caracterizar os doentes com paniculite observados numa Unidade de Reumatologia Pediátrica. **Métodos:** Estudo descritivo, transversal, retrospetivo, de janeiro de 2004 a dezembro de 2020. Foram estudados dados demográficos, clínica, exames laboratoriais, biópsia de pele e tratamento de dois grupos: eritema nodoso (EN) e não eritema nodoso (Não-EN). As paniculi-

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tes Não-EN foram confirmadas por histologia. Critérios de exclusão: EN atípico sem histologia. Foram comparadas características laboratoriais e clínicas. **Resultados:** Foram incluídos 27 doentes (raparigas: 80%; idade mediana de início: 11 anos). As principais doenças associadas ao EN (n = 19) foram: indeterminada (37%), infeção estreptocócica (32%) e doença de Crohn (11%). Todos doentes com EN relataram dor, 26% febre e 11% perda de peso; todos foram medicados com anti-inflamatórios não-esteroides. Oito paniculites Não-EN foram incluídas: paniculite lipoatrófica (n = 3), paniculite lúpica (n = 2), paniculite histiocítica citofágica (n = 1; PHC), linfoma subcutâneo de células T tipo paniculite (n = 1; LSCTP) e poliarterite nodosa cutânea (n = 1); 38% apresentou-se com nódulos, 38% tinham febre e 38% dor. Sete paniculites Não-EN foram inicialmente tratadas com corticóides. Os doentes com PHC e LSCTP entraram em remissão após imunossupressão e quimioterapia, respetivamente; os restantes mantém-se sob terapêutica imunomoduladora. Os doentes com EN tiveram mais nódulos dolorosos e artralgia/artrite relativamente aos Não-EN. **Discussão:** Sintomas constitucionais de novo em doentes com EN devem motivar investigação de segunda linha. Nódulos ou placas endurecidas e com alteração da cor devem evocar paniculite. A histopatologia pode ser importante na paniculite Non-EN, orientando para diagnóstico específico e tratamento adequado.

***Palavas-chave:*** Paniculites. Eritema nodoso. Pediatria. Reumatologia. Tecido adiposo subcutâneo.

## Keypoints

**What is known**
- Panniculitis is characterized by inflammation of the subcutaneous adipose tissue, presenting with nodules or plaques. Many of these conditions are rare in pediatric age, leading to a paucity of published case series.
- Erythema nodosum is the most common panniculitis. Infection is its most frequent etiology and in most cases the course of disease is benign. First-line therapy is non-steroidal anti-inflammatory drugs and bed rest.
- Other type of panniculitis, such as conditions associated with autoimmune disease or malignant diseases are rare and potentially severe. They can have a similar presentation (nodules or plaques), making differential diagnosis challenging.

**What is added**
- We present a case series of 27 patients with panniculitis, evaluated by a Pediatric Rheumatology Unit over a seventeen-year span.
- Histopathology, following first-line assessment, is a powerful tool for diagnosis and timely treatment of non-EN panniculitis.
- When possible, early and specific treatment should be offered, as some forms of panniculitis can be disfiguring or may be a sign of severe disease.

## Introduction

Panniculitis is a group of disorders that is rare in children, characterized by inflammation of the subcutaneous adipose tissue. Clinically, they present with solitary or multiple inflammatory subcutaneous nodules and/or infiltrated plaques. They occur mostly in the legs, thighs, buttocks or cheeks, and can be tender and accompanied by systemic symptoms (such as fever, arthralgia, malaise and weight loss)[1].

Etiologies vary, sometimes related to previous or concomitant infection, autoimmune disorders (such as connective tissue diseases or inflammatory bowel disease [IBD]), autoinflammatory disorders (such as familial Mediterranean fever) and even physical factors like trauma or cold weather[1]. There are some well-known pediatric-specific forms of panniculitis, such as subcutaneous fat necrosis of the newborn, cold panniculitis and post-steroid panniculitis and others that can present at any age, such as erythema nodosum (EN)[2]. Other types of panniculitis are rarer, particularly in pediatrics, leading to a paucity of case series in this age group[1].

Despite different etiologies, the initial clinical appearance can be similar, therefore associated symptoms and laboratory examinations can guide initial testing. Even so, ruling out typical EN and subcutaneous fat necrosis of the newborn, a definite diagnosis will only be possible after histological evaluation. Histologically, panniculitis is classified as lobular, septal or mixed, depending on where the inflammatory infiltrate is mainly located[1,3].

The aim of this study is to characterize the patients with panniculitis who were evaluated in a Pediatric Rheumatology Unit over the course of seventeen years.

## Methods

This is a descriptive and retrospective study from January 2004 to December 2020, carried out in a tertiary referral hospital. We included all patients with a confirmed diagnosis of panniculitis evaluated by the Rheumatology team. We divided the patients into two

groups: EN and non-erythema nodosum panniculitis (non-EN).

The diagnosis of EN was based on clinical characteristics: acute multiple nodular (> 1 cm), erythematous violaceous and tender lesions localized in the lower legs (pre-tibial area), with scarless spontaneous resolution up to eight weeks[4]. Patients with an absence of pre-tibial lesions, unilateral and/or ulcerated nodules and lasting longer than 8 weeks, without a histological evaluation, were excluded. The diagnosis of non-EN was based on histological testing.

We evaluated the medical records and included demographic data (age at onset of the disease, sex, disease and follow-up duration); epidemiologic context; clinical characteristics at presentation (fever, weight loss, anorexia, arthralgia, arthritis, oral aphthous ulcers and diarrhea); characteristics of the subcutaneous nodules and/or plaques; treatment and outcome. We reviewed relevant laboratory data: blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tuberculin skin test (TST), interferon gamma release assay test (IGRA), serum immunoglobulins, throat culture, antistreptolysin O titer (ASLO), anti-DNAse B titer, viral serologies, serum angiotensin-converting enzyme (SACE), antinuclear antibodies (ANA) and microbiological cultures (throat and stool). Imaging exams as well as histopathological evaluation of biopsied lesions were also reviewed.

Previous streptococcal infection was defined by a positive rapid antigen detection test (RADT) for Group A *Streptococcus* (GAS) in the four weeks prior to clinical presentation or an elevated ASLO (> 500 U/ml) or Anti-DNAse B titer (> 500 U/ml)[5] with subsequent declining levels. Behcet's disease was diagnosed using the 2015 Pediatric Behçet's Disease Group criteria[6]. Anemia was defined as hemoglobin < -2 standard deviation for age and sex[7] and ESR was considered elevated if > 20 mm/hour.

We compared the clinical and laboratory characteristics of the two groups using SPSS® Statistics 22. A Mann–Whitney U test was used for the continuous variables and Fisher's exact test for the categorical variables. We considered $p < 0.05$ as statistically significant.

## Results

Twenty-seven patients were enrolled, 70% (n = 19) were girls, with a female: male ratio of 2.5:1. The median age at symptom onset was 11 (min. 0.5; max. 17) years. Twenty-three (85%) patients presented with tender, erythematous or violaceous, subcutaneous nodules and six with an area of erythema that progressed to atrophic plaques (Fig. 1). Nineteen patients (70%) had EN and eight (30%) had non-EN panniculitis. Two (7%) were discharged in the first consultation. The remaining patients had a median follow-up duration of 10 (min. 1; max. 120) months.

### *Erythema nodosum (n = 19)*

The median age for presentation was 12 (min. 3; max. 17) years and 68% (n = 13) were girls (eight girls under 12 years of age). The most common associated disease was streptococcal infection (32%). Two had active pharyngitis (RADT positive), two had odynophagia four weeks earlier and two had no history of respiratory symptoms. These last four patients had ASLO and ADNase B titers compatible with previous GAS infection and no evidence of other concurrent etiology. Crohn's disease (CD) was the second most frequent etiology (12%), with EN as the initial manifestation. In 37% of the patients, no underlying etiology was diagnosed. EN was the first sign of CD. Associated diseases, as well as clinical and relevant laboratory examinations, are summarized in table 1.

Eighteen patients (95%) had pre-tibial nodules, two of whom also had lesions on the extensor surface of the arms. One (5%) had nodules only on the posterior surface of the legs. All patients reported pain and had local erythema and heat.

The main reported symptoms were arthralgia in 37%, fever in 26%, asthenia in 21%, arthritis in 16%, odynophagia in 16%, abdominal pain in 16%, weight loss in 11%, ocular disease (uveitis and episcleritis) in 11%, diarrhea in 11% and oral aphthous ulcers in 5%.

Anemia was present in 11% of patients and a CRP level ≥ 6 mg/dl was also found in 11% of cases. Skin biopsies, performed in two patients (11%), showed septal panniculitis without vasculitis.

All patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs) and, when diagnosed, due to its etiology, oral prednisolone (PDN, 1-2 mg/Kg/day) was associated in 16% of patients. Five (26%) were treated with antibiotics at the first observation, two with amoxicillin for GAS pharyngitis (after RADT) and three with flucloxacillin for suspected cellulitis. There was more than one episode in 37%.

Two (with streptococcal associated disease) were discharged in the first Rheumatology consultation and the remaining patients had a median follow-up duration of four (min. 1; max. 84) months. Patients with IBD were followed up in a gastroenterology consultation.

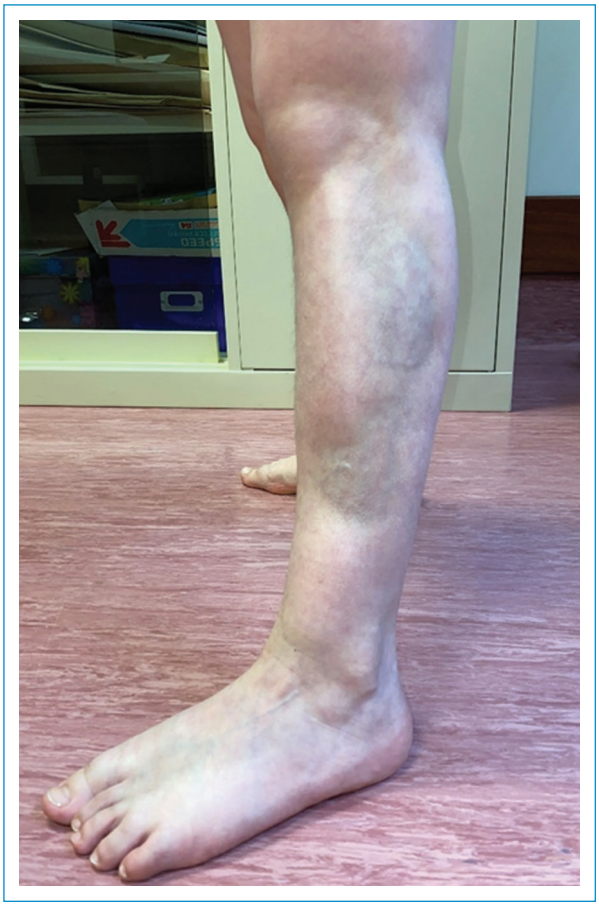

**Figure 1.** Atrophic plaque in a patient (patient 5 [Table 2]) with lipoatrophic panniculitis.

### *Non-erythema nodosum panniculitis (n = 8)*

The median age at presentation was 10.5 (min. 0.5; max. 16) years, the median time until diagnosis was nine (min. 0.5; max. 72) months and the median time of follow-up was 4.5 (min. 0.25; max. 10) years.

The most common diagnosis was lipoatrophic panniculitis (n = 3 [38%]) followed by lupus panniculitis (n = 2 [25%]). Table 2 summarizes the demographic characteristics, clinical manifestations, laboratory, treatment and clinical course of this group.

Three patients (38%) presented with tender nodules and five (62%) with inflammatory plaques. In the latter group, four evolved to atrophic, depressed and hyperpigmented lesions and one, with subcutaneous panniculitis-like T-cell lymphoma (SPTCL, patient 7 [Table 2]), developed multiple subcutaneous nodules two months after presentation.

Reported symptoms were fever in 38%, pain in 38%, asthenia in 25%, weight loss in 25%, oral aphthous ulcers in 13%, diarrhea in 13% and acrocyanosis in 13%.

There was no evidence of infection when systemic symptoms were present, despite extensive laboratory investigations. A skin biopsy was performed in all non-EN panniculitis patients (Table 2). Two patients (25%) had anemia (patients 1 and 7 [Table 2]) and two (26%) had leukopenia (patients 6 and 7 [Table 2]) at presentation. ANA were positive in 38% (patients 1, 2 and 4 [Table 2]).

Patient 6 (Table 2), with cytophagic histiocytic panniculitis (CHP), had a myelogram which showed "very rare histiocytes with hemophagocytosis", a normal lymphocyte subpopulation and burst test.

Patient 8 (Table 2), with cutaneous polyarteritis nodosa (cPAN), presented with persistent cutaneous nodules that resembled EN as well as acrocyanosis. After six months, a skin biopsy was performed and histology showed "septal panniculitis with medium-sized artery vasculitis". ANCA antibodies were negative and adenosine deaminase 2 (ADA2) levels, as well as the urinalysis and electromyography, were normal. The only case with recurrent relapses was in this group.

Both CHP and SPTCL patients are in remission after immunosuppressive therapy and chemotherapy, respectively. The latter was followed up by the Pediatric Oncology team. Patient 1 evolved to systemic lupus erythematous and transitioned to adult care seven years after the initial presentation.

### *Statistical analysis*

We found no statistically significant difference between the two groups regarding ESR (U = 35.000; $p = 0.09$) and CRP (U = 46.000; $p = 0.50$). There was no association between the two groups in the context of anemia ($X^2_{(1)} = 0.02$; $p = 1$), leukopenia ($X^2_{(1)} = 2.214$; $p = 0.32$), fever ($X^2_{(1)} = 0.25$; $p = 0.66$), weight loss ($X^2_{(1)} = 0.82$; $p = 0.56$), asthenia ($X^2_{(1)} = 0.79$; $p = 0.63$), aphthous ulcers ($X^2_{(1)} = 0,43$; $p = 0.51$) and abdominal pain ($X^2_{(1)} = 1,42$; $p = 0.53$). There was an association between EN and painful nodules ($X^2_{(1)} = 6.68$; $p = 0.20$) and arthralgia/arthritis ($X^2_{(1)} = 6.68$; $p = 0.20$).

## Discussion

We describe a sample of pediatric patients with panniculitis observed by the Rheumatology Unit over a seventeen-year span, composed of EN and non-EN patients. Some of the non-EN cases are secondary to very rare disorders.

**Table 1.** Etiologies or associated disease, clinical and laboratory data on the patients with EN

| Diagnosis | n = 19 (%) | Age (years) (median [range]) | Associated symptoms (n) | Leukocyte count (uL) (median [range]) | CRP (mg/dl) (median [range]) | ESR (mm/1st h) (median [range]) | Other relevant laboratory results (n) | Treatment (n) | Recurrences (n) |
|---|---|---|---|---|---|---|---|---|---|
| Streptococcal infection | 6 (32%) | 13 (5-17) | P (6), A (2), Ar (2), O (2) | 11070 (6610-16200) | 0.9 (0.17-2.7) | 24 (10-48) | Positive RADT (2), ↑ASLO*(4), ↑Anti-DNAse B †(3) | NSAIDs (6), amoxicillin (2), flucloxacillin (2) | 0 (4), 1 (1), 2 (1) |
| Crohn's disease | 2 (11%) | 11 (10-12) | P (2), A (2), F (1), Art (1), AP (2), WL (2), D (1) | 10680 (8560-12800) | 4.8-6.6 | 74.5 (74-75) | Anemia (2), Calprotectin - 7760 ug/mg (1) | NSAIDs (2), PDN (1) | 0 (1), > 4 (1) |
| Probable reactive arthritis | 2 (11%) | 7.5 (3-12) | P (2), AP (1), Art (2), E (1), F (1), D (2) | 11595 (9800-13390) | 7.5 (6.7-8.3) | 77 (64-90) | Negative stool culture | NSAIDs (2), PDN (1) | 1 (1), > 4 (1) |
| Abscess secondary to *Staphylococcus aureus* cervical lymphadenitis | 1 (5%) | 5 | p | 13700 | 4.1 | 103 | Normal IgG, lymphocyte subpopulation and burst test | NSAIDs | 0 |
| Behcet disease | 1 (5%) | 10 | P, U, AU | 10320 | 0.7 | 17 | Negative ANA | NSAIDs | 0 |
| Idiopathic | 7 (37%) | 12 (7-17) | P (7), F (3), Ar (5), O (1) | 9540 (6280-15300) | 6 (1.18-7.8) N = 5 | 42 (17-95) N = 6 | Positive ANA (1) | NSAIDs (7), PDN (1), flucloxacillin (1) | 0 (5), 1 (1), > 4 (1) |

*Elevation of initial ASLO titer with subsequent declining levels: 2 with > 1000 U/ml and 2 with 600-1000 U/ml.
†Elevation of initial Anti-DNAse B titer (> 600 U/L) with subsequent declining levels: 2 with > 1000 U/ml and 2 with 600-1000 U/ml
A: asthenia; ANA: anti-nuclear antibodies; AP: abdominal pain; Ar: arthralgia; Art: arthritis; ASLO: anti-streptolysin; AU: aphthous ulcers; D: diarrhea; E: episcleritis; F: fever; NSAIDs: non-steroidal anti-inflammatory drugs; O: odynophagia; P: pain; PDN: prednisolone; RADT: positive rapid antigen detection test for Group A *Streptococcus*; U: uveitis; WL: weight loss.

**Table 2.** Clinical details and disease course of non-EN panniculitis

| Patient | Sex | Diagnosis | Age of onset (years) | Initial lesion | Evolution | Associated symptoms | ESR (mm/1st h) | CRP (mg/dl) | Histology | Initial treatment | MT | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | Lupus Pn | 11 | RT: 5 x 3 cm, hyperpigmented, linear plaque | RT (initial lesion): 20 x 9 cm brown, indurated, depressed, linear plaque. Developed two similar plaques in the RUA (3 x 3 cm). | P, AU, F, C | 90 | 8.5 | LP + lymphoid follicles with germinative center | PDN | PDN + AZA | SLE stable |
| 2 | F | Lupus Pn | 10 | RT: 3 x 5 cm, indurated depressed plaque | Developed three similar plaques. LT: 1.5 x 1.3 cm; RUA: 2 x 1 cm; LUA: 0.5 x 0.5 cm. | Ø | 8 | Ø | LP + SP + lymphoid and plasma cells | PDN | HC | Stable |
| 3 | F | Lipoatrophic Pn | 2 | LL: 4 sc nodules, < 1 cm | LL (nodules converged): indurated, depressed plaque. Developed two plaques in the RL and LFA. | F, A | 20 | 0.3 | LP + SP + histiocytic cells | PDN | MTX | Stable |
| 4 | F | Lipoatrophic Pn | 1 | LL: 1 cm erythematous plaque | LL (initial lesion): 13 x 4 cm, hyperpigmentation, atrophy. Developed three similar plaques: LT: 4 x 4 cm; LF: 3 x 2 cm. | Ø | 15 | 0.04 | LP + predominant plasmocytic cells | PDN + MTX | MTX | Stable |
| 5 | F | Lipoatrophic Pn | 9 | LL: 8 x 6 cm, erythematous warmth plaque | Initial lesion: deep sc atrophy. | Ø | 18 | 0.26 | LP + polymorphous infiltrate | PDN + LFN | LFN | Stable |
| 6 | M | SPTCL | 16 | RT: painful, warm and indurated plaque | Multiple sc nodules in the right hip and thigh, thorax (anterior surface) and back. | F, P, A, WL | 22 | 1.3 | LP + atypical lymphocytes + necrosis | AB | Chemotherapy (oncology) | Remission |
| 7 | M | CHP | 0.5 | 10 – 15 sc tender nodules, with < 1 cm in LUA, LL, back and abdomen. | | F, P, A, WL, D | 100 | 15 | LP + SP + histiocytic cells + macrophages in cytophagocytosis | MPDN (high dose) | CS | Remission |
| 8 | F | cPAN | 11 | Bilateral multiple nodules with purple coloring (legs and feet). | | P Acrocyanosis | 29 | 2.37 | SP + vasculitis (ANCA negative) | PDN + LFN | PDN + AZA + HCQ + nifedipine | Recurrence |

A: asthenia; Ant: anterior; AU: aphthous ulcers; AZA: azathioprine; C: cough; CHP: cytophagic histiocytic panniculitis; cPAN: cutaneous polyarteritis nodosa; CS: cyclosporin; CT: corticosteroid; D: diarrhea; ESR: erythrocyte sedimentation rate; F: fever; HCQ: hydroxychloroquine; LF: left foot; LFA: left forearm; LFN: leflunomide; LL: left leg; LP: lobular panniculitis; LT: left thigh; LUA: left upper arm; MPDN: methylprednisolone; MT: maintenance treatment; MTX: methotrexate; N: (described) normal; AU: aphthous ulcers; P: pain; PDN: prednisolone; Pn: panniculitis; RL: right leg; RT: right thigh; RUA: right upper arm; sc: subcutaneous; SLE: systemic lupus erythematosus; SP: septal panniculitis; SPTCL: subcutaneous panniculitis-like T-cell lymphoma; WL: weight loss.

EN is the most common type of panniculitis in all ages and the incidence peaks between the second and fourth decades of life. Among children, it is less frequent in prepubertal children and rare below two years of age[4-8], which is corroborated by our study, as our youngest patient was three years of age. There is a female predominance in adults, but in children, there is generally no difference regarding sex[4-8]. In our sample, we still had a female predominance under 12 years of age (67%).

In our series, EN accounts for 70% of cases, one third secondary to streptococcal infection, the most common disease implicated in EN etiology[4-8]. The frequency of undetermined etiology varies between series, ranging from 13.5-43%[9-12] and in this study 37% were classified as idiopathic (Table 1).

Skin biopsies were performed in one patient with idiopathic typical EN, before being referred to our unit, and one with atypical presentation (nodules on the posterior surface of the legs), later diagnosed as CD.

EN is a known cutaneous manifestation of IBD and occurs in 4-15% of patients with CD and 3-10% of patients with ulcerative colitis[4-8]. During follow-up, both patients developed abdominal pain, weight loss and arthralgias that motivated screening and referral to gastroenterology (Table 1). Diarrhea appeared four months after the diagnosis of EN in both cases. Ileum histopathology confirmed CD.

In our series, we had two patients with probable reactive arthritis. Both had previous diarrhea treated with antibiotics (with a negative stool culture). One had episcleritis and oligoarthritis (knee and elbow), and was treated with prednisolone after ruling out infection and went into remission after more than four recurrences.

Our patient with Behçet disease had EN, uveitis and recurrent aphthous ulcers, fulfilling criteria for this vasculitis[6]. The laboratory evaluation was innocent, and ANA were negative.

We had no evidence of EN secondary to drug intake, one of the multiple causes of EN[4], but we believe that in the patient with staphylococcal abscess, previous antibiotic intake could also have played a role in its etiology. He had been empirically treated with amoxicillin plus clavulanic acid before a course of flucloxacillin.

All our EN patients were under symptomatic treatment, the first-line therapy[4-8], with NSAIDs and bed rest, most of whom had a favorable outcome. In three patients, with more recurrences, oral PDN was associated after ruling out infectious diseases.

One third of our sample had more than one episode. One patient with CD (before achieving remission) had frequent EN recurrences temporally related to bowel flares.

Two patients with streptococcal infection-associated EN were discharged after the first observation by the Rheumatology team as they were already asymptomatic, with declining ASLO and DNAse titers.

We report a 30% prevalence of non-EN panniculitis. In 2010, Moraes et al.[9] reported 17% non-EN panniculitis cases (diagnosed previously as cases of Weber-Christian disease).

In the non-EN group, systemic symptoms such as fever, asthenia and weight loss were present in two patients, one with SPTCL and one with CHP, reflecting systemic involvement. They can be present in other types of panniculitis and in our series, one girl with lipoatrophic panniculitis had fever and asthenia in the prodromic phase.

Lipoatrophic panniculitis is a rare entity, occurring mainly in children[14], and it has an inflammatory phase that can resemble EN (such as patient 3 [Table 2]). Lesions are typically located in the legs and ankles and can progress to permanent lipoatrophy. Some reported cases are related to autoimmune disorders[14]. We present three patients with lipoatrophic panniculitis with a typical presentation.

Lupus panniculitis is a rare cutaneous form of lupus erythematosus and has rarely been reported in children[1]. In a multicentric study in 2019, only six out of 847 (0.7%) child-onset systemic lupus erythematosus (SLE) patients had lupus panniculitis[15]. It can be a chronic cutaneous disease or a preceding manifestation of SLE. We have two patients with lupus panniculitis, both with positive ANA antibodies.

Patient 1 (Table 2) was sent to our unit for suspected SLE. She had a previous history of recurrent oral ulcers and a histological diagnosis of lupus panniculitis treated with 0.1% tacrolimus ointment. Two months before referral there was clinical worsening, with anorexia, fever, anemia and an increase in the panniculitis size and atrophy (Table 1). An SLE diagnosis was confirmed, as she fulfilled Systemic Lupus International Collaborating Clinics (SLICC)[16]: lupus panniculitis, oral ulcers, significant proteinuria (501 mg/24 hours), positive ANA (titer 1:320) and positive lupus anticoagulant. She was treated with oral PDN, improving quickly, and clinical stability was achieved with low-dose PDN plus azathioprine. At 18 years of age, she transitioned to adult care. Patient 2 (Table 2) had an exclusively cutaneous disease. Diagnosis was based on clinical, histological and laboratory (low C3 and positive ANA) findings. She was treated with hydroxychloroquine

for two years and, to date, has not fulfilled SLICC criteria[16].

CHP is a disorder consisting of lobular panniculitis with infiltration of cytophagic hystiocytes. It can be an isolated skin disease or it can be associated with triggering infections or malignant disease, such as SPTCL. SPTCL is a rare primary cutaneous lymphoma, and its T-cell clonal proliferation is frequently associated with an autoimmune disease[17]. Both entities, very rare in pediatric age, can be associated with secondary hemophagocytic lymphohistiocytosis, a severe systemic inflammatory syndrome that courses with fever, splenomegaly, cytopenias, hypertriglyceridemia and high ferritin, and may be lethal if untreated[18].

The patient with CHP (patient 7 [Table 2]) presented at six months of age with fever and diarrhea and initially was treated with intravenous ceftriaxone for suspected sepsis. He also had anemia (9.1 g/dl) and leukopenia (3700 uL) with neutropenia (600 uL). Even so, fever persisted, anemia worsened (minimum 8.2 g/dl), ferritin rose (maximum 528 ng/ml) and there was evidence of hemophagocytosis in bone marrow histology. He was successfully treated with cyclosporine A after methylprednisolone pulses. Given the initial symptoms, we believe that a preceding infection may have contributed to the development of CHP, even though there was no microbiological evidence in stools, urine or blood. Immunodeficiency screening was negative.

Before histological diagnosis, the initial clinical findings of the patient with SPTCL (patient 6 [Table 2]) resembled cellulitis and he was treated unsuccessfully with flucloxacillin. Initial laboratory evaluation revealed low ESR and CRP but showed leucopenia (2620 uL). The persistence of fever, weight loss and severe pain led to further investigation.

PAN is a necrotizing vasculitis of small and medium-sized arteries and is the third most common vasculitis in childhood[19]. Exclusive cutaneous involvement is more common in pediatric age. Differential diagnoses include deficiency of ADA2[20], a monogenic disorder, that was ruled out in our patient. Our patient (patient 8 [Table 2]), with a previous diagnosis of systemic juvenile idiopathic arthritis, was under PDN and leflunomide when cutaneous nodules appeared. EN was ruled out after histology results and the PDN dose was raised (maximum 0.25 mg/kg) with temporary improvement. She is currently under PDN, hydroxychloroquine, azathioprine and nifedipine and continues to suffer relapses of cutaneous vasculitis. The diagnosis for systemic PAN includes other criteria that the patient does not have, such as musculoskeletal pain, hypertension, peripheral neuropathy and renal involvement[21].

All EN panniculitis patients had favorable outcomes. The non-EN panniculitis cases had varying degrees of scarring.

We did not find a statistically significant difference between most clinical and laboratory characteristics. The small size of the non-ED group likely reduces the strength of the statistical study. The association of painful nodules and arthralgias in the EN group is expected, since the first of these is one of the diagnostic criteria and the second is a common symptom.

In conclusion, streptococcal infection is still the most common cause of EN, and although in the vast majority of cases the course is benign, in some patients it can be the first sign of severe disease. Follow-up of cases with an unknown etiology allows observation of eventual disease progression and early intervention. New-onset asthenia and anorexia, abdominal pain and arthralgia should prompt second-line EN investigation.

In the other hand, indurated, discolored or atrophic nodules or plaques should raise the suspicion of panniculitis other than EN. Different etiologies need to be considered, some of which are life-threatening and require prompt treatment. Histopathological assessment and an adequate clinical-pathological correlation can guide specific diagnosis and appropriate management.

## Authors' contribution

L. Silva: 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; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. F. Cardoso: Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. L. 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. P. Estanqueiro: 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. J. Nascimento: 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. M. Salgado: 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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**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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REVIEW ARTICLE

# Anemia of prematurity: a narrative review

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## Abstract

Anemia of prematurity is a condition that is prevalent in neonatal intensive care units, especially among extremely low birth weight infants. Despite extensive practice and research, several preventive and therapeutic strategies remain controversial, giving rise to significant differences among centers. Preventive strategies include delayed cord clamping, umbilical cord milking, autologous and allogeneic cord blood transfusion, and reducing iatrogenic blood loss through innovative methods like microsample devices. The effectiveness of erythropoiesis-stimulating agents in reducing transfusions remains limited. Red blood cell transfusions, while beneficial, carry risks. Defining transfusion thresholds based on hemoglobin levels remains a challenge, with practices varying globally. Recent trials advocate for a restrictive transfusion approach, reducing the number of transfusions with no significant adverse effects. Near Infrared Spectroscopy evaluates tissue oxygenation, potentially aiding transfusion decisions based on individualized physiological markers of anemia. This review provides a summary of the latest literature on anemia of prematurity, emphasizing aspects related to pathophysiology, preventive measures, and therapeutic interventions to assist clinicians in managing this condition.

***Keywords:*** Anemia. Hemoglobin. Preterm infants. Red blood cell transfusion.

## *Anemia da prematuridade: revisão narrativa*

## Resumo

A anemia da prematuridade é uma condição prevalente nas unidades de cuidados intensivos neonatais, especialmente em recém-nascidos prematuros com extremo baixo peso ao nascimento. Apesar da ampla prática e investigação, várias estratégias preventivas e terapêuticas permanecem controversas, resultando em diferenças significativas na prática clínica entre os diversos centros. As estratégias preventivas incluem a clampagem tardia do cordão umbilical, a expressão do cordão umbilical, as transfusões autóloga e alogénica de sangue do cordão e a redução da perda sanguínea iatrogénica através do uso de micro-amostras. A eficácia dos agentes estimuladores da eritropoiese na redução do número de transfusões permanece limitada. As transfusões de glóbulos vermelhos, apesar de benéficas, acarretam riscos. Definir os limiares de transfusão com base nos níveis de hemoglobina continua a ser um desafio, com práticas variadas a nível global. Ensaios recentes defendem uma abordagem de transfusão restritiva, demonstrando redução das transfusões sem efeitos adversos significativos. A espectroscopia próxima de Infravermelhos mostra-se promissora na avaliação da oxigenação dos tecidos, podendo auxiliar nas decisões de transfusão com base em marcadores fisiológicos de anemia individualizados. Esta revisão apresenta um resumo da literatura mais recente sobre a anemia da prematuridade, enfatizando aspetos relacionados com a fisiopatologia, medidas preventivas e intervenções terapêuticas, com o objetivo de auxiliar os clínicos no manejo desta condição.

***Palavras-chave:*** Anemia. Hemoglobina. Recém-nascido pré-termo. Transfusão de glóbulos rubros.

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## Keypoints

**What is known**

- Anemia of prematurity is a condition that is prevalent in neonatal intensive care units, particularly among extremely low birth weight infants.
- Red blood cell transfusions are the primary treatment for anemia of prematurity, yet global practices vary as there is no universal hemoglobin threshold.
- The use of erythropoiesis-stimulating agents is not currently recommended due to the limited benefits.

**What is added**

- Preventive strategies include delayed cord clamping, umbilical cord milking, minimizing iatrogenic blood loss with microsampling, and autologous/allogeneic cord blood transfusion.
- A restrictive transfusion strategy leads to a decrease in transfusions with no significant adverse effects.
- Near Infrared Spectroscopy is being studied as a potential adjunct for determining transfusion needs, based on individualized physiological markers of anemia.

## Introduction

Neonatal anemia, characterized by hemoglobin (Hb) or hematocrit (Hct) concentrations more than two standard deviations below the mean for the postnatal age, is often observed in neonatal intensive care units (NICUs). Neonates, particularly extremely low birth weight (ELBW at < 1000 g) infants, are one of the most commonly transfused groups, with approximately 90% receiving at least one red blood cell (RBC) transfusion during their NICU stay, resulting, in some cases, in a cumulative replacement of 100-200% of their estimated total circulating volume at birth[1-3].

Most RBC transfusions in the NICU occur in the context of medically stable preterm infants who have developed chronic anemia, referred to as "anemia of prematurity" (AOP)[4]. The primary goal is to enhance oxygen delivery to vital organs. Despite widespread practice and a century of research and clinical advancements, the indications for RBC transfusion in neonates remain controversial due to the absence of uniformly accepted physiological or evidence-based criteria[5]. Moreover, there is a lack of conclusive data on the long-term effects of RBC transfusions[5]. As a result, neonatologists worldwide exhibit considerable variation in practices related to neonatal transfusions, often relying on expert opinion rather than a scientifically-robust evidence base[4,6].

The aim of this paper is to provide a comprehensive review and update of the pathophysiology, preventive strategies, and management of AOP according to the most recent literature.

## Pathophysiology of AOP

After birth, all infants undergo a gradual decline in Hb, resulting in varying degrees of anemia. In healthy term infants, the nadir Hb value seldom drops below 10 g/dL between six and 12 weeks of age (Table 1)[7]. This physiological anemia of infancy is a well-tolerated benign phenomenon, reflecting several principles: a progressive shift from fetal Hb (HbF), characterized by higher oxygen affinity, to adult Hb (HbA) between 34 to 36 weeks' gestation and three to four months post-term; a shorter lifespan of RBC in newborns compared to adults (approximately 40 to 60 days versus 120 days); a postnatal rise in intra-erythrocyte 2,3-diphosphoglycerate, facilitating oxygen release from Hb; adaptive cardiovascular mechanisms compensating for the reduced oxygen-carrying capacity of anemia; and a transitional decrease in plasma erythropoietin relative to the degree of anemia, with a reduction in erythropoiesis compared to adults[3,4,8-10].

In preterm infants, this decline occurs earlier than in term infants, reaching a nadir at an average Hb concentration of 7-8 g/dL by a postnatal age of four to six weeks (Table 1)[7]. The severity is more pronounced, accompanied by clinical symptoms and signs of anemia such as tachycardia, tachypnea, higher oxygen requirements, increased frequency of apnea, bradycardia, pallor, and poor weight gain[4,11,12]. Due to these symptomatic manifestations and their consequences, anemia is not considered a benign event in preterm infants. The degree and severity are determined by gestational age and a combination of multiple physiological and non-physiological factors[13].

### *Physiological factors*

Among the physiological factors contributing to AOP is the presence of low plasma erythropoietin (EPO) levels in response to anemia, attributed to decreased EPO production and accelerated catabolism[3]. Additionally, EPO is predominantly produced in the liver during the fetal and early preterm period, which is less sensitive to anemia and tissue hypoxia compared to the kidney, resulting in a relatively attenuated response to falling hemoglobin levels[8,9,12].

Another contributing factor relates to HbF, which constitutes 70-80% of the total Hb content in term newborns and can reach up to 97% in preterm infants[14]. Under similar conditions, the release of oxygen to tissues

**Table 1.** Hemoglobin: normal levels at birth and postnatal nadir

| | Hb at birth (g/dL) | Hb nadir (g/dL) | Age at which Hb nadir is reached (weeks) |
|---|---|---|---|
| Term newborn | 17 (14-20) | 9.5-11 | 6-12 |
| Preterm newborn 1.2-2.5 kg | 16.4 (13, 5-19) | 8-10 | 5-10 |
| Preterm newborn < 1.2 kg | 16 (13-18) | 6.5-9 | 4-8 |

Hb: hemoglobin.
*Adapted from Sánchez-Gabriel M. Anemia y policitemia neonatal. Protocolos de la Sociedad Española de Neonatología, SENeo 2023, 301-305.*

is more challenging in preterm newborns[14]. Accelerated catabolism, a shortened lifespan of red blood cells (surviving only 35 to 50 days in the most premature infants, compared to 90 days and 120 days in term infants and adults, respectively), higher extrauterine growth and blood volume increase, and insufficient iron storage, are additional physiological factors contributing to AOP[13].

### *Non-physiological factors*

Frequent laboratory blood tests required for hematological, biochemical, and other parameter monitoring, are a significant iatrogenic contributor to AOP[3]. Very low birth weight infants (VLBW at < 1500 g) commonly experience routine blood losses of approximately 11-22 ml/kg per week (~ 15-30% of an infant's total blood volume) during the first six weeks of life[3,4,8]. Also, various non-physiological conditions can exacerbate the development of neonatal anemia, including blood loss, hemolysis, infection/sepsis, cardiorespiratory disease, and nutrient deficiencies necessary for erythropoiesis (iron, folate, protein, vitamins E and B12)[2-4]. Generally, the severity of AOP is inversely proportional to gestational age and birth weight, with younger and smaller infants requiring more RBC transfusions during their NICU stay[2,4,8].

Anemia at birth is universally considered pathological for both term and preterm infants, requiring further investigations if the cause is not identified antenatally or at delivery[15]. The pathological causes of anemia are outlined in table 2[4,15].

### *Laboratory monitoring*

The diagnostic approach for AOP typically involves a comprehensive evaluation, including the family and maternal medical history, details about the pregnancy, delivery, and postpartum period, a physical examination, and laboratory tests[2].

For laboratory diagnosis, a complete blood count is essential[2]. Newborns' Hb or Hct levels should be assessed based on reference values appropriate for the gestational age and the site of sampling[12]. Hct or Hb concentration should be monitored weekly, or according to the clinical status, in ELBW infants during the first weeks of life[1,2,12]. Subsequently, weekly routine monitoring of Hct or Hb in healthy growing preterm infants is unnecessary. However, the serum Hb value must be known before hospital discharge[12]. Additional laboratory assessments may include reticulocytes, red cell indices, a peripheral blood smear, and indices of hemolysis (total and indirect bilirubin, lactate dehydrogenase, direct and indirect Coombs test, and haptoglobin), conducted stepwise and utilizing the smallest possible volume of blood[1].

## Preventive strategies

Several practices have been employed to prevent and mitigate the degree of AOP, with the most relevant strategies outlined below (Table 3).

### *Non-pharmacological interventions*

*Delayed umbilical cord clamping*. Interest in delaying umbilical cord clamping (DCC) during birth has surged in recent years as a potential method to enhance the transfer of blood from the placenta to the newborn, consequently reducing the need for subsequent RBC transfusions[16]. A recent meta-analysis conducted by Cochrane, encompassing data from 15 randomized trials involving a total of 738 infants born between 24 and 36 weeks of gestation, revealed that DCC for at least 30 seconds, as opposed to immediate clamping, appears to be correlated with a reduced necessity for transfusions, improved circulatory stability, decreased occurrences of intraventricular hemorrhage (IVH), and a lower risk of necrotizing enterocolitis (NEC)[16,17]. Subsequent to this, another meta-analysis pooling data from 27 clinical trials involving 2,834 preterm infants validated that clamping the cord at 30 seconds or more after birth was linked to a decrease in hospital mortality rates and a reduced need for transfusions[18]. A recent randomized trial

**Table 2.** Pathological causes of anemia in infants

| Blood loss | Bone marrow disorders | Increased RBC destruction |
|---|---|---|
| Feto-maternal hemorrhage<br>Twin-to-twin transfusion syndrome<br>Umbilical cord rupture<br>Abruptio placenta<br>Intra- and extra-cranial hemorrhages (e.g. intra- and periventricular, subgaleal)<br>Phlebotomies | Fanconi anemia<br>Diamond-Blackfan syndrome<br>Transient erythroblastopenia of childhood<br>Congenital infections (e.g. TORCH)<br>Nutritional deficiencies (e.g. vitamin B12, folate, iron) | Alloimmune hemolytic disease of newborn<br>Inherited RBC enzyme abnormality<br>Inherited RBC membrane defects<br>Haemoglobinopathies<br>Disseminated intravascular coagulopathy<br>Metabolic disorders |

*Adapted from Saito-Benz M, Flanagan P, Berry MJ. Management of anaemia in pre-term infants. Br J Haematol. 2020, 188: 354-366.*

**Table 3.** Evidence level for preventive strategies for anemia of prematurity

| Strategy | Quality of evidence | Strength of recommendation | Recommendation of the Standards Committee of the SENeo |
|---|---|---|---|
| Delayed cord clamping | 1A | High/substantial A | Recommended for routine clinical practice |
| Initial cord/placental blood tests | 2B | Moderate/moderate B | Recommended for routine clinical practice |
| Reducing phlebotomy losses | 1B | Moderate/substantial B | Recommended for routine clinical practice |
| Erythropoietin | 1A | Moderate/moderate B | Further research is required to recommend its clinical use |

*Adapted from Sánchez-Gabriel M. Anemia y policitemia neonatal. Protocolos de la Sociedad Española de Neonatología, SENeo 2023, 301-305.*

comparing early clamping (within 10 seconds) and delayed clamping (at least 60 seconds) in 1,566 preterm neonates indicated no significant differences in the primary outcome of death or major morbidities[19]. However, fewer infants in the DCC group required subsequent RBC transfusions by 36 weeks of postmenstrual age[19]. Consequently, DCC is increasingly acknowledged as a standard practice during preterm delivery[4].

The optimal duration for DCC remains uncertain, although the 2021 European Resuscitation Council Guidelines recommend, when immediate resuscitation or stabilization isn't imperative, DCC for a minimum of 60 seconds, ideally after the aeration of the lungs[20]. Limited follow-up studies indicate that DCC may lead to enhanced neurodevelopmental outcomes in the initial year of life[19,21]. Concerns regarding polycythemia and jaundice necessitating significant intervention do not seem to be supported by evidence from randomized trials[20,21].

*Umbilical cord milking*. Umbilical cord milking (UCM) involves manually moving blood from the unclamped umbilical cord to the infant, typically carried out three to five times before clamping, aiming to facilitate an autotransfusion of blood into a preterm neonate[17]. DCC is not recommended in cases where placental blood flow is compromised due to conditions like placental abruption, cord prolapse, vasa previa, cord avulsion, or maternal hemorrhage[20]. In such situations, UCM is considered as an alternative method[19]. However, this remains a controversial topic, with some authors expressing concerns about potential fluctuations in systemic blood pressure and cerebral blood flow[17].

In a randomized trial comparing UCM to immediate cord clamping in 256 newborns born before 34 weeks of gestation, UCM showed higher levels of Hb and Hct, reduced occurrences of anemia in early infancy and at six months postpartum, fewer RBC transfusions during hospitalization, and improved iron stores compared to immediate cord clamping[22]. Other meta-analyses have indicated that UCM during preterm birth was relatively safe and associated with reduced exposure to RBC transfusions and a lower incidence of complications such as IVH, NEC, and mortality[23]. As per the 2021 European Resuscitation Council Guideline, when DCC is not feasible, cord milking in infants above 28 weeks of gestation should be considered[20]. Although the available data is limited, some authors strongly advocate that UCM should no longer be viewed as an experimental technique; rather, it should be recognized as an established intervention ensuring that premature neonates above 28 weeks of gestation receive an adequate placental transfusion at birth[17,20].

*Autologous and allogenic cord blood transfusion*. An alternative to DCC and UCM is the use of autologous blood

from the placenta immediately following delivery for later transfusion to the same patient[24]. Although there are challenges associated with this practice as relatively small volumes are collected (~ 10-30 ml/kg), this strategy is attractive because it reduces an infant's exposure to life-threatening viral infections associated with iatrogenic blood products while conserving limited blood resources[24-26]. Alternatively, allogeneic cord blood transfusion effectively reduces exposure to adult donor RBC and may have a role in neonatal transfusion practice in the future[27].

*Minimizing iatrogenic blood loss*. Reducing iatrogenic blood loss is crucial in managing AOP. A significant contributor to this issue is the blood drawn for laboratory testing. However, adjustments in practice can help minimize phlebotomy-related blood losses[17]. Another method involves employing microsample point-of-care devices[17,25]. These devices have shown a 43% reduction in the mean volume of RBC transfusions among ELBW infants[28]. They achieve this by reducing unnecessary laboratory testing, optimizing the frequency, and using collection tubes with minimal volumes[28].

Moreover, umbilical cord blood serves as a valuable resource for conducting neonatal blood typing, screening, complete blood count with differential, and blood culture assessments[29]. Utilizing 'in-line' umbilical arterial catheter devices offers another avenue[8,17,29]. These devices make it possible to analyze blood gas, Hct, and electrolytes without drawing blood directly from the infant; instead, they return dead-space blood draws to the infant[17,29].

## Pharmacological intervention

*Erythropoiesis-stimulating agents*. The impaired production of EPO in AOP has prompted the exploration of erythropoiesis-stimulating agents (ESAs), particularly recombinant human EPO (rhEPO), as a potential therapy[12]. Research has extensively investigated the role of rhEPO, indicating its ability to enhance both erythropoiesis and the reticulocyte count in a dose-dependent manner[30]. However, its effectiveness in significantly reducing transfusions and blood donor exposure for infants, regardless of early initiation (less than eight days of life) or later administration (after the first two weeks of life), remains limited[8,12,30].

Initial studies, including the Cochrane review on early rhEPO therapy, demonstrated marginal benefits in reducing transfusions but suggested an increased risk of severe (stage ≥ 3) retinopathy of prematurity (ROP)[30,31]. As a result, early rhEPO therapy was not recommended based on these findings[31]. Subsequent meta-analyses, including more trials with ESAs initiated before eight days of age, showed a slight reduction in RBC transfusions and donor exposure[32]. However, the clinical significance of these findings remains modest. Importantly, the updated review confirmed the safety of early ESA administration with no significant difference in the rate of severe ROP[32]. Additionally, the rate of significant neonatal morbidity, including NEC, IVH, and periventricular leukomalacia, appeared lower in the ESA-treated group. Nevertheless, differing results from major trials and substantial heterogeneity in analyses suggest the necessity for more trials before drawing definitive conclusions[32].

A recent double-blind randomized controlled trial (RCT) administering high-dose EPO within 24 hours of birth in extremely preterm infants (< 28 weeks gestational age) exhibited fewer transfusions and a decreased cumulative transfused volume[33]. A significant proportion of infants in the EPO group remained transfusion-free at 12 weeks of age compared to the placebo group. However, the trial found no differences in primary outcomes such as death or severe neurodevelopmental impairment at 22-26 months of corrected gestational age. Moreover, rates of ROP, NEC, IVH, or bronchopulmonary dysplasia (BPD) did not differ significantly between the groups[33]. Similarly, evidence supporting the late administration of ESAs is inconclusive, demonstrating minimal clinical benefits and conflicting safety profiles[34]. While it may reduce the need for one or more RBC transfusions, the total volume of RBC transfused per infant remains unchanged. Moreover, donor exposure isn't effectively avoided, as most studies included infants who received RBC transfusions before entering the trial[34].

In summary, based on current findings, the International Guidelines do not recommend the early or late administration of rhEPO[32-34].

*Iron supplementation*. Premature infants have lower iron levels at birth compared to full-term infants since the significant transfer of iron occurs mainly during the third trimester of gestation[35]. Consequently, the iron reserves in preterm infants are often depleted by the age of two to three months[35]. The standard practice in NICUs worldwide involves enteral supplementation of iron for preterm infants, typically initiated once they can tolerate enteral feeds (> 100 ml/kg)[36,37]. This supplementation generally involves administering 2-3 mg/kg/day of iron throughout the first year of life[36-38]. While iron supplementation does not prevent AOP, using iron-fortified formula instead of non-fortified formula offers more iron substrate when erythropoiesis is stimulated[36-37]. This strategy helps in reducing iron-deficiency anemia, a condition for which preterm infants are at a higher risk during their first year of life[12,35-38].

## RBC transfusions to treat AOP

RBC transfusions continue to be the primary treatment for AOP, typically recommended when the severity of the anemia leads to symptoms or affects the delivery of oxygen[1,3]. However, significant controversy surrounds the potential advantages and risks associated with RBC transfusions in preterm infants, as well as the ideal transfusion thresholds for this specific population[4,12,39].

### *Potential benefits and risks*

RBC transfusions are commonly administered in the context of AOP to enhance cardiorespiratory stability and promote weight gain[25,40]. Generally, they provide benefits by elevating circulating Hb levels, leading to improved tissue oxygenation, reduced cardiac output, and enhanced weight gain[40]. However, these transfusions also carry well-recognized risks, which can be categorized as follows: the transmission of infections (viral, bacterial, and parasitic), adverse effects due to leukocytes (including immunomodulation, graft-versus-host disease, transfusion-related acute lung injury, and alloimmunization), acute volume or electrolyte disturbances, increased exposure to donors, and rare blood group incompatibilities (often due to transfusion errors)[12,41]. While all transfusion-transmitted infections pose risks to newborns, cytomegalovirus (CMV) infection can be particularly serious for extremely immature infants[42,43]. The adoption of universal leukoreduction in NICUs has contributed to reducing the risk of CMV infection[42,43]. Rare conditions such as transfusion-related acute lung injury and transfusion-associated circulatory overload may go unnoticed, particularly in critically ill ELBW newborns exhibiting respiratory symptoms[44].

In preterm infants, RBC transfusions have been associated with the development of conditions like BPD, ROP, NEC, and IVH, although a direct causal relationship has not been firmly established[44]. Some observational studies suggest an association between NEC and transfusions[45]. However, findings from randomized clinical trials do not consistently support this correlation[46,47]. In a prospective multicenter cohort study analyzing 1,430 transfusion exposures in VLBW infants, NEC appeared to be associated more with severe anemia (Hb ≤ 8 g/dL) rather than directly linked to RBC transfusion[46]. Most meta-analyses investigating these associations rely on observational and cohort studies, which carry the potential for confounding factors and biases. Hence, large prospective randomized trials are still necessary[46,47].

### *Selection of RBC products*

Upon deciding to administer RBC transfusions, selecting the appropriate RBC product becomes crucial, taking into consideration the various efficacy and safety concerns aimed at mitigating potential risks[25]. Strategies in blood banking, such as stringent donor selection criteria, pathogen inactivation techniques, and infectious disease testing, have significantly reduced the likelihood of developing transfusion-transmitted diseases[25,41,42]. Moreover, specific practices in blood banking include using stored rather than fresh RBC to minimize donor exposure, opting for white blood cell (WBC)-reduced (leucodepleted) RBC to eliminate complications related to WBCs, and prescribing gamma-irradiated RBC to prevent graft-versus-host disease[4,25].

The risks associated with RBC transfusions have notably decreased due to the adoption of single-donor and small-volume pack units (pedipacks), which can be stored for up to 35 days[44]. These units have donor plasma replaced by anticoagulant additive solutions and utilize additives like mannitol and glucose[13]. Furthermore, using leucodepleted and gamma-irradiated RBC is universally recommended for transfusions in preterm infants[4,41].

Conventionally, transfusion volumes ranging from 10 to 20 mL/kg have been typical for newborns, yet evidence on the optimal volume remains limited[48]. A survey assessing transfusion practices in preterm infants across Europe revealed a median RBC transfusion volume of 15 mL/kg[49]. Several studies suggest that volumes of 20 mL/kg might offer benefits with no adverse respiratory effects, reducing the necessity for frequent transfusions[48]. However, transfusion volumes exceeding 20 mL/kg could elevate the risk of volume overload[41,48]. Transfusions should ideally be administered over two to four hours[12,41].

### *Transfusion thresholds for preterm infants*

The variability in transfusion practices across different medical units is significant[49]. Most guidelines for RBC transfusions rely on Hb or Hct levels, in conjunction with the patient's clinical condition. These thresholds may differ based on postnatal age, oxygen requirements, and the type of respiratory support provided[4,12]. Predictors for a reduced need for subsequent RBC transfusions include higher birth weight and higher Hb levels at admission, while occurrences of sepsis are significantly associated with an increased need for additional transfusions[3,8].

Currently, there is no universally-accepted Hb threshold guiding RBC transfusion decisions. Consequently, clinicians base their decisions on clinical judgment and national or local guidelines[8,40]. The substantial variation in RBC transfusion thresholds across different regions and medical practices is outlined in table 4, comparing guidelines from various countries[11,40,48,50-52].

The observed diversity in transfusion thresholds highlights the absence of international and European consensus on transfusion criteria. Until recently, there has been a dearth of evidence regarding whether neonatal RBC transfusion therapy should follow a restrictive or liberal approach[49].

## *Restrictive versus liberal transfusions—evidence from clinical trials*

Recent years have witnessed a transition in neonatal practice towards a more restrictive approach to RBC transfusions[53,54]. Several studies have examined restrictive transfusion guidelines to ascertain the safety of tolerating lower Hb levels[54]. This shift was initially prompted by concerns over exposure to blood products and multiple donors[54]. Subsequently, RCT began assessing whether restrictive or liberal transfusion practices impact short-term morbidities (e.g., BPD and ROP) and long-term neurodevelopmental outcomes[8].

Before 2020, clinical practice was partially guided by two significant RCT: the Premature Infants in Need of Transfusion (PINT) and the Iowa trials[55,56].

The PINT trial, involving 451 ELBW preterm infants, investigated mortality and morbidity at discharge as its primary outcome. It found no significant differences between ELBW infants receiving transfusions based on higher (liberal group) or lower (restrictive group) Hb thresholds. Consequently, the application of higher Hb thresholds increased transfusion frequency with no strong evidence of the benefits[41,55-57].

Concurrently, the Iowa study (n = 103, birth weight 500-1300 g) compared restrictive and liberal thresholds during a similar period to the PINT trial[56]. Although their restrictive thresholds mirrored those in the PINT trial, the liberal thresholds were notably higher (approximately 2 g/dL). Infants in the restrictive group were more likely to experience major neurological adverse events and increased frequency of apnea at NICU discharge[41,51,55-57].

The PINT study showed no statistically significant differences in combined death or disability at 18 months corrected gestational age. However, a post-hoc analysis favored high Hb thresholds regarding less severe Bayley II mental developmental index outcomes, impacting this primary outcome[49,55]. In a 2011 Cochrane Review analyzing the PINT and Iowa trials, the need for further studies to elucidate the long-term implications of restrictive versus liberal transfusion thresholds for V/ELBW infants was emphasized[4,58].

The scarcity of data suggesting that higher Hb thresholds could mitigate cognitive delay led to the development of two multicenter randomized trials: the Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants (ETTNO) trial and the Transfusion of Prematures (TOP) trial[6,59,60].

The ETTNO trial randomized 1,013 neonates across 36 European NICUs and the TOP trial included 1,692 neonates from 19 US centers. Their primary outcome was neurodevelopmental impairment at 24 (22-26) months corrected age or death before assessment. In both trials, no significant differences were observed in the primary outcomes or secondary outcomes like NEC, BPD, ROP, brain injury, and nosocomial infection[41,59-61].

The TOP trial did not indicate improvements in cognitive outcomes in infants assigned to higher Hb thresholds or other clinically-relevant outcomes during the initial hospital stay or at 22 – 26 months. Despite more frequent transfusions in the higher Hb threshold group, there was no difference in NEC rates[41,55].

Practitioners are advised to adhere to transfusion thresholds within the ranges of the ETTNO and TOP trials[59-60]. These trials suggest that Hb transfusion thresholds should not exceed 13 g/dL or fall below 11 g/dL for critically ill newborns in their first week of life or requiring significant respiratory support. For stable older infants with no critical illness and who do not require significant respiratory support, thresholds should not exceed 10 g/dL or drop below 7 g/dL. Most guidelines now recommend a restrictive transfusion strategy for preterm neonates. Anyone proposing thresholds beyond those studied should bear the burden of proving their safety[12,41,51].

The Spanish Society of Neonatology encourages units to adopt specific guidelines aligned with local clinical practices to minimize heterogeneity[41].

## *NIRS as a way to monitor anemia*

Guidelines typically offer Hb thresholds for transfusion decisions; however, several unconsidered factors might also influence such decisions. These factors encompass a patient's transfusion history, reticulocyte counts, expected phlebotomy losses, nutritional status, concurrent illnesses, the severity of these, and the use of ESAs[61].

**Table 4.** Comparison of British, American, Australian, Canadian and Portuguese practice guidelines for RBC transfusion in newborn infants

| Clinical status | BCSH guideline | American Red Cross practice guideline | Australian National Blood Authority guideline | Canadian Blood Services guideline | Portuguese guideline SPN |
|---|---|---|---|---|---|
| Anemia in the first 24h | Hb < 12 g/dL or Hct < 36% | - | No respiratory support: Hb 10-12 g/dL Respiratory support Hb 11-13 g/dL | On ECMO and congenital cyanotic heart disease Hb < 15 g/dL | - |
| Infants receiving intensive care. Severe cardiopulmonary disease (FiO2 > 0.35) | Hb < 12 g/dL or Hct < 36% | Hct 40-45% | Hb 11-13 g/dL | Hb < 12 g/dL | Hb ≤ 10 g/dL Htc ≤ 30% |
| Chronic oxygen dependency Moderate cardiopulmonary disease (CPAP or O2) | Hb < 11 g/dL | 1Hct 30-35% | Hb 8.5-11 g/dL | Hb < 10 g/dL | Hb ≤ 8 g/dL Htc ≤ 25% |
| Late anemia, stable patient | Hb < 7 g/dL | Hct 20-25% | Hb 7-10 g/dL | Hb < 7 g/dL | Hb ≤ 7 g/dL Htc ≤ 20% |

BCSH: British Committee for Standards in Haematology; SPN: Portuguese Neonatology Society; Hb: hemoglobin; Hct: hematocrit; ECMO: extracorporeal membrane oxygenation; CPAP: continuous positive airway pressure.
*Adapted from Howarth C, Banerjee J, Aladangady N. Red blood cell transfusion in preterm infants: current evidence and controversies. Neonatology. 2018;114 (1):7-16 and Anemia of Prematurity Consensus, revised in 2013 by the Portuguese Neonatology Society*

Near Infrared Spectroscopy (NIRS) presents as a potential avenue for guiding transfusion practices in the future[62,63]. NIRS serves as a physiological marker for tissue hypoxia and has been utilized clinically to monitor regional mixed venous oxygen saturation in the central nervous system[62,63]. NIRS enables the measurement of oxygen consumption, represented by the fractional total oxygen extraction (FTOE), which reflects the ratio of consumption to supply. Although NIRS is commonly employed to assess brain oxygenation, its applicability extends to other tissues such as peripheral and gut perfusion[64]. Several small observational studies and recent reviews have associated increasing anemia with decreasing cerebral oxygen saturation or a compensatory rise in cerebral oxygen extraction (cFTOE), suggesting that elevating cFTOE could potentially serve as a physiological indicator of worsening anemia[61,63,64].

A secondary analysis of the TOP trial revealed an improvement in tissue oxygenation in both brain and mesenteric regions following transfusion, regardless of the Hb threshold group[65]. Infants experiencing cerebral saturation below 50% exhibited a higher incidence of death or neurodevelopmental impairment at 22 to 26 months corrected age. These results suggest that cerebral NIRS could be a valuable target for enhancing survival with no neurodevelopmental impairment in infants facing various levels of anemia. A prospective investigation comparing the current Hb threshold-based transfusion practices with an individualized guideline based on cerebral NIRS measurements is warranted[61,63-65].

## Conclusion

Anemia is prevalent among premature infants, particularly those born below 30 weeks of gestation, making RBC transfusion a crucial and common aspect of neonatal intensive care. Most RBC transfusions are administered to medically stable newborns to enhance their oxygen-carrying capacity during the critical phase of growth and development.

Despite the frequent use of transfusions in this population, there is an incomplete understanding of the potential benefits and drawbacks of these procedures. This has led to significant variations in approaches among clinicians, institutions, and countries.

Preventing AOP is vital, achievable by minimizing blood draws and utilizing capillary microsampling methods. Other preventive measures include DCC, UCM, and rhEPO therapy. However, the benefits of EPO usage remain limited[13].

Transfusion carries rare but established risks. The primary goal of ideal transfusion practices is to minimize unnecessary transfusions while ensuring that neonates who genuinely benefit from transfusions receive them appropriately. Most trials have used varying thresholds of anemia for transfusion, making systematic reviews and meta-analyses challenging to interpret. Clinical

trials consistently demonstrated that adopting a restrictive transfusion practice decreases exposure to transfusions without raising morbidity or mortality[55,56,59,60].

The integration of physiological biomarkers indicating tissue hypoxia into transfusion guidelines is a current area of research in neonatology. The use of NIRS to assess end-organ tissue oxygenation shows the potential for employing non-invasive methods to determine therapeutic thresholds[8,65].

In summary, the most effective approach for experts in this field is preventing anemia induced by prematurity through the implementation of protocols and the adoption of restrictive transfusion strategies. Each unit should endorse the specific guideline that aligns best with local clinical practices and promote strict adherence to it, aiming to minimize variability in clinical practice.

### Authors' contribution

S.A. Santos: 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; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. G. Rocha: 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. H. Soares: 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; 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 disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were

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CASE REPORT

# Rare ectodermal dysplasia present at birth: regarding a case report

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## Abstract

**Introduction:** Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome/Hay-Wells syndrome, is a rare disease, with autosomal dominant transmission, caused by mutations in the TP63 gene, which encodes a developmental transcription factor in the embryonic ectoderm. 70% of cases occur sporadically with no previous family history. It presents at birth and diagnosis is based upon the identification of distinctive signs of a child's phenotype. Molecular genetic tests confirm the diagnosis if TP63 gene mutation is detected. **Case report:** The authors describe the case of a newborn that presented at birth with areas of de-epidermization of the scalp, back, and scrotum, erythroderma, nail dystrophy, and posterior cleft palate. Genetic screening showed a heterozygous mutation of the TP63 gene. He is currently two years old, showing good clinical development, and in terms of his psychomotor development, he has a speech/language delay. **Discussion:** The approach is multidisciplinary and therapy is symptom-guided, correcting the cleft palate/lip, promoting skin barrier integrity, and accelerating the epidermization process. Genetic counseling/psychological support are recommended.

***Keywords:*** Newborn. AEC syndrome. Ectodermal dysplasia. Genetic. Case report.

## *Displasia ectodérmica rara presente ao nascimento: a propósito de um caso clínico*

## Resumo

**Introdução:** A síndrome AEC (*ankyloblepharon, ectodermal defects, cleft lip/palate*)/*Hay-Wells syndrome*, doença rara, de transmissão autossómica dominante, é causada por mutações no gene TP63, que codifica um fator de transcrição do desenvolvimento ectodérmico embrionário. 70% dos casos ocorrem esporadicamente, sem história familiar prévia. Presente ao nascimento, o diagnóstico é baseado nos sinais característicos do fenótipo da criança. Testes genéticos moleculares confirmam o diagnóstico ao detetar a mutação no gene TP63. **Relato de caso:** Os autores descrevem o caso de um recém-nascido, ao nascimento com áreas de desepidermização no couro cabeludo, dorso e bolsa escrotal, eritrodermia, distrofia ungueal e fenda palatina posterior. O rastreio genético revelou uma mutação heterozigótica - gene TP63. Atualmente com dois anos, boa evolução clínica e atraso fonoaudiológico relativamente ao desenvolvimento psicomotor. **Discussão:** A abordagem é multidisciplinar, a terapia guiada pela sintomatologia, corrigindo a fenda/lábio palatino, promovendo a integridade da barreira cutânea e acelerando o processo de epidermização. Aconselhamento genético/apoio psicológico são recomendados.

***Palavras-chave:*** Recém-nascido. Síndrome AEC. Displasia ectodérmica. Genética. Caso clínico.

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## Keypoints

**What is known**

- Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome/Hay-Wells syndrome, is a rare disease, with autosomal dominant transmission caused by mutations in the sterile alpha motif (SAM) domain of the TP63 gene. These TP63 mutations lead to a varied range of phenotypes in patients affected by AEC syndrome. Seventy percent of cases occur sporadically, with no previous family history.
- The clinical findings of AEC syndrome can overlap with those of other ectodermal dysplasia syndromes and are heterogenous in presentation, complicating the diagnosis and additional characterization of these disorders.
- An individualized, multidisciplinary, and long-term follow-up should be guaranteed for affected subjects and their families, aimed at identifying associated morbidities and preventing and/or mitigating potential serious complications and adverse outcomes.

**What is added**

- The authors highlight the atypical presentation of this case since the diagnosis was made in the absence of ankyloblepharon, which is part of the classic triad of this syndrome's features.
- The field of genetics is constantly evolving and new methods of addressing these rare syndromes will continue to grow and begin to define a new era in genetic epidemiology.
- Multidisciplinary monitoring is key to providing early intervention in the light of findings, especially those unrelated to dermatological changes, that are present in this syndrome.

## Introduction

Ankyloblepharon-ectodermal dysplasia-cleft lip/palate (AEC) syndrome, also known as Hay-Wells syndrome, belongs to a large, heterogeneous group of ectodermal dysplasias that affect the embryonic development of ectodermal tissues[1]. It is a rare genetic disorder, with about 100 patients reported to date. The female to male ratio is 1:1[2]. The exact prevalence is unknown due to the number of distinct ectodermal dysplasia syndromes and ambiguous definitions because of overlapping phenotypes and genotypes[1,2].

AEC syndrome is associated with a heterozygous mutation of the tumor protein p63 (TP63) gene, an important regulatory gene encoding a developmental transcription factor in the embryonic ectoderm that appears to control processes related to epidermal proliferation and differentiation. These TP63 mutations lead to a range of different phenotypes in patients affected by AEC syndrome[1,3].

Seventy percent of AEC syndrome cases occur sporadically with no previous family history (new or "*de novo*" mutation), with only thirty percent having an affected parent[4].

This syndrome is present at birth and diagnosis is based on the child's phenotypic features, a detailed clinical history, and a thorough clinical evaluation. A variety of specialized tests can aid in the diagnosis. Molecular genetic tests confirm AEC syndrome when they detect the mutation in the TP63 gene[4].

The authors seek to describe the case of a male newborn that presented at birth with a phenotype compatible with AEC syndrome, with a heterozygous mutation for the TP63 gene, as it is a rare disease with very few cases reported worldwide.

## Case report

Term, caucasian newborn, 38 weeks post-menstrual age, who is the result of an uneventful pregnancy, monitored in primary health care, with healthy, non-consanguineous parents. It is of note that a 4$^{th}$-degree maternal cousin has ectodermal dysplasia. Prenatal diagnosis of cleft palate in prenatal ultrasound at 21 weeks and an amniocentesis showed 46 XY. Negative serology and negative group B streptococcus screening test. For prolonged rupture of membranes (> 18 hours) the mother received three doses of intrapartum ampicillin prophylaxis.

A boy, weighing 2960 g and measuring 48.5 cm in length, with a head circumference of 34.5 cm, an Apgar score of 9/10 with good adaptation to extra-uterine life and no oxygen requirement, was born by vaginal delivery. At birth, he presented with extensive areas of de-epidermization and erosions of the scalp, back, and scrotum, erythroderma, nail dystrophy, and posterior cleft palate (Fig. 1A-D).

Due to the risk of infection, the newborn underwent blood tests and cultures for infectious screening, that came out negative, and was started on empiric antibiotics with ampicillin and gentamicin, completing eight days of antibiotic therapy.

Because of the large transdermal losses, the newborn required intravenous hydration during his first days and treatment with topical antibiotics/antifungals and emollient/re-epithelizing creams.

The congenital cardiopathy screening was negative. Ophthalmological evaluation was normal. The head, abdominal, and pelvic ultrasound, as well as the hearing screening, were normal. The heart ultrasound


**Figure 1. A-D:** phenotypic features at birth showing de-epidermization and erosions of the scalp, back, and scrotum, erythroderma, and nail dystrophy.

revealed an ostium secundum-type interatrial communication with mild left to right shunt.

The skin lesions presented with good clinical development, with gradual epidermization and resolution of the erosions. He was discharged at 13 days of age, clinically well, and with adequate ponderal development. He was to undergo multidisciplinary monitoring with dermatology, pediatric surgery, otolaryngology, and neonatology consultations.

Given the patient's phenotypic features, a diagnostic hypothesis of AEC/Hay-Wells syndrome was considered, and skin biopsy and genetic testing were performed.

The skin biopsy revealed mainly surface erosions and atrophy of the sebaceous glands, that although not specific, are described in AEC syndrome. The genetic testing identified a heterozygous mutation of the TP63 gene and based on the clinical and genetic findings, a diagnosis of AEC syndrome was made. The newborn was then referred for genetic consultation. Gene sequencing was extended to the parents, with the results pending.

A dermatology follow-up consultation at approximately one and a half months old showed good clinical development (Fig. 2A-D).

The cleft palate was surgically repaired at the age of 14 months, which was uneventful. The boy was then referred for a physical medicine and rehabilitation consultation. Due to a speech/language delay in terms of his psychomotor development, speech therapy was initiated.

He is currently 26 months old, presents with dysmorphic facial features, has a good weight-growth development according to his age and aside from a speech/language delay, has adequate psychomotor development with regular acquisition of neuromotor milestones. He also experiences chronic middle ear infections (otitis media) with no apparent development of hearing loss. The child remains under close dermatological follow-up in consultations and still requires topical emollient/re-epithelizing creams, showing hypotrichosis and sparse, brittle hair, a dry scalp with flaking on the surface, and nail dystrophy with micronychia. The skin is dry mainly due to some hypohidrosis.

## Discussion

AEC syndrome is a form of ectodermal dysplasia, a group of conditions characterized by a wide variety of symptoms that can affect the skin, hair, nails, teeth, certain glands, and other ectodermal structures. The symptoms are highly variable with a broad clinical spectrum evident at birth[5].

Most newborns will have some degree of skin erosion, ranging from the mild involvement of a specific area to the severe, even life-threatening, involvement of the whole body. The scalp is most frequently involved and is usually affected more severely than other areas. Scalp erosions may lead to severe scarring and alopecia. Skin erosions can be recurrent throughout childhood, often involving the head and neck, palms, soles, and skin folds. Both hyperpigmentation and hypopigmentation are noted in nearly all individuals with AEC syndrome. Hair is light-colored and brittle, and eyelashes and eyebrows are usually sparse or absent. Nails are absent or dystrophic and dental abnormalities, including hypodontia and conical teeth, are common. Additional skin abnormalities may also be present. The characteristic skin erosions may be associated with a diffuse reddish coloration (erythroderma)[4,6]. Cleft palate with or without cleft lip occurs in all AEC syndrome patients. Some children experience chronic middle ear infections (otitis media) and approximately 90% develop hearing loss due to the failure of sound waves conducted through the middle ear, that can lead to conductive hearing loss and subsequent delays in speech development. Conversely, rare clinical findings, including heart defects, may occur[4,7]. Aside from

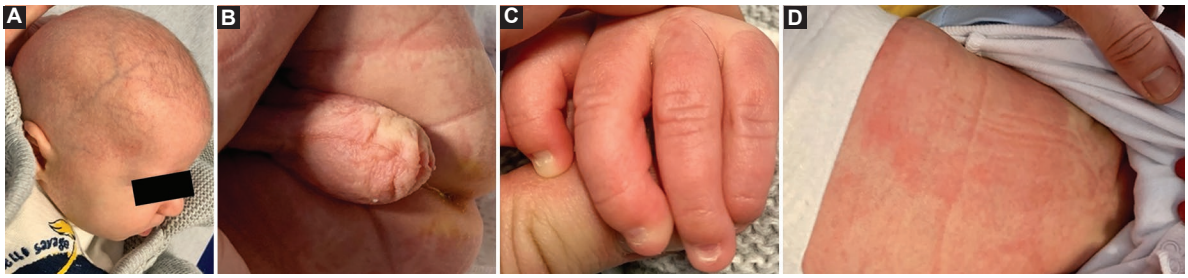


**Figure 2. A-D:** complete epidermization. Erythema on scalp and back. Less dystrophic nails.

the dental alterations, the features mentioned above were all observed in our newborn.

AEC syndrome may also cause decreased sweat production, resulting in thermal intolerance. Hypohidrosis is due, in part, to a lower number or absence of sweat glands[4]. Other glands may also be affected, such as in our case with the skin biopsy showing atrophy of the sebaceous glands.

Approximately 70% of individuals with AEC syndrome have ankyloblepharon filiforme adnatum (fusion of the eyelids), which can be partial, nearly complete, or even just a decrease in the size of the palpebral fissure[6,8].

Other rare clinical findings include ear canal atresia, supernumerary nipples, limb anomalies, and hypospadias. Poor weight gain, growth deficiencies, and short stature can also occur[4].

AEC syndrome has many clinical features in common with other TP63-related disorders that are forms of ectodermal dysplasia syndromes, such as ectrodactyly-ectodermal dysplasia-clefting (EEC) and Rapp-Hodgkin syndrome (RHS), the most important differential diagnosis for Hay-Wells Syndrome. Ankyloblepharon, when present, differentiates AEC syndrome from the other two conditions, although the degree of ankyloblepharon can vary and it may not be present in about 30% of patients, as in our case and others reported in literature. Clinical distinction between RHS and AEC syndrome is no longer considered important. Many reports indicate that AEC syndrome and RHS syndrome may be the same disease presenting differently. The minor differences between the two also suggest that these syndromes are variants of a single clinical entity. A recent review suggests that scalp erosions, rather than ankyloblepharon, may be the most important feature for distinguishing AEC and RHS from other p63-associated clefting and ectodermal dysplasia syndromes[6,8].

Due to the presence of erythrodermia and extensive areas of erosion, differential diagnoses should also include ichthyosis and epidermolysis bullosa, from which, however, AEC syndrome is distinguished by the occurrence of eye alterations or cleft lip/palate. It is thought that scalp lesions can disappear with age or lead to alopecia[9,10].

Curly hair-ankyloblepharon-nail dysplasia (CHAND) syndrome also has overlapping features with AEC syndrome but does not have skin erosions or cleft lip/palate[6].

A diagnosis of AEC syndrome is then based upon identifying characteristic symptoms, a detailed patient history, and a thorough clinical evaluation. A variety of specialized tests can aid in a diagnosis. Molecular examination of small samples of skin tissue (skin biopsy) may reveal specific features such as atrophy of the outer layer of the skin. Molecular genetic testing can confirm a diagnosis of AEC syndrome if they detect mutations in the TP63 gene known to cause the disorder. The condition shows an autosomal dominant pattern of transmission with 30% of patients having an affected parent, while 70% have a "*de novo*" TP63 pathogenetic variant[4].

The molecular basis of AEC syndrome has been shown mainly to involve heterozygous mutations in the sterile alpha motif (SAM) domain within the tail region of TP63 located on chromosome 3 (3q28). Atypical mutations include an intronic splice site mutation and a single amino acid insertion, but these also occur within the SAM domain. This region of TP63 is thought to be important in protein-protein interactions, for example in binding TP63 to the RNA splicing protein, apobec1 binding protein (ABBP1)[1,10].

TP63 is a homologue of the TP53 tumor suppressor gene, encoding for the p63 protein, a member of a family of transcription factors involved in regulating both proliferation and differentiation of the epidermal keratinocytes, as well as many other processes, including limb and facial development. It is also known that mutations in TP63 lead to skin erosions[1,10].

Mortality results from hydroelectrolyte imbalance due to fluid loss, anemia, secondary infection, and sepsis, so accurate, early diagnosis is essential. Prognosis is generally good, depending upon the early and

aggressive management of potentially life-threatening skin erosions, careful management of fluids and nutrition, and ongoing management of the multiple clinical manifestations noted in AEC syndrome[6].

The approach must therefore be multidisciplinary, and long-term follow-up should be assured, coordinating the efforts of a team of specialists such as pediatricians, dermatologists, ophthalmologists, dentists, audiologists, otolaryngologists, a geneticist, speech therapist, and other healthcare professionals that may need to plan an affected child's treatment systematically and comprehensively[4]. Prenatal and preimplantation genetic testing are options for future pregnancies if a pathogenic variant in TP63 has been identified in an affected family member[6].

Therapy is guided by the symptoms, correcting the cleft palate/cleft lip, promoting the integrity of the skin barrier with emollients, preventing trauma and, where erosions are present, avoiding superinfection, and accelerating the epidermization process. Genetic counseling and psychological support are recommended for the patient and family.

### Authors' contribution

J. Sousa-Marques: Conception and design of the study, report, review or other type of work; 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. A.G. Oliveira: 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. C. Gomes: 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. Coelho: 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. Andrade: 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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None.

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

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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CASE REPORT

# Posterior embryotoxon and Axenfeld-Rieger syndrome: a case report

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## Abstract

**Introduction:** We report the case of a 14-month-old girl with ocular and craniofacial malformations that prompted a comprehensive evaluation and subsequent diagnosis of Axenfeld-Rieger syndrome (ARS). This case emphasizes the importance of thoroughness and a multidisciplinary approach in patient evaluation. **Case report:** A 14-month-old girl exhibited abnormal craniofacial and ocular features, including marked posterior embryotoxon with iris strands attached to the Schwalbe's line and patchy iris due to stroma hypoplasia. Systemic testing revealed only minimal mitral regurgitation as the only other finding. Genetic testing later confirmed the diagnosis of ARS and a familial study identified the same variant in the proband's mother. **Discussion:** ARS is a rare genetic disorder characterized by developmental abnormalities, including anterior segment malformations of the eye, along with classic systemic findings, notably craniofacial dysmorphisms, dental anomalies and periumbilical redundant skin. Diagnosis primarily relies on clinical assessment, particularly the ocular findings. Upon considering this hypothesis, further investigation for systemic malformations should occur, with genetic testing confirming the diagnosis.

***Keywords:*** Axenfeld-Rieger syndrome. Ocular abnormalities. Craniofacial dysmorphisms.

## *Embriotoxon posterior e síndrome de Axenfeld-Rieger: um caso clínico*

## Resumo

**Introdução:** Relato do caso de uma criança de 14 meses, sexo feminino, com malformações oculares e craniofaciais que motivaram uma avaliação completa com diagnóstico *a posteriori* de Síndrome de Axenfeld-Rieger (ARS). Este caso enfatiza a importância da avaliação clínica minuciosa e multidisciplinar. **Caso clínico:** Criança de 14 meses, sexo feminino, com anomalias craniofaciais e oculares, incluindo embriotoxon posterior evidente e hipoplasia da íris. O estudo sistémico revelou insuficiência mitral ligeira, sem outras alterações. O diagnóstico de ARS foi confirmado geneticamente e o estudo familiar identificou a mesma variante genética na mãe da doente. **Discussão:** A ARS é uma doença genética rara caracterizada por anomalias do desenvolvimento, incluindo malformações do segmento anterior do olho e achados sistémicos clássicos, nomeadamente dismorfias faciais, anomalias dentárias e pele periumbilical redundante. O diagnóstico é clínico e baseado nas alterações ao exame oftalmológico. Após considerar esta hipótese, outras malformações sistémicas associadas devem ser pesquisadas e o diagnóstico deve ser confirmado geneticamente.

***Palavras-chave:*** Síndrome de Axenfeld-Rieger. Anomalias oculares. Dismorfias craniofaciais.

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## Keypoints

**What is known**

– Axenfeld-Rieger syndrome is a rare genetic disease characterized by anterior segment malformations of the eye and craniofacial dysmorphisms, along with various other multisystemic findings, requiring a comprehensive approach.

**What is added**

– We report a rare case of ARS, aiming to review suggestive findings and illustrate the ocular abnormalities that should prompt further investigation by pediatricians during routine care.

## Introduction

Axenfeld-Rieger syndrome (ARS) is a rare, genetically and clinically heterogeneous syndrome with an autosomal dominant inheritance pattern and high penetrance. It comprises a spectrum of conditions with variable severity, characterized by developmental abnormalities of both ocular and extraocular structures[1-3].

We report the case of a 14-month-old girl with classic ocular and craniofacial malformations, indicative of this diagnosis. Pediatricians should be aware of this syndrome, which is primarily suggested by the ocular findings. The multisystemic manifestations make it essential to prompt a systemic clinical evaluation.

## Case report

A 14-month-old girl was observed at a general pediatrics clinic due to ocular and facial dysmorphisms after being examined by a pediatric ophthalmologist for suspected strabismus. The gestation progressed without complications, and fetal ultrasounds were normal. The infant was delivered by cesarean section at 38 weeks' gestation, weighing 2000 g, with a body length of 47 cm and an occipitofrontal circumference of 33 cm. Apgar scores at one minute, five minutes, and 10 minutes were 9/9/10, respectively. Psychomotor development and staturo-ponderal growth were appropriate for the child's age and gender. The personal history was uneventful, with a normal neonatal auditory screening. The family history included familial short stature and maternal sensorineural hypoacusia, hypertelorism, mild retrognathia, and two previous abortions. The infant has one healthy sibling. During the physical examination, abnormal craniofacial features were observed, including hypertelorism without telecanthus, a broad nasal bridge, and microretrognathia, with no dental defects. The ocular features included a marked posterior embryotoxon with iris strands attached to the Schwalbe's line, patchy iris due to stroma hypoplasia, left eye corectopia, and an oval pupil (Fig. 1).

Given the ophthalmological findings and facial dysmorphisms, the diagnostic hypotheses were either Alagille Syndrome or ARS. The laboratory workup showed normal liver function. The abdominal and renal ultrasounds were normal. The spinal radiograph revealed no abnormal vertebrae. The cardiac ultrasound showed minimal mitral regurgitation with no hemodynamic significance. The ocular malformations, which are very specific to ARS, along with the absence of findings on the spinal radiograph and cardiac and abdominal ultrasound, made the diagnosis of Alagille Syndrome less likely. The genetic study revealed heterozygosity for duplication of segments 93 to 111 at exon 1 of the *FOXC1* gene - variant c.93_111dup(p.(Thr38Glyfs*51)), which has been associated with ARS type 3. This confirmed the final diagnosis at the age of 27 months. The familial genetic study demonstrated that the proband's mother had the same genetic variant with no ophthalmological abnormalities. Multidisciplinary follow-up was warranted with pediatric cardiology, otorhinolaryngology (ORL), ophthalmology, clinical genetics, and general pediatrics. During the pediatric cardiology consultation at three years of age, mild mitral insufficiency was still present, along with a persistent oval foramen. The ocular anatomic dysgenesis remained stable. The patient also presented high bilateral hyperopia (glasses were prescribed) and intermittent exotropia of the left eye. At three years of age, she began to develop ocular hypertension, which has been controlled with timolol plus dorzolamide eye drops with no visible damage to the optic nerve. Follow-up by ORL revealed mild hearing impairment after performing auditory evoked potentials at four years of age. The spinal radiograph was normal, and statural growth has been adequate (50$^{th}$ percentile), as has neurological development. Currently, the proband is five years old and has adequate growth and neurological development, nearly normal vision (visual acuity recorded as 10/10 in the right eye and 8/10 in the left eye, using the Snellen scale), mild hearing deficit, mild mitral insufficiency, and some classic dysmorphic features and eye abnormalities.

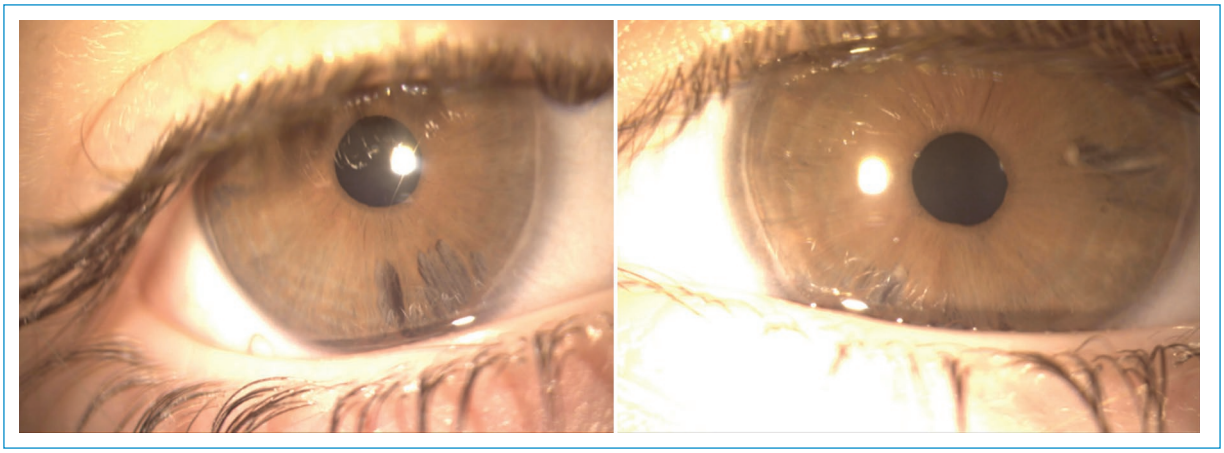

**Figure 1.** Posterior embryotoxon and iris atrophy.

## Discussion

ARS was originally divided into Rieger and Axenfeld anomalies (ocular features with and without pupillary anomalies, respectively) and Rieger and Axenfeld syndromes (ocular and extraocular abnormalities). However, the realization that these were all part of the same spectrum of conditions with overlapping phenotypes made the term ARS increasingly popular[2,4].

The ocular malformations affect the iris (stromal hypoplasia, pseudopolycoria, corectopia, and ectropion uvea), the cornea (posterior embryotoxon with iris strands attached to the Schwalbe's line), and the anterior chamber angle (usually open, although there may be a high insertion of the iris). A posterior embryotoxon is characterized by a prominent and anteriorly displaced Schwalbe's line and presents as a visible ring around the cornea. These malformations are often bilateral, although they may be asymmetric or unilateral. Extraocular muscle insertions may also be altered, leading to strabismus. These features can result in increased intraocular pressure (IOP) and later, the development of glaucoma, which is eventually diagnosed in at least half of patients. Iris abnormalities and posterior embryotoxon are important and common findings that suggest the diagnosis of ARS but may not be present in every patient[1,3-6].

Classic systemic findings include craniofacial dysmorphism (hypertelorism, telecanthus, maxillofacial hypoplasia, an abroad forehead, flat nasal bridge, thin upper lip, and prominent lower lip), dental anomalies (microdontia, oligodontia, and root, crown, or enamel abnormalities), and periumbilical redundant skin. Less frequent features are cardiac outflow tract defects, omphalocele, hypospadias, anal stenosis or atresia, sensorineural hearing loss, and pituitary and skeletal abnormalities (affecting the limbs and vertebrae), resulting in short stature[1,3-5].

Three types of ARS have been described: type 1, with both ocular and systemic findings; type 2, more frequently associated with dental abnormalities and, to a lesser extent, maxillary hypoplasia and umbilical defects; and type 3, which usually only exhibits ocular features, despite hearing loss and cardiac malformations being more common in this type[1].

The genetic defect is unknown in approximately 60% of cases. However, different mutations have been associated with this syndrome, and two major genes have been identified: *PITX2* (usually associated with systemic features and related to ARS type 1) and *FOXC1* (mainly detected in patients with exclusively ocular findings, associated with ARS type 3). In both genes, the same mutation can lead to variable expressivity and result in different phenotypes, with a wide range of clinical manifestations and severity. A *6p25* microdeletion syndrome, with a distinctive autosomal recessive phenotype, has also been described. Different phenotypes have been reported within the same and different families[1,3,4,7,8]. *De novo* mutations have been described in up to 70% of patients who underwent molecular diagnosis. Some studies suggest that intrauterine viral infections may be responsible for the genetic mutations associated with abnormal ocular development, as well as certain forms of ARS. Moreover, the asymmetric phenotypes often observed in the eyes of the same patient might be explained by varying viral loads[6].

Diagnosis is primarily clinical and is mainly suggested by the ocular findings, especially the iris abnormalities, as described in this case. Once this hypothesis is considered, further systemic malformations should be searched for, and the diagnosis should be confirmed

by genetic testing[3,5]. The differential diagnosis of ARS includes other disorders that also present with anterior segment dysgenesis, such as Iris Hypoplasia Syndrome, Peters anomaly, and Primary Congenital Glaucoma. Alagille Syndrome should also be considered in patients who present with posterior embryotoxon[3,5].

Once the diagnosis is confirmed, a cardiac and pituitary axis evaluation should be conducted, along with routine examination by an ophthalmologist to assess the need for glaucoma treatment, and an otorhinolaryngologist to promptly diagnose progressive sensorineural hearing loss through serial audiometry[3-5].

This case illustrates the importance of thoroughness and a holistic approach when dealing with patients, as many syndromes present with multi-organ or progressive symptoms. ARS is a rare genetic condition that should always be considered when iris abnormalities and/or posterior embryotoxon are present. The presence of classic craniofacial features and other malformations may also suggest the diagnosis. Although mutations are not inherited in most cases, early referral and genetic testing should be considered for individuals with a family history of ARS, as it follows an autosomal dominant inheritance pattern. Once the diagnosis is confirmed, a multidisciplinary approach should be pursued, including evaluation by ophthalmology, otorhinolaryngology, and cardiology.

### Authors' contribution

For all: All authors intervened in the conception and design of the case report, as well as acquiring data from the patient. BPN reviewed research studies and literature and analysed and interpreted its data. BPN and TM drafted the article. PFC and AM participated with the critical review of the article for intellectual content.

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None.

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**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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# The black hairy tongue phenomenon

## *O fenómeno da língua vilosa nigra*

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## Keypoints

**What is known**

- *Lingua villosa nigra* is a benign condition characterized by an abnormal brownish-black coating of the tongue[1-4].
- Predisposing factors include poor oral hygiene, certain medications, smoking, and xerostomia[1-3].
- First-line treatments include practicing good oral hygiene, discontinuing predisposing habits or medications, and gentle brushing or scraping of the tongue[2,4].

**What is added**

- Black hairy tongue usually appears in people over 40 years of age, being uncommon in infants[2].
- Diagnosis is clinical, following a thorough anamnesis and a simple, gentle scrape test with a tongue depressor or toothbrush[2-4].
- To prevent infants from undergoing unnecessary diagnostic procedures and treatments, it is important to be aware of this clinical entity[2-4].

A previously healthy, exclusively breastfed three-month-old female presented in the emergency room because of a persistent black coloration of her tongue, which had developed over the course of two weeks. She had a concurrent history of rhinitis.

The infant was started on topical nystatin due to a presumptive diagnosis of oral thrush, with no improvement.

Dark, blackish, elongated tongue papillae were observed, with a hairy appearance, detachable with a spatula (Fig. 1), with no other changes on physical examination. The diagnosis of *lingua villosa nigra* was made, and the baby was discharged, with instructions for daily gentle tongue brushing. The lesion disappeared after two weeks.

*Lingua villosa nigra*, also known as black hairy tongue, is a relatively uncommon and benign condition characterized by hypertrophy and elongation of filiform

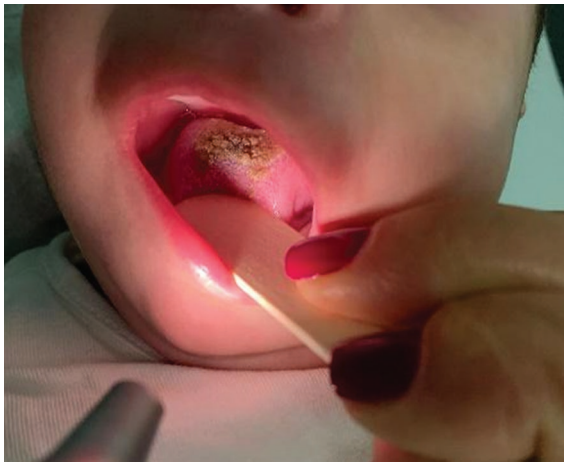

**Figure 1.** Macroscopic aspect of elongated filiform papillae and green discoloration on the dorsum of the tongue.

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papillae on the dorsum of the tongue, with a hairy appearance. Despite its alarming name, it is typically a harmless condition[2-4].

This condition is more commonly observed in adults, particularly in individuals over 40 years of age, and is extremely rare among infants. In pediatric patients, the occurrence of *lingua villosa nigra*[2] may be associated with factors such as antibiotic use, mouth breathing, or prolonged use of pacifiers or bottles. Additionally, certain predisposing factors, including a high carbohydrate diet or poor oral hygiene practices, may contribute to the development of the condition in children[3].

Prognosis is good, and treatment consists of gentle tongue brushing, resolving in a few days to a few weeks[2-4].

### Authors' contribution

For all: Idea behind, and design of, the study, report, review, or other type of paper. Data acquisition from patients, research studies, or literature. Analysis or interpretation of data 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 held accountable for the accuracy or integrity of the paper.

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