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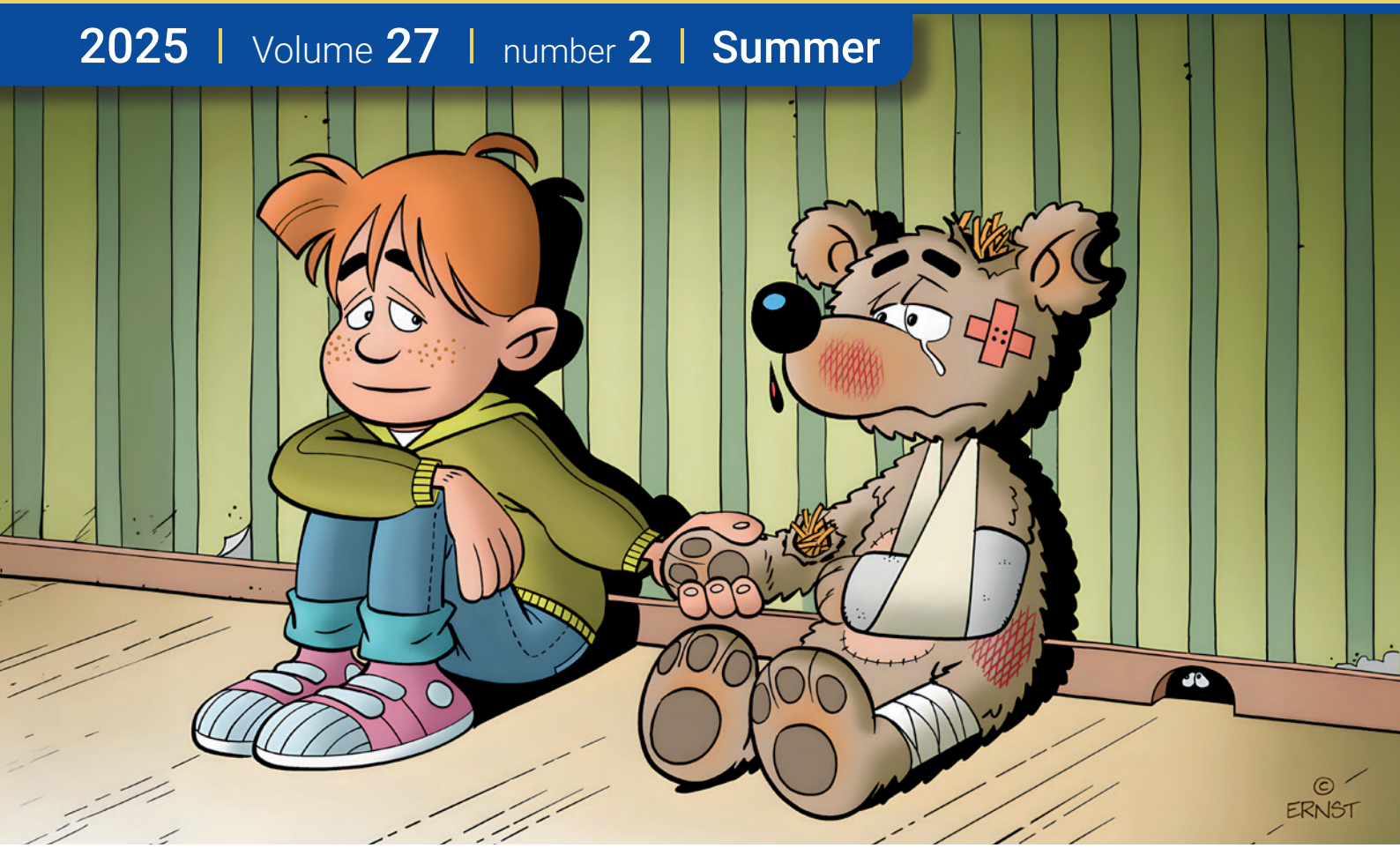

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Excipients à effet notoire : Ce médicament contient 0,1 mg de polysorbate 80 (E433) pour chaque dose de 50 mg (0,5 mL) et 0,2 mg pour chaque dose de 100 mg (1 mL). FORME PHARMACEUTIQUE Solution injectable. Solution limpide à opalescente, incolore à jaune, de pH 6.0. INDICATIONS THÉRAPEUTIQUES Beyfortus est indiqué pour la prévention des infections des voies respiratoires inférieures dues au virus respiratoire syncytial (VRS) : - chez les nouveau-nés et les nourrissons au cours de leur première saison de circulation du VRS. – les enfants jusqu'à l'âge de 24 mois qui demeurent vulnérables à une infection sévère due au VRS au cours de leur deuxième saison de circulation du VRS (voir rubrique 5.1). Beyfortus doit être utilisé conformément aux recommandations officielles en vigueur. POSOLOGIE ET MODE D'ADMINISTRATION Posologie Nourrissons au cours de leur première saison de circulation du VRS La dose recommandée est une dose unique de 50 mg administrée par voie intramusculaire pour les nourrissons dont le poids est <5 kg et une dose unique de 100 mg administrée par voie intramusculaire pour les nourrissons dont le poids est ≥5 kg. Beyfortus doit être administré dès la naissance chez les nourrissons nés au cours de la saison d'épidémie à VRS. Pour les nourrissons nés en dehors de la saison, Beyfortus doit être administré idéalement avant la saison d'épidémie à VRS. La posologie chez les nourrissons dont le poids est compris entre 1,0 kg et 1,6 kg est basée sur une extrapolation, aucune donnée clinique n'est disponible. L'administration du traitement chez les nourrissons de moins de 1 kg est susceptible d'entraîner une exposition plus élevée que chez les nourrissons pesant plus de 1 kg. Par conséquent, les bénéfices et les risques de l'utilisation du nirsévimab chez les nourrissons de moins de 1 kg doivent être soigneusement évalués. Les données disponibles sont limitées chez les enfants extrêmement prématurés âgés de moins de 8 semaines (âge gestationnel [AG] < 29 semaines). Il n'y a pas de données cliniques disponibles chez les nourrissons dont l'âge post-menstruel (âge gestationnel à la naissance + âge chronologique) est inférieur à 32 semaines (voir rubrique 5.1). Enfants qui demeurent vulnérables à une infection sévère due au VRS au cours de leur deuxième saison de circulation du VRS La dose recommandée est une dose unique de 200 mg administrée en deux injections intramusculaires (2 x 100 mg). Beyfortus doit être administré idéalement avant le début de la deuxième saison d'épidémie à VRS. Chez les individus devant subir une chirurgie cardiaque avec circulation extracorporelle, une dose supplémentaire peut être administrée dès que l'individu est stable après l'intervention, afin de garantir des taux sériques de nirsévimab adaptés. Si l'intervention a lieu dans les 90 jours suivant l'administration de la première dose de Beyfortus, la dose supplémentaire au cours de la première saison d'épidémie à VRS doit être de 50 mg ou de 100 mg selon le poids, ou de 200 mg au cours de deuxième saison d'épidémie à VRS. Au-delà de 90 jours, la dose supplémentaire peut être une dose unique de 50 mg indépendamment du poids au cours de la première saison d'épidémie à VRS, ou de 100 mg au cours de la deuxième saison d'épidémie à VRS, afin de couvrir le reste de la saison de circulation du VRS. La sécurité et l'efficacité du nirsévimab chez les enfants âgés de 2 à 18 ans n'ont pas été établies. Aucune donnée n'est disponible. Mode d'administration Beyfortus doit être administré uniquement par voie intramusculaire. Il doit être administré par voie intramusculaire, de préférence dans la partie antérolatérale de la cuisse. Le muscle fessier ne doit pas être utilisé systématiquement comme site d'injection en raison du risque de lésion du nerf sciatique. Si deux injections sont nécessaires, des sites d'injection différents doivent être utilisés. Pour les instructions concernant les précautions particulières de manipulation du médicament, voir la rubrique 6.6. CONTRE-INDICATIONS Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1. EFFETS INDÉSIRABLES Résumé du profil de tolérance L'effet indésirable le plus fréquent était les éruptions cutanées (0,7 %) survenues dans les 14 jours suivant l'administration. La majorité des cas étaient d'intensité légère à modérée. De plus, une fièvre et des réactions au site d'injection ont été rapportées à un taux respectif de 0,5 % et 0,3 % dans les 7 jours suivant l'administration. Les réactions au site d'injection étaient non graves. Liste des effets indésirables Ci-dessous sont présentés les effets indésirables rapportés chez 2 966 nourrissons nés à terme et prématurés (AG ≥29 semaines) ayant reçu du nirsévimab dans le cadre d'études cliniques et dans le cadre de la surveillance après commercialisation (vor rubrique 4.4). Les effets indésirables rapportés au cours des études cliniques contrôlées sont répertoriés par classe de systèmes d'organes (SOC) MedDRA. Au sein de chaque SOC, les termes préférentiels sont présentés par fréquence décroissante puis par gravité décroissante. La fréquence de survenue de chaque effet indésirable est définie comme suit : très fréquent (≥1/10) ; fréquent (≥1/100 à <1/10) ; peu fréquent (≥1/1 000 à <1/100) ; rare (≥1/10 000 à <1/1 000) ; très rare (<1/10 000) et fréquence indéterminée (ne peut être estimée à partir des données disponibles). Affections du système immunitaire · Indéterminé – Hypersensibilité 1 1 Effet indésirabe rapporté dans le cadre de notification spontanée Affections de la peau et du tissu sous-cutané · Peu fréquent - Eruptions cutanées 2 2 L'éruption cutanée était définie par les termes préférentiels groupés suivants : rash, rash maculopapuleux, rash maculeux. Troubles généraux et anomalies au site d'administration · Peu fréquent - Réaction au site d'injection3 ; Fièvre 3 La réaction au site d'injection était définie par les termes préférentiels groupés suivants : réaction au site d'injection, douleur au site d'injection, induration au site d'injection, œdème au site d'injection, gonflement au site d'injection. Nourrissons avec un risque plus élevé d'infection sévère par le VRS au cours de leur première saison de circulation du VRS La sécurité d'emploi a été évaluée dans l'étude MEDLEY chez 918 nourrissons à risque plus élevé d'infection sévère par le VRS, dont 196 très grands prématurés (AG <29 semaines) et 306 nourrissons porteurs de maladie pulmonaire chronique ou d'une cardiopathie congénitale hémodynamiquement significative pendant leur première saison d'épidémie à VRS, qui ont reçu du nirsévimab (n=614) ou du palivizumab (n=304). Le profil de sécurité du nirsévimab chez les nourissons l'ayant reçu au cours de leur première saison d'épidémie du VRS était comparable à celui du comparateur palivizumab et cohérent avec celui observé chez les nourrissons nés à terme et prématurés d'AG ≥29 semaines (études D5290C00003 et MELODY). La sécurité d'emploi a également été évaluée au cours de l'étude MUSIC, étude ouverte, non contrôlée, à dose unique, menée chez 100 nourrissons et enfants immunodéprimés d'âge ≤ 24 mois, qui ont reçu du nirsévimab lors de leur première ou deuxième saison d'épidémie à VRS. Les sujets présentaient au moins l'une des conditions suivantes : immunodéficience (combinée, en anticorps ou autre étiologie) (n = 33) ; corticothérapie systémique à forte dose (n = 29) ; greffe d'organe ou de moelle osseuse (n = 16) ; chimiothérapie immunosuppressive (n = 20) ; autre traitement immunosuppresseur (n = 15) et infection par le VIH (n = 8). Le profil de sécurité du nirsévimab était cohérent avec celui attendu pour une population d'enfants immunodéprimés et avec celui observé chez les nourrissons nés à terme et prématurés d'AG ≥ 29 semaines (études D5290C00003 et MELODY). Le profil de sécurité du nirsévimab chez les enfants pendant leur deuxième saison d'épidémie à VRS était cohérent avec celui observé pendant leur première saison d'épidémie à VRS. Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via : Belgique: Agence Fédérale des Médicaments et des Produits de Santé : www.afmps.be – Division Vigilance : Site internet: www.notifieruneffetindesirable.be – e-mail: adr@fagg-afmps.be Luxembourg: Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé – Site internet : www.guichet.lu/pharmacovigilance TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly, France NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ EU/1/22/1689/001 50 mg, 1 seringue préremplie à usage unique EU/1/22/1689/002 50 mg, 1 seringue préremplie à usage unique avec aiguilles EU/1/22/1689/003 50 mg, 5 seringues préremplies à usage unique EU/1/22/1689/004 100 mg, 1 seringue préremplie à usage unique EU/1/22/1689/005 100 mg, 1 seringue préremplie à usage unique avec aiguilles EU/1/22/1689/006 100 mg, 5 seringues préremplies à usage unique DATE DE PREMIÈRE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION Date de première autorisation: 31 octobre 2022 DATE DE MISE À JOUR DU TEXTE Date d'approbation : 01/2025. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu

* au cours de leur première saison de circulation du VRS

Référence:
1. Beyfortus RCP, jan 2025.

Sanofi Belgium - MAT-BE-2500285-V1.0-05/2025

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Contents

Pampers

Baby wipes unwrapped

In the baby bag, by the changing station, or on the go, if you have a little one, chances are that you'll have a pack of baby wipes well within your reach. But what gives wipes their magic touch? How do Pampers® get babies' bottoms squeaky clean while helping to keep their skin protected?

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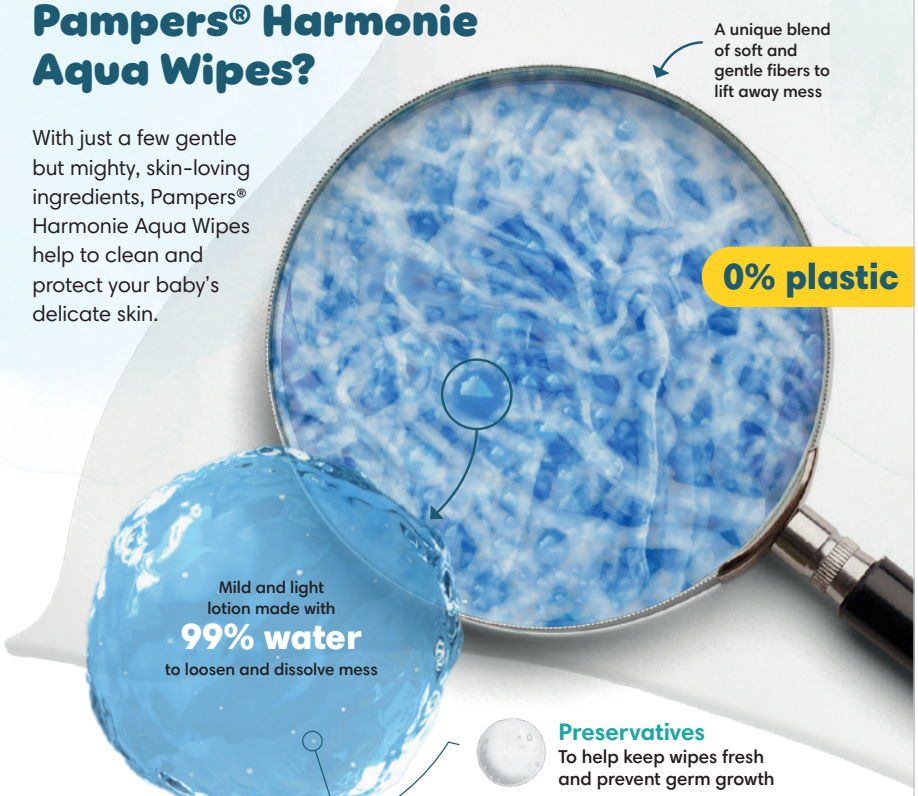

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Editorial

BACK TO THE FUTURE …

We are thrilled to present the summer issue of the Belgian Journal of Paediatrics. As we put the finishing touches to this issue and prepare for its release, we have a little evasive thought as we imagine all those unique and relaxing places where you might take and read your copy of the BJP. Wherever you will be, whatever you will do, we hope you will enjoy reading this issue! Whether it's on the beach, by the pool, in the mountains or simply in the garden, or perhaps waiting for the bus or the underground to go to work or to visit a museum, on a terrace or beside a river, we also hope that this issue will motivate you even more to commit to paediatrics and inspire you to come back and take care of children in the autumn! And for those of you who have forgotten their hard copy, we're delighted to announce that the journal is (and always will be) available free of charge on our website: https://www.belgjpaediatrics.com.

The theme of this issue is devoted to child abuse. We would like to sincerely thank our two guest editors, Marjolein Mattheij and Patrick Schlesser, who have done an enormous amount of work in preparing this subject. With the help of numerous authors who are experts in the field, they develop a comprehensive, realistic and respectful approach to these situations, which are always delicate and increasingly frequent. Marjolein Mattheij and Patrick Schlesser explain this in the following page.

We would also like to take the opportunity of this editorial to look back… and introduce a future section of the journal. At the 53rd annual Belgian Paediatric Congress in March 2025, the plenary session presentations on climate change and its impact on health were of particular interest to many of us. As paediatricians, the doctors of tomorrow's men and women, we cannot stand by and watch these upheavals take hold without speaking out. As medical practitioners and advocates for children, our role is, at the very least, to maintain hope, to explore new avenues, to publicise them, and to initiate or strengthen initiatives that can have a positive impact.

It became apparent that a significant number of actions are already being taken, either on an individual basis or within departments or hospitals. In the '**Seeds of change**' section, we invite paediatricians and caregivers who read our journal to share details of their projects and actions to promote biodiversity and sustainability.

« Do you care not only for children, but also for the world they grow up in? Do you have a project in your practice or hospital that has a positive impact on: the climate, biodiversity, sustainable mobility, waste reduction or recycling? We want to hear from you! We're looking for inspiring projects or stories from paediatricians who think and act sustainably. Whether it's a small idea or a big initiative — your story matters! »

A specific section is opened on the submission platform under the short/brief communication type. The texts will be directly reviewed by the editors. We ask you to describe the project or action undertaken or in progress, to explain the aim pursued, the results observed or expected, and the difficulties and facilitating events involved in bringing the project to a successful conclusion. The first stories will be published in the winter issue devoted to climate change and health.

Tall oaks from little acorns grow…

We wish you all a wonderful and rejuvenating summer holiday, and look forward to hearing from you in December!

Christophe Chantrain and Marc Raes

UW VRAGEN
OF COMMENTAAR

VOS QUESTIONS
OU COMMENTAIRES

Belgian Academy of Paediatrics
FUSION OF BVK-SBP, GBPF & VVK

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*Bébés sortis de néonatologie, en cas d'exposition inévitable et dans le respect des recommandations face au soleil.

Guest Editors' Editorial

«Our societies still struggle to recognise that the family is often the place where children are most exposed to psychological, physical, or sexual violence (de Becker).»

We are delighted to welcome you to this special issue of the Belgian Journal of Paediatrics (BJP), which is devoted to the subject of child abuse.

Child abuse is a community-wide problem with profound and lasting consequences for both the child, the family, and the community. Beyond the immediate harm for the child, its consequences extend to impairments in the child's physical and psychological development, while also elevating the risk of engagement in antisocial behaviour later in life. Those involved in child protection services believe that the vicious circle of abuse, which is often perpetuated to the next generation, must be broken. Within family systems, abuse can take various forms, each requiring a nuanced and comprehensive response. Early recognition is essential, as timely identification and intervention are critical to prevent further harm and support recovery. Addressing child maltreatment effectively calls for a multidisciplinary approach that balances protection with tailored support for families, aiming to foster long-term, positive change. In Belgium, we are fortunate to operate within a system that enables the detection and management of abuse outside of legal proceedings, provided the situation allows for it. By decree, Belgian legislation recognises the leading role regarding the detection of and intervention in cases of child abuse of the SOS Enfants teams in the Wallonia-Brussels Federation and the Child Abuse Trust Centres (Vertrouwenscentra Kindermishandeling) in the Flemish Community. Additional multidisciplinary organizations enhance this system by offering specialized knowledge, including the Sexual Assault Centres that are recently established in our country that provide a more effective response to sexual violence.

This themed issue concerning child abuse is approached holistically and systemically, in the same way that care is provided in the field. As a result, we invite you to explore a wide range of aspects related to child abuse that are incorporated in this issue, including how to identify possible signs of physical abuse, how to adequately perform relevant additional investigations, and how to understand different intervention approaches. Recognition of possible cases of child abuse by school teachers will be addressed in the article from Van Orshoven. The collaborative work of professionals will be examined through the notion of the 'partnership envelope' (de Becker) and by evaluating the establishment of a child abuse helpline for professionals in Germany (Berthold). Further somatic medical concepts will be covered by a practical guide concerning the skeletal survey (Mattheij) and a quiz on suspected sexual abuse (Bosteels). The article from Vanderpas addresses the role of inpatient assessment after urgent intervention concerning 4 siblings. The article from Loop provides an in-depth reflection on the needs of children and the complexity of child abuse due to inappropriate parenting.

Once abuse has been detected, confirmed or diagnosed as credible, the procedure for protecting the child, whether within or outside the family, should be implemented promptly and effectively. It must be said that the accompanying measures in our country are currently not sufficient. Support structures are overwhelmed, resulting in waiting times that frequently extend to several months or even years. In Belgium, hundreds of vulnerable children are waiting to be placed in appropriate care. We firmly believe that this problem requires urgent attention, as both the children involved and society as a whole will bear the consequences of this shortcoming.

Child abuse is a medico-psycho-social diagnosis. It is not our responsibility to identify the perpetrator. Our focus is the child and it´s opportunity to grow up in a safe, supportive, and loving environment. Emphasizing this focus towards the parents can help to establish a relationship of trust and respect. Ultimately, we can tell parents: « Our main priority is your child's safety and well-being, and we believe that by working together, we can find the best way to support your child's development in a safe and nurturing environment. »

We would like to express our gratitude to all the authors whose valuable contributions have shaped this edition of BJP into what it is. We also want to thank Mark Wojciechowski for his professional and detailed editorial check-up of all the submitted manuscripts.

Marjolein Mattheij and Patrick Schlesser

Door de unieke samenstelling, optimaal voor diagnose KMEA

DIAGNOSE

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Meer weten?

Child Maltreatment – The Important Interface Between Healthcare and Child Protection Services

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Keywords

Child abuse ; delivery of health care ; referral and consultation.

Abstract

Introduction

Healthcare professionals play a central role in preventing child maltreatment. However, major uncertainties remain regarding appropriate interventions and legal frameworks. In Germany, a 24/7 telephone helpline provides counselling to medical professionals. This article examines the topics raised by callers to the helpline and characteristics of cases.

Methods

The telephone counselling service is available to healthcare professionals, child and youth welfare workers and family court professionals. The counsellors are trained physicians who offer expert guidance on medical aspects related to cases of child maltreatment. A descriptive statistical analysis of calls from 2017 onward was conducted and free text case descriptions were assessed. Where possible, the characteristics of consultations were compared to the nationwide data of child protection service assessments of a risk to a child's wellbeing.

Results

Of 9,315 calls recorded, 78.0% (6,805) were from healthcare professionals, 10.0% (999) from child and youth welfare professionals and 0.6% (54) from professionals involved in court cases. Affected children were predominantly either of pre-school age or young adolescents, a majority was female (55.9%). The most prevalent form of child maltreatment was physical abuse and all forms of neglect.

Discussion

Most consultations originated from healthcare professionals, often regarding uncertainties with the threshold for reporting to the authorities. Although physical abuse was the most commonly reported form, sexual abuse was over-represented compared to data from child protection service. This suggests that this form causes particular concern in healthcare professionals. Uncertainty about child protection service involvement highlights the need for training.

Introduction

Child maltreatment and Adverse Childhood Experiences (ACEs) in general have enormous costs for individuals and society. While child maltreatment as an umbrella term includes physical and emotional neglect as well as physical, sexual and emotional abuse of children, the concept of adverse childhood experiences is broader and includes growing up in a household with a mentally ill or substance abusing parent, intimate partner violence, an incarcerated parent or instability due to divorce (1). While some affected children prove resilient and go on to lead normal lives, for others the burden means lifelong mental and physical health problems such as depression and anxiety, as well as a higher risk for common diseases such as hypertension, type 2 diabetes, cancer and others (2). A societal cost estimate by Klika et al. reported a total lifetime cost of $ 2.94 trillion for all U.S. child maltreatment cases assessed in 2018, including lost work, medical and welfare costs (3).

In many European countries, the responsibility for providing support to families and protecting vulnerable children from maltreatment lies with child protection services (CPS) (4, 5). Healthcare providers, on the other hand, have unique opportunities for primary, secondary and tertiary prevention: these include programs for primary prevention of abusive head trauma, screenings for early detection of cases of maltreatment in emergency departments and trauma focused treatments (6-9). However, the World Health Organization estimates that 90 per cent of child maltreatment goes undetected by healthcare professionals (10). Furthermore, collaboration and communication at this pivotal interface between the healthcare system and CPS have only recently been incorporated into nationwide medical training regulations, and they remain significantly deficient (11). In 2018, the German Medical Association has issued updated recommendations for specialist training, including basic knowledge on child abuse prevention and treatment for pediatricians, child and adolescent psychiatrists and pediatric surgeons.

Health care professionals are a highly relevant target group for prevention efforts. Reasons for missed opportunities for prevention are more likely on the individual level than in legislation (12). Common reasons for not pursuing a suspicion of child abuse

or neglect cited by healthcare professionals include that it was perceived as an "uncomfortable" topic, superiors were not willing to deal with the topic, a lack of training, particularly in dealing with the legal ramifications of medical confidentiality, involvement of CPS, or law enforcement (13-16).

Responses to this problem vary from country to country. In many cases, however, specialized collegial consultation facilities for physicians have been established at the interface between child protection services and the healthcare sector. Examples include the Dutch Expertise Centre for Child Abuse and the child abuse evaluation clinics in the German Land of Berlin (17, 18). Furthermore, in 2017 the German federal Ministry for Families, Senior Citizens, Women and Youth established a nationwide child abuse helpline for professionals (CAHP).

The service functions as a low-threshold medical point of contact by telephone, offering guidance to healthcare professionals on potential cases of child maltreatment. The counselors' role is not to adopt the case, but rather to provide guidance to professionals seeking assistance, empowering them to initiate effective child protection interventions.

The present article aims to analyze the specialist disciplines and care settings of the professionals seeking advice, as well as the characteristics of the cases in terms of forms of maltreatment and the age distribution of the children affected. These data will be compared to the national statistics of child protection services in Germany (19). A particular focus is placed on pediatricians working in outpatient and inpatient settings, and the most common consultation topics are presented herein. The reader will be able to draw two conclusions: Firstly, what areas of child abuse and neglect are particularly important in training health care professionals? Secondly, what questions can be expected for similar counselling services in other countries?

Methods

Participants

The CAHP offers a telephone advisory service that is operational on a 24/7 basis for professionals working in healthcare, child and youth welfare and judges in "family courts". The latter, as opposed to criminal courts, refers to courts, which deal with the non-criminal issues of child abuse and neglect, such as out-of-home placement and custody issues. The telephone advisory service is available free of charge. Callers are directly connected with one of the consulting physicians who are either pediatricians, child and adolescent psychiatrists or forensic physicians. All have a certificate in child abuse medicine, which is not a board-certified pediatric subspecialty in Germany as it is for example in the U.S. A senior specialist from each of the three subspecialties is available to the consultants for advice at any time. The caller can give their own name and place of work but must describe the case anonymously regarding the child concerned. This ensures maintenance of medical confidentiality. Furthermore, the name of the caller is not recorded (figure 1).

In Germany, professionals bound by legal obligations to maintain professional confidentiality (e.g. physicians, psychotherapists, dentists, occupational and speech therapists, nurses and paramedics) are required to adhere to specific legal stipulations in instances of suspected child abuse and neglect. They are required to undertake measures to protect the child, including discussing their concern with the parents, give advice and recommend supplementary support services. If these measures prove insufficient to address the concerns of the professional, there is authority to inform CPS. However, the parents should be informed of this beforehand, unless this would jeopardize the protection of the child. Accordingly, there exists no obligation to report child abuse in Germany. Rather, each healthcare professional is bound by professional responsibility to take action to protect the patient. The duty to act provides a broader scope than the duty to report. In everyday practice, however, it is uncommon for professionals to be held responsible for failing to protect a child.

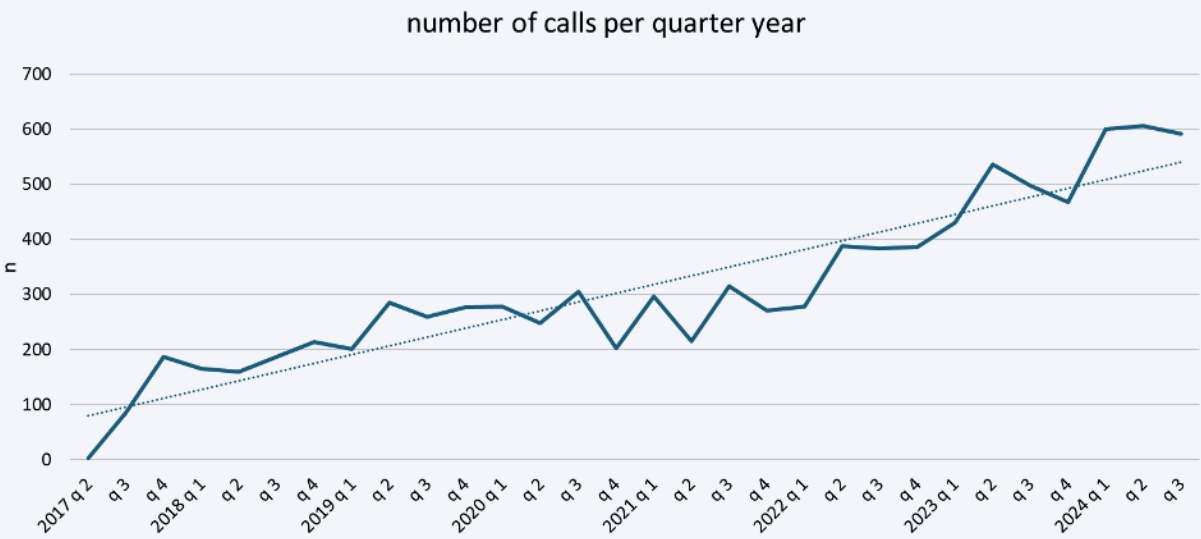
Professionals working in child protection services and judges who are involved in child abuse cases at family courts can seek advice on medical issues concerning a case of child maltreatment.

Procedure

All calls are directly connected to a physician working in the CAHP. The caller is asked to present the case anonymously regarding the child and family who are affected (index patient). Typically, a minimum set of information is requested, such as the caller's profession and the professional relation he or she has to the index

FIGURE 1: The child abuse helpline for professionals.

FIGURE 2: Number of calls to the CAHP from July 1st, 2017 until October 26th, 2024.



patient, along with age and gender of the index patient. The caller is then invited to describe the case and ask questions.

The counselling physicians document each consultation on a secure online platform, recording standard information in a structured manner (e.g. the caller's profession, specialist discipline, working environment, the professional role in relation to the index patient and data on the index patient). In addition, a case description is recorded in free text, which enables a qualitative evaluation of the consultations.

A descriptive analysis of the data regarding the callers and index patients for calls recorded between July 1st 2017 and October 26th, 2024 was performed, as well as a review of common topics of consultation.

Institutional review board approval

On the grounds of anonymous counseling, the institutional review board of Ulm University ruled in January 2017 that no formal approval is required to carry out the consultation and to publish the data.

Results

During the period of interest, a total of 9,315 calls were recorded at the CAHP. Of these, 6,805 (78.0%) were from healthcare professionals, 999 (10.0%) from child and welfare professionals (including CPS), and 798 (9.0%) from a heterogeneous group of teachers, police officers and non-professionals such as parents or relatives of children affected by abuse or neglect. Non-professionals (victims of abuse, relatives and other bystanders) have specialized counseling services available on their own, the latter mentioned professional groups are subject to such divergent legal frameworks that a counsel by physicians appears to be ineffective, such as police officers. However, there are currently discussions about whether the service should be opened up to teachers. In addition, 54 calls (0.6%) were from judges and other legal professionals. 216 calls (2.5%) were of an obviously non-serious nature (e.g. prank calls). Of note: CAHP service was opened to child and youth welfare professionals, judges and other legal professionals only since 2021, which can partly explain the comparatively low number of callers from these groups.

The number of calls has shown a consistent rise during the period of interest (see figure 2). It is important to note the unusual fluctuations in calls recorded in 2020, which appear to follow a sawtooth-like pattern. The most significant external influencing factor during this period was the course of the Covid 19 pandemic in Germany. The first documented case of the virus in Germany was on January 27, 2020, followed by a series of national lockdowns in March 2020, and then in December 2020 and January 2021.

Minor and maltreatment characteristics

All consultations concerned potential cases of child abuse and neglect, so at least indirectly one or more minors in focus (MIF) were the focus of the consultation. However, not all callers were able to provide detailed information on the MIFs. For instance, psychiatrists may become concerned that the children of a patient treated for substance abuse may be at risk. In these cases, they could often not provide detailed information on the MIF. Furthermore, the risk to children might be even more diffuse, when only a patient with pedophilia is known and the reason of the call is to decide whether there is a risk for children, but the children are not known to the caller.

However, the majority of calls (n=5,641, 60.6%), at least one MIF could be identified by the caller. If disclosed during the consultation, age and gender of the MIF were documented.

The age distribution of MIFs exhibited a double peak pattern for pre-school children and young adolescents (4 to 6 years and 13 to 15 years, respectively), as illustrated in figure 3. The age distribution of children who were subject to child protection assessments in Germany in 2023 is illustrated in 4 (19).

In 688 cases (11.8%), gender information was not recorded. Of the 4,973 cases for which gender information was available, 2,781 (55.9%) were recorded as female, 1,999 (40.2%) as male and 193 (3.9%) as other. "Other" refers to instances where the child's gender is not specified or where there is more than one child.

The gender distribution of children subjected to CPS assessments in Germany in 2023 was as follows: female in n=101,886 (48.1%) and male in n=109,809 (51.9%) cases (19).

In 5,987 CAHP cases, at least one form of child maltreatment could be identified. The most prevalent forms of maltreatment that were addressed in counseling sessions were physical abuse

FIGURE 3: Age distribution of minors in focus (MIFs) of calls to the CAHP, n=5,641.

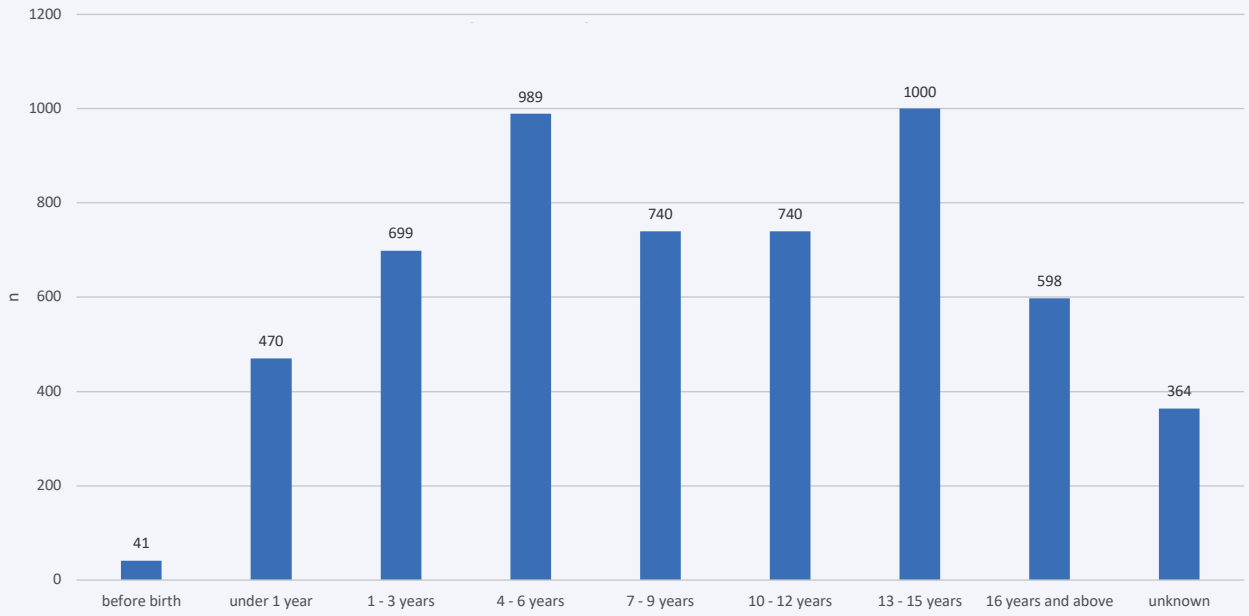
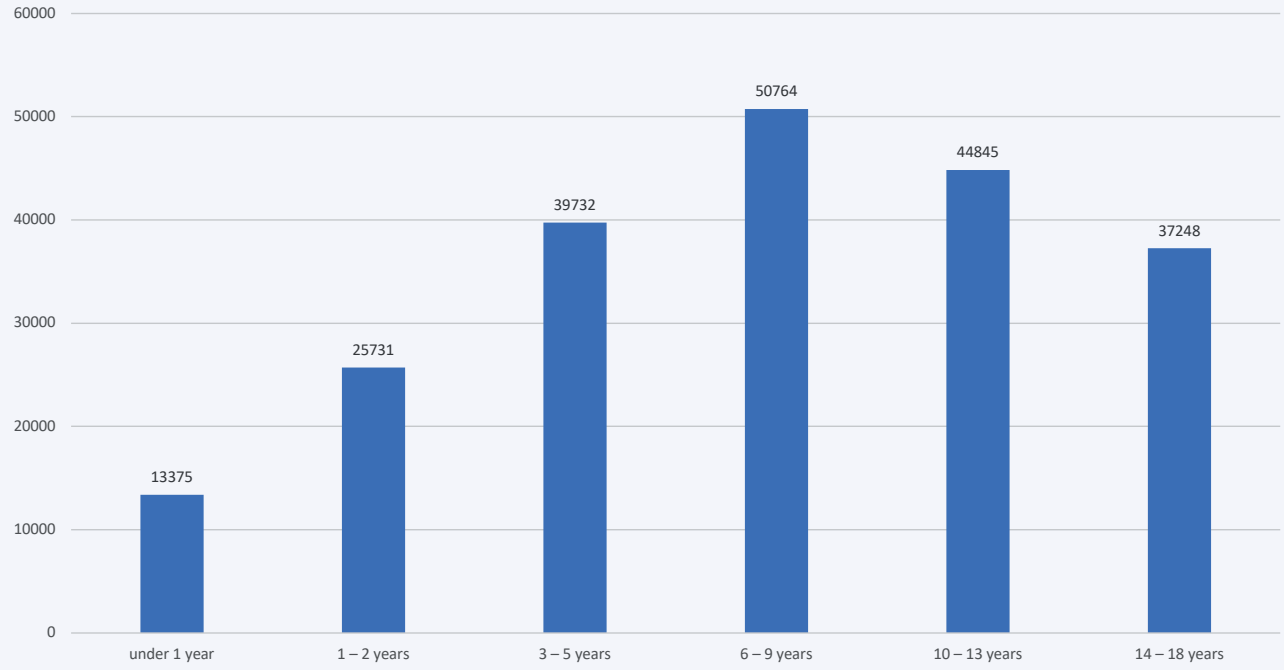


FIGURE 4: Age distribution of minor assessed by German CPS in 2023, n=211,695, taken from (19).



and all forms of neglect, followed by sexual abuse (see figure 5 for a comparison of CAHP cases, CPS assessments in 2023 and population-representative data from 2017 (19, 20)).

Caller characteristics

In 4,492 calls from health care professionals, the subspeciality of the caller was most commonly either child and adolescent psychiatric or pediatric. Adult psychiatry or psychotherapy was the third most common specialty. For details, see figure 6.

Contents of counseling

The majority of consultations pertained to matters of collaboration with CPS (n=2,643, 53.8%), encompassing inquiries into the degree of concern that would necessitate the involvement of such services. One typical question was, for example: "Do my findings constitute reasonable suspicion that would be requisite to breach medical confidentiality?" Additionally, inquiries addressed more structural concerns, such as how to contact CPS, particularly in circumstances where immediate intervention during nocturnal hours or on weekends appeared imperative. Finally, there were instances where respondents expressed stereotypes regarding

FIGURE 5: Comparison of maltreatment forms in calls to the CAHP, confirmed cases of "acute risk" in assessments of the German CPS in 2023 (n=34,286) (19) and in the population based study by (20).

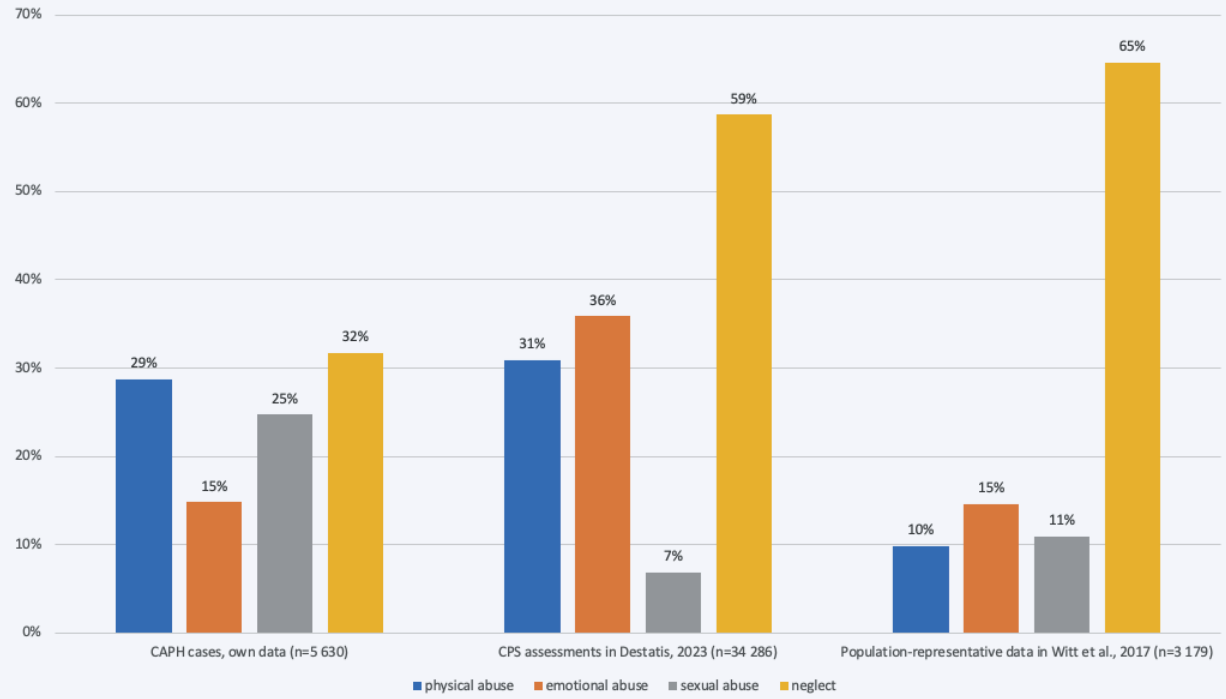
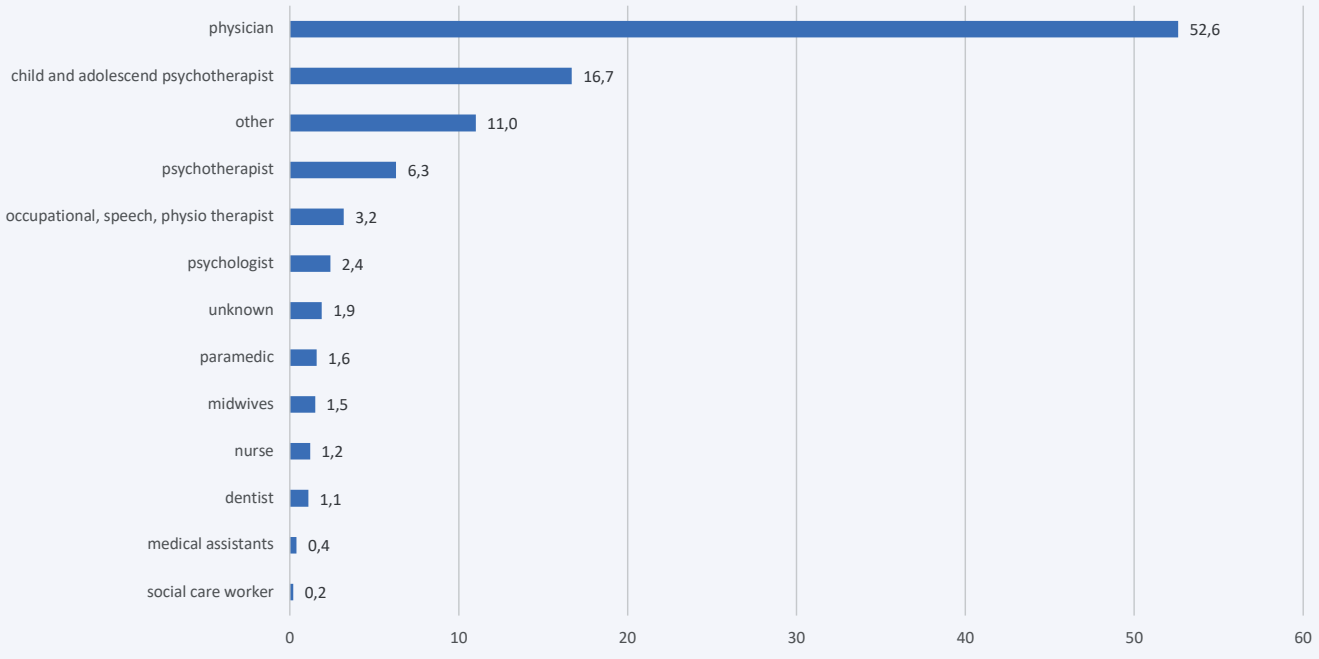


FIGURE 6: Professions of callers to the CAHP, n=4,492.



CPS, often holding the misconception as the agency which automatically takes children from their parents when involved.

Discussions of the specificity of medical findings regarding abuse and how to talk to MIF and their parents were approximately equally prevalent, with n=1,416 (28.8%) and n=1,255 (25.6%), respectively. Examples for the former topic include the specificity of certain genital infections like herpes, molluscum contagiosum, genital warts, lues etc. in prepubertal children for sexual abuse, the specificity of findings in abusive head trauma or the specificity of attachment disorders for emotional abuse or neglect. As stated above, German law requires that, where reasonable, the parents be spoken to before CPS is informed. Therefore, preparing those conversations is an important part in the consultations to the helpline. The question of whether and how to broach the subject of sexual abuse with affected children is also a frequent topic of counselling. In rare cases, CAHP consultants are asked to provide a second opinion on visible findings, such as bruises or x-ray or

MRI images. In these cases, CAHP refers to forensic medicine institutes that offer such a service. CAHP does not provide a second opinion on visible findings.

Next were questions regarding reporting laws in n=1,148 (23.4%) cases. Questions on networking partners in child protection, including child advocacy centers, advice and counselling centers, law enforcement and others, were asked in n=839 (17.1%) cases. The discussion encompassed specific counsel on medical procedures, predominantly concerning the treatment of minors after sexual assaults in n=552 (11.2%) cases. Finally, the implementation of legally secure documentation of the findings was discussed in n=415 (8.5%) cases.

Caller satisfaction was evaluated by the Deutsches Jugendinstitut at two points in time: 2018/19 and 2022. Callers rated the benefits as very positive. Of 107 respondents who completed an online questionnaire after a consultation, 80.8% stated that the consultation was very useful for understanding the child protection system. For the specific case and their next steps, 92.4% found the consultation very useful and 88.3% said they were able to better place their own findings in the context of child protection (21, 22).

Discussion

The data offers valuable insight into the experiences of medical professionals handling cases of suspected child abuse and neglect. The majority of these calls originated from the healthcare sector, which is not unexpected, given that the initiative commenced as a counseling service for healthcare professionals. Subsequently, professionals from CPS and family courts were included as target groups. Additionally, the healthcare professional population is considerably larger than those in child and youth welfare and family courts. This discrepancy is particularly pronounced in the context of family courts, where the number of calls remains comparatively low.

The fluctuation of calls in 2020 and 2021 correlates with the fact that there was a drastic decline in the number of patients in all areas of the healthcare system during the Covid 19 pandemic (23, 24). While patient numbers have only gradually returned to pre-pandemic levels, the CAHP has documented a period of overcompensation following the conclusion of lockdown measures, accompanied by a subsequent and accelerated increase in call volumes relative to prior levels. Extensive media coverage on whether domestic violence, child physical and sexual abuse became more prevalent during the pandemic, might have brought the topic more to the awareness of professionals.

Compared to the age distribution of assessments by CPS in Germany, callers to the CAHP tend to see a higher percentage of younger children (19). This observation Is in line with the fact that not all preschool children at risk are seen in daycare facilities, but almost all of them at least visit a pediatrician more or less regularly.

In Germany, the legal definition of a child commences at birth. Consequently, assessments of the danger to a child's best interest are only possible from birth. In contrast, concerns regarding the current and future well-being of a fetus may arise for healthcare professionals, either due to substance abuse by the pregnant woman or due to the situation of older siblings. This is why "before birth" is an age category in the consultations of the medical helpline, but not in assessments by CPS.

With respect to the various forms of maltreatment, the sample from the child abuse helpline consultations varies significantly both from the assessments of child protection services and population-based research (19, 20). While neglect is the most prevalent form of maltreatment in CAHP data, CPS assessments and population-based research, physical and sexual abuse are almost as prevalent in the consultations of the CAHP. Conversely, emotional abuse is more prevalent in CPS assessments, while sexual abuse is comparatively uncommon. The order of the forms of abuse are the same in the population-representative study; however, a comparatively higher prevalence of sexual abuse is observed. Overt manifestations of child maltreatment are more prevalent in calls to the CAHP. This could indicate that medical professional often overlook emotional forms of abuse. The alternative explanation that healthcare professionals feel confident in dealing with cases of emotional abuse and therefore do not need guidance in these cases seems unlikely. Sexual abuse in particular has been found to be particularly distressing and disconcerting for professionals, so that professionals feel they need advice on how to deal with cases of sexual abuse disproportionately often.

The sample of MIFs in consultations at the CAHP was female to a higher percentage compared with the children under assessment by CPS in general. This can be partially attributed to the relatively high proportion of consultations regarding sexual abuse compared to the assessments of CPS. In child sexual abuse, female children and adolescents are more often affected than male children and adolescents (20, 25).

In terms of consultation topics, it is not surprising that the most common concern expressed by physicians was cooperation with CPS – as intersectoral collaboration and communication is only recently starting to be part of medical training, structured curricula are only recently being developed. In this context, numerous consultations refer to the determination of whether a particular finding or situation already constitutes reasonable suspicion (in German: "gewichtige Anhaltspunkte") for a child being at risk. This term is the legal expression for the precondition of being allowed to disclosure information to child abuse services. However, this term remains undefined in German law. Consequently, the evaluation of the data from the CAHP aligns with the findings of earlier studies, which identified a lack of understanding of legal terms as a significant impediment to cooperation between healthcare and child and youth welfare (26). CPS, as a state authority with sovereign tasks, are subject to completely different processes and logics than clinical medicine. One of the main problems at this interface is the different understandings of urgency and prognosis. The failure of physicians to communicate their findings to CPS and the inability of CPS professionals to pose the appropriate questions to physicians, can result in the child being subjected in further or even additional harm. Many providers in the healthcare sector offer their services on a 24/7 basis, while child protection services are de facto not available 24/7 in all administrative districts – although this is required by law.

CPS possesses a wide range of options for intervention in Germany, the permanent placement of children in foster care remains the last resort used in rare cases. However, this form of intervention is the one most frequently mentioned when healthcare hesitate to inform the CPS. This underscores the necessity for additional training in the future. In summary, it can be stated that the differentiated obligation to act as intended by the legislature nevertheless largely leads to the question of whether a particular case should or must be "reported" or not. It is only through the counseling provided by CAHP that these professionals become aware of their options for action and the legal conditions for passing on information.

Limitations

First, it is important to keep in mind the nature of the service, which is to provide guidance to professionals struggling with uncertainties concerning cases of suspected child maltreatment. The primary limitation in the generalizability of the data stems

from the fact that the sample does not constitute a representative sample of healthcare professionals. The observed fluctuation in calls, whether occurring over a short or long term, cannot be directly interpreted as indicative of a general trend in child maltreatment incidence. Additionally, the evaluation is derived from counselling dialogues rather than structured interviews developed for research purposes, resulting in a certain heterogeneity of the data.

Conclusions

The hesitancy of medical professionals in collaborating with CPS, as evidenced in previous studies, is also apparent in the counsel sought from the CAHP. This suggests that the service is commensurate with the existing demand. Moreover, there is a pronounced necessity for additional training in the domains of intersectoral collaboration, legal frameworks and communications skills.

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The Radiological Investigation of the Skeleton in Suspected Non-Accidental Injury in Children – A Practical Guide for the Skeletal Survey

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Keywords
Non-accidental injury ; child ; fractures, bone ; diagnostic imaging ; skeletal survey.

Abstract
Imaging plays an important role in the assessment of children with possible non-accidental injury. Studies have shown that there is significant variability in imaging performed to identify fractures in children with possible non-accidental injury. In 2013 the European Society of Paediatric Radiology (ESPR) voted in favour of adopting the RCR/SCoR/RCPCH guideline concerning the radiological investigation for non-accidental injury in children. We present a poster illustrating the required radiographic investigations of the skeleton in suspected non-accidental injury in children, that can serve as a practical tool to facilitate adherence to the guideline. We also provide a summary of the key points of the guideline, and discuss challenges and possible solutions for these challenges for implementation of the guideline in the Belgian context.

Introduction

Paediatric non-accidental injury (NAI) is a considerable health problem, and imaging plays a fundamental role in it assessment. Over the last decades, several national surveys performed in the UK, the USA and The Netherlands, have shown significant variability in imaging performed to identify fractures in suspected NAI in children (1-3). In 2008 the Royal College of Radiologists (RCR) and the Society and College of Radiographers (SCoR) endorsed by the Royal College of Paediatric and Child Health (RCPCH) published a joint British guideline concerning the radiological investigation for NAI in children. In 2011 a study was performed aimed to determine the practice among members of the European Society of Paediatric Radiology (ESPR) and their affiliated institutions with regards to imaging of paediatric NAI (4). Practice at that time was compared with the joint guideline by the RCR/SCoR/RCPCH. The study concluded that the survey data demonstrated significant variation in the protocols of the contributing institutions. The authors identified a need for a European consensus protocol and recommended implementation of the RCR/SCoR/RCPCH guidance. During the ESPR meeting in 2013 there was an overwhelming vote in favour of adopting the RCR/SCoR/RCPCH guideline as the standard across Europe. Since then the guideline has been updated in 2017 and in 2018 (5).

Guideline summary

The RCR/SCoR/RCPCH guideline identifies imaging that should be undertaken when NAI in a child is suspected. The guidance is designed to assist clinicians, paediatricians, radiographers, radiologists, and nuclear medicine technologists who request, perform or report imaging by setting out clear recommendations on each stage. In the development of the guidance, the authors incorporated evidence-based research for the type of imaging conducted to detect occult injuries, while minimizing radiation exposure and patient distress. When it comes to imaging of the skeleton in search of fractures the guideline states that children under two years of age should undergo a full skeletal survey, with a standard series of views, which can be found in Appendix A of the guideline (5). The choice of imaging in older children should be considered on a case-by-case basis. The guideline further states that the skeletal survey should be performed by two radiographers with documented education and training in imaging of suspected NAI and forensic radiography techniques. Two radiologists with at least six months of specialist paediatric radiology training, including experience of suspected NAI in children, should provide a consensus report within 24 hours. This allows new radiographs to be taken in a timely manner if indicated. When serious injury is identified in a child due to

FIGURE 1: Poster illustrating the required radiographic investigations of the skeleton in suspected non-accidental injury in children.

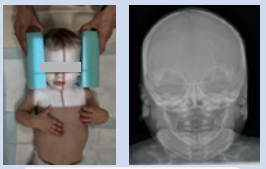
Skeletal survey for suspected non-accidental injury in children

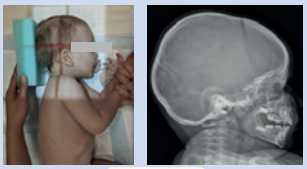
Practical guidance for following the RCR guideline [reference see below]

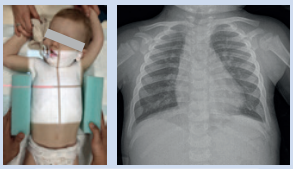
UZA

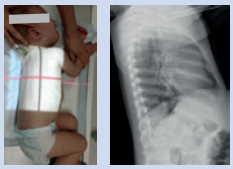
This is an example of the skeletal survey in a larger child. For a small child, the following images can be combined:

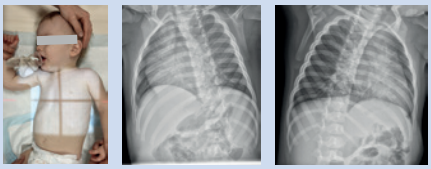
- Lateral cervical, thoracic and lumbar spine (into 'Lateral whole spine'),
- AP humerus and forearm (into 'AP whole arm, centre at elbow'),
- AP femur, tibia and fibula, knee and ankle (into 'AP whole lower limb, hip to ankle').

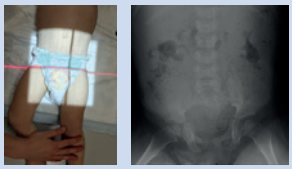

Anterior-posterior (AP) skull

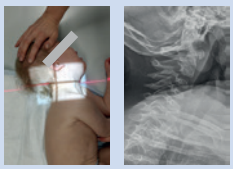

Lateral skull

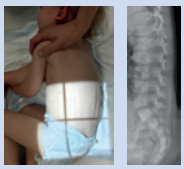

AP chest (including shoulders)

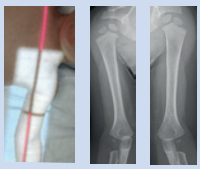

Lateral chest & thoracic spine

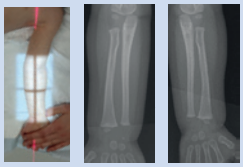

Right & left oblique chest (show both sides, ribs 1-12)

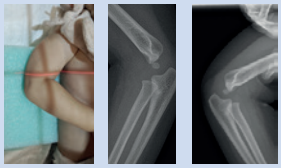

AP abdomen and pelvis

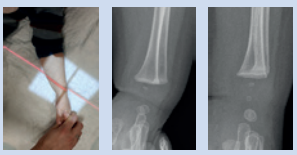

Lateral cervical spine


Lateral lumbosacral spine

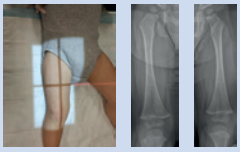

AP right & left humerus (shoulder to elbow)

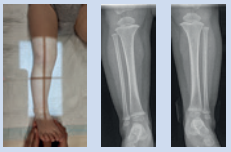

AP right & left forearm (elbow to wrist)

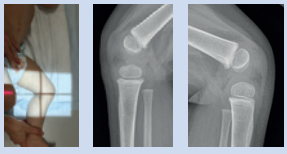

Coned right & left lateral elbow


Coned right & left wrist

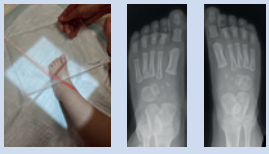

AP right & left hand and wrist


AP right & left femur (hip to knee)


AP right & left tibia and fibula (knee to ankle)


Coned right & left knee


Coned right & left ankle


AP right & left foot

Follow-up imaging is required as part of the complete skeletal survey and should be obtained ideally between 11-14 days after the initial skeletal survey, or as soon as possible thereafter.

Follow-up radiographs should be performed of any abnormal or suspicious areas on the initial skeletal survey plus the following views: chest AP and both obliques, AP upper limbs, AP lower limbs (without coned views of joints).

The radiological investigation of suspected physical abuse in children

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suspected NAI, any multiple birth siblings of the index case less than two years old should undergo the same imaging as the index case. Age-appropriate imaging should be considered in all siblings and children older than two years old living in the same household on a case-by-case basis. The guideline also states that skeletal surveys should be undertaken in a child-friendly environment within a radiology department that is equipped for paediatric imaging, in the presence of a registered paediatric nurse or an appropriately educated health or care practitioner, and where sedation of a child and involvement of play therapists can be offered. Even if the initial skeletal survey is normal, all children should have follow-up imaging, since follow-up imaging may identify fractures that only become visible when healing. Follow-up imaging may also provide invaluable information about fractures identified or suspected on the initial imaging and can assist with dating the injuries. Follow-up imaging should be performed ideally within 11 to 14 days, and no later than 28 days after the initial skeletal survey. When it comes to radioisotope bone scanning, the guideline describes that a bone scan can highlight areas of suspicion, but that further imaging is necessary to confirm whether or not there are any fractures. In addition, bone scanning cannot help with dating of injuries and this procedure involves a high radiation dose: the guideline concludes that bone scans are therefore not indicated in the search for skeletal injuries in suspected NAI in children.

To the best of our knowledge, there are no studies concerning the adherence to the RCR/SCoR/RCPCH guideline in Belgium. However, a recently established multidisciplinary collaboration between various hospitals in Antwerp identified substantial variability in imaging protocols for children suspected of non-accidental injury. It is possible that this is also a problem in other parts of Belgium. We strongly advocate for adherence to the RCR/RCPCH guideline, but are aware of several challenges when it comes to strict adherence to this guideline within the Belgian healthcare system and setting. First of all, care for paediatric patients in Belgium is offered by public, private and university hospitals, polyclinics and private physicians, which can make spreading the message about the existence of this guideline a challenge, something we hope this article can help with. We believe that lack of familiarity with the practical execution of the skeletal survey - specifically the exact sequence and positioning techniques - creates another barrier to the correct implementation of the current guideline. In order to overcome this, we provide a practical guide for performing the skeletal survey in suspected NAI in children, with the hope that this will be a helpful tool for paediatricians, radiographers and radiologists (Figure 1).

In Belgium, the specialty training in radiology follows the recommendations of the European Society of Radiology (ESR). The ESR developed the European Training Curriculum for Radiology, designed to provide a template for radiologists in training, which states that knowledge should be developed concerning "the most frequent disorders of the skeletal system in the paediatric population, in particular traumatic (accidental and non-accidental)" (https://www.myesr.org/education/training-curricula/). However, a formal fellowship or training for radiographers or radiologists in (forensic) paediatric radiology does not exist in Belgium, neither does a specific training in imaging of suspected NAI in children. Moreover, the profession of radiographers is a shortage occupation in Belgium (https://www.vdab.be/beroep/f684faca-cdfa-4ad8-bc86-b833cc389dfc/technoloog-medische-beeldvorming), which can be attributed to the low influx from the Bachelor´s degree in Medical Imaging and Radiotherapy, and Nursing.

Given these challenges, it is crucial to consolidate expertise in Belgium regarding the performance and interpretation of skeletal surveys in children with suspected NAI. We strongly encourage structured collaboration between university and non-university hospitals, with agreements on which hospitals are responsible for conducting skeletal surveys. Our tool aims to enhance the accuracy and reliability of NAI evaluations for fractures in children. To ensure consistent interpretation of the results of skeletal surveys, systematic case-by-case consultations between radiologists and radiologists in training should become standard practice, ideally with the active involvement of the referring physician. Establishing such a structured, nationwide approach is essential to improve the evaluation and detection of NAI, ultimately ensuring better protection for vulnerable children.

Acknowledgements

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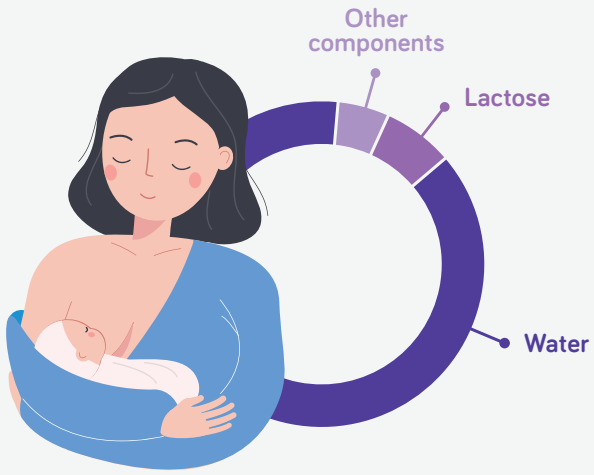
The role of lactose in infant formulas for cow's milk allergy (CMA): addressing misconceptions

Breast milk is universally recognized as the golden standard in infant nutrition, including for infants diagnosed with cow's milk allergy (CMA). Among its components (Figure 1), lactose plays a critical role as the primary carbohydrate, providing not only energy but also multiple physiological benefits. These include a prebiotic effect that supports the growth of beneficial gut microbiota, and enhanced absorption of calcium and magnesium via fermentation-driven acidification. Moreover, the addition of lactose to hypoallergenic formulas can help approximate the microbiota profile of breastfed infants, fostering gut health and immune balance..[1-4]

Figure 1: Composition of breast milk - highlighting lactose as central nutrient.



Lactose contributes to a range of functional advantages for infants:[1,2,5]

- Higher palatability: brings taste closer to breast-milk
- Promotes bifidogenic microbiota and reduces pathogens,
- Supports intestinal villi repair,
- Softens stools, particularly in combination with prebiotic fiber blends such as scGOS:lcFOS.

Clarifying the confusion: CMA vs lactose intolerance[2,5-7]

Despite their distinct pathophysiology, CMA and lactose intolerance are often conflated by parents and even healthcare providers. While CMA is an immune-mediated reaction to cow's milk proteins, lactose intolerance results from lactase enzyme deficiency, leading to impaired lactose digestion.CMA has an estimated prevalence of 2%–3% in the first year of life whilst primary lactose intolerance is rare in infants under five.

This distinction is vital in guiding clinical decisions and parental advice.

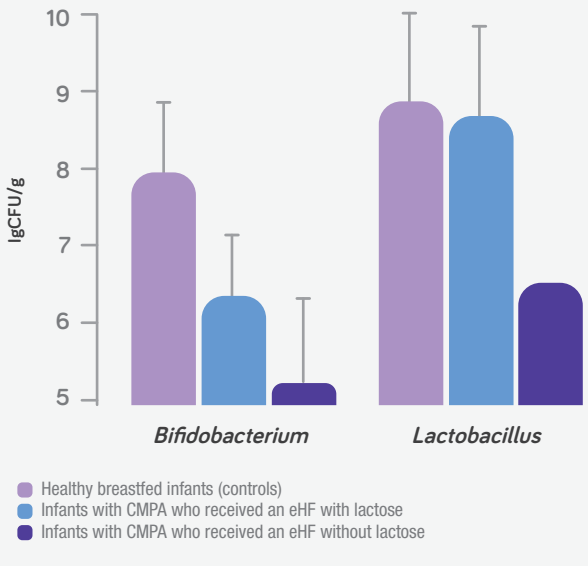
A discrepancy between parental perceptions and physiological reality[8-10]

A significant proportion of parents using infant formulas for cow's milk allergy (CMA) believes their infant also experiences (some level of) lactose intolerance. This illustrates a common confusion between CMA and lactose intolerance.

These misconceptions may lead to unnecessary exclusion of lactose from the infant's diet, potentially depriving them of its known benefits. In fact, lactose remains an important ingredient in some CMA-tailored formulas, supporting gut health and mimicking the composition of breast milk.

Breastfeeding remains the ideal standard for infant nutrition. It provides balanced amounts of macro- and micronutrients, along with a wide range of bioactive compounds - including immunoglobulins, growth factors, and oligosaccharides - that support immune function, gastrointestinal development, and healthy growth. When breastfeeding is not possible

Figure 2: Gut colonisation with beneficial bacteria in infants receiving extensively hydrolyzed formulas with or without lactose.[1]



or needs to be supplemented, healthcare professionals may prescribe specialized hypoallergenic formulas. These include extensively hydrolyzed milk protein formulas, formulas based on free amino acids, and formulas derived from rice protein hydrolysates. Both amino acid-based formulas and rice protein hydrolysate formulas are completely free of cow's milk proteins and lactose, while some extensively hydrolyzed protein formulas available in Belgium do contain lactose.

It is important to emphasize that cow's milk allergy and lactose intolerance are distinct conditions with different underlying mechanisms. Excluding lactose is generally not warranted in the management of CMA, except in rare specific cases. Moreover, concerns about trace amounts of cow's milk proteins in pharmaceutical-grade lactose are not supported by current scientific evidence; allergic reactions related to these trace quantities in infants with CMA are extremely rare.

Authoritative bodies such as ESPGHAN and FAO/WHO clearly state that the exclusion of lactose is not required/desired in the dietary management of CMA.

Extensively hydrolyzed formulas containing lactose: a gut-friendly option for CMA management

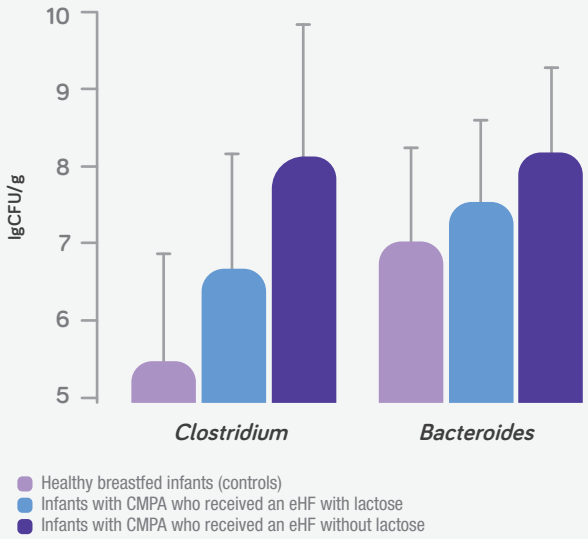
For non-breastfed infants with mild to moderate cow's milk allergy (CMA), extensively hydrolyzed formulas (eHFs) are the recommended first-line dietary option. These formulas, available both with and without lactose, have been used safely and effectively for decades in the nutritional management of CMA. Importantly, lactose exclusion is generally unnecessary, except in rare instances where the infant presents with severe, persistent diarrhea. In line with this, the latest ESPGHAN guidelines explicitly support the use of lactose-containing extensively hydrolyzed formulas, recognizing their potential additional benefits.[1,2,5-9]

Emerging evidence shows that extensively hydrolyzed formulas containing lactose promote greater colonisation of beneficial gut bacteria, such as *Bifidobacterium* and *Lactobacillus*, compared to lactose-free formulations ($p<0.05$).[1]

Conversely, the colonisation of potentially pathogenic bacteria, including *Clostridium* and *Bacteroides*, was found to be significantly lower in infants fed extensively hydrolyzed formulas with lactose ($p<0.05$), suggesting a more favorable gut microbiota profile.[1]

Therefore, the presence of lactose may positively influence gut health, bringing the microbiota profile closer to that of breastfed infants. In this context, lactose-containing extensively hydrolyzed formulas represent a valuable option that combines nutritional adequacy with microbiome-supportive properties, in line with modern principles of early-life nutrition and immune development.[1]

Figure 3: Gut colonisation with potentially pathogenic bacteria in infants receiving extensively hydrolyzed formulas with or without lactose.[1]



Should lactose then never be avoided?

In the few occasions where lactose intolerance is present in children, it usually concerns secondary lactose intolerance. This is a temporary condition caused by damage to the intestinal mucosa, often following infectious gastrointestinal illness, such as coeliac disease or inflammatory bowel disease. These conditions cause general malabsorption or maldigestion, which is not limited to lactose intolerance alone. In this small group of infants, lactose-free medical nutrition may be appropriate. Such formulas typically include hydrolyzed proteins and medium-chain triglycerides (MCT fats). Once the underlying condition is resolved, the intestinal mucosa can begin to heal, and lactose can often be gradually reintroduced into the diet.[2]

Lactose is the primary carbohydrate in breast milk and plays a central role in early-life nutrition. It supports gut microbiota development, mineral absorption, and contributes to the overall health of the gastrointestinal tract. Despite its importance, CMA is often confused with primary lactose intolerance, a condition that is rarely seen in children under the age of five. These two conditions have distinct pathophysiological mechanisms, and current scientific evidence does not support adverse reactions to lactose in infants with CMA. On the contrary, in the absence of enteropathy, the use of extensively hydrolyzed formulas containing lactose is even preferred for the management of mild to moderate CMA, as endorsed by the ESPGHAN guidelines. Furthermore, both ESPGHAN and FAO/WHO recommend lactose and glucose polymers as the preferred carbohydrates in formulas based on cow's milk proteins and hydrolyzed proteins.[1,2,9,10]

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Partnership Envelope: a Therapeutic Dimension Relevant in Situations of Abuse

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Keywords

Child abuse ; emotional abuse ; violence ; sex offenses ; parents ; referral and consultation ; patient care team.

Abstract

Objectives

Our societies still struggle to recognize that the family is often the place where a child is most at risk of psychological, physical, or sexual violence. Child maltreatment fundamentally challenges the foundations of connection, relationships, and personal boundaries.

These are complex phenomena with multiple facets, including physical and psychological abuse, neglect, sexual abuse, exposure to spousal violence, highly conflictual parental separation, and institutional abuse. These forms of violence typically occur within a specific relational context, usually the family. The para- or intra-family framework, which should provide a safe environment for the child's development, is instead compromised. This presents a fundamental paradox: the very setting meant to protect and nurture the child becomes a source of trauma.

Methods

We revisit some considerations on the concept of psychic trauma, including the impact of certain events that cause "injuries" to the psyche. A "traumatic" event is one that brutally confronts an individual with death, the threat of death, serious injury, or violent circumstances.

Rather than proposing a specific framework for addressing trauma related to child abuse, we are developing a therapeutic approach that could serve as a meaningful avenue of support and care for the affected child and their surrounding environment.

Results

While not exhaustive, we propose three interrelated guiding principles aimed at supporting practitioners in navigating the challenges that arise in these complex situations.

The first principle emphasizes the need for a well-defined framework for intervention. The therapeutic framework, a fundamental element of any practice in the humanities, is particularly strained in cases of domestic abuse. Families with abusive dynamics often challenge and disrupt the very structure that, in theory, should provide a safe and trust-based environment for intervention.

The second principle focuses on the establishment of an intermediate space and a partnership framework. These concepts form the foundation of an approach that helps mitigate risks of dysfunction. Every therapeutic encounter, regardless of its format, serves as an intermediate space where knowledge, representations, and emotions can be processed and worked through.

The third principle highlights the importance of network-based practice. In the humanities, the concept of a network is closely linked to that of a system, incorporating the dimensions of relationships. From this perspective, every individual must be understood not only in terms of their intrapsychic experiences but also as part of a broader, more or less structured and expansive social system.

Conclusions

Multi-stakeholder collaboration thus forms the foundation of the "partnership envelope." Professionals involved create a dynamic group, shaped by emotions and personal reactions. This necessitates dedicated time to analyze the interplay between relational dynamics within the multi-professional team and those present in the family system.

Through multidisciplinary team meetings, this collective process is established, put into practice , and refined. Such a multi-stakeholder approach emphasizes consultation and aims to prevent fragmentation in the care of families, particularly those experiencing abusive dynamics.

Introduction

In the face of increasingly complex cases of child abuse—partly due to the diverse family structures in today's society—professionals must demonstrate both creativity and perseverance (1-3). These situations, which generate a range of traumatic consequences, inevitably raise critical questions in clinical practice, theoretical frameworks, and ethics (4).

Ideological stances can sometimes influence professionals toward two extremes: either prioritizing "bonding with and within the family" at all costs or enforcing a strict "zero tolerance" protective policy, which may lead to the rapid placement of children into care.

Rather than advocating a fixed framework for addressing trauma related to child abuse, we are developing a therapeutic approach that serves as a meaningful avenue of support for the affected child and their surrounding environment. This approach

involves creating a collaborative framework that unites various stakeholders, fostering a partnership that moves beyond the divisions and rivalries often seen in current networking policies.

Child abuse

Child maltreatment fundamentally challenges the foundations of connection, relationships, and personal boundaries. It encompasses a range of complex phenomena, including physical and psychological abuse, neglect, sexual abuse, exposure to spousal violence, highly conflictual parental separation, and institutional abuse.

These forms of violence occur within a specific relational context, most often within the family. The para- or intra-family framework, which should provide a safe environment for the child's development, is instead compromised. This presents a fundamental paradox: the very setting meant to protect and nurture the child becomes a source of trauma.

Moreover, the perpetrator is often closely linked to the child, and despite the abuse, this connection remains significant for the young person's sense of identity (5-7).

This paradox has several characteristics:

- Abusive relationship dynamics occur within a system, most often a family system, which must be seen as a whole to prevent the recurrence or displacement of abuse.
- The child often maintains a sense of loyalty to the perpetrator, whether it is a parent, sibling, family friend, or other close figure.
- Abuse exists on a continuum—any kind of violence against a child stems from these dysfunctional relationships. Without intervention, the severity of abuse typically escalates, making early intervention crucial.
- Abuse occurs within a broader societal context and evolves over time as social norms and values change. Consequently, approaches to addressing abuse must be regularly reassessed and adapted.
- The primary focus of intervention should be on protecting and caring for the child, parallel to punitive measures.

Abuse often originates within a complex family system. Therefore, it is useful to examine each situation of abuse from social, psychological, medical, and legal perspectives. These different aspects are helpful in identifying violent relational dynamics and offering appropriate help. The clinic of abuse is, in most cases, closely linked to the clinic of trauma (8-10). While some children and adolescents appear to go through abuse events without apparent trauma (though possibly latent), many do manifest obvious discomfort.

Psychological trauma and complex trauma

Psychological trauma can originate when certain events lead to "injuries" of the psyche. A "traumatogenic" event is one that confronts an individual with death, the threat of death, serious injury, or violent contexts. Knowing someone who has been injured or killed in such an event, or, as a professional, being repeatedly exposed to stress, is now viewed as potentially traumatic (11, 12).

In practice and literature, several types of trauma are distinguished. Type I refers to single, time-limited exposure to an isolated, unexpected event. Type II reflects repeated or long-term exposure, most often interpersonal, including resignation (no surprise). Type III incorporates multiple, pervasive, and violent early-onset and long-lasting events, such as child maltreatment.

Another concept is Developmental Trauma Disorder (DTD), which can account for the difficulties experienced by a traumatized person. DTD is based on five criteria: childhood exposure to multiple and prolonged traumas, difficulties in physiological and emotional regulation, difficulties in regulating attention and behavior, difficulties in regulating social relations, identity problems, and traumatic symptoms similar to those observed in post-traumatic stress disorder (PTSD).

Furthermore, the concept of "complex trauma" refers to the dual reality of prolonged exposure to particularly pervasive traumatic situations. Domestic abuse and the multiplicity of negative impacts of this exposure as well as its lasting effect on the dynamics and functioning of the victim is one example. Two intrinsic characteristics of trauma explain severe and lasting impacts: the interpersonal nature of the traumatic events or situations specific to complex trauma and the fact that these traumas occur at key periods in the individual's development.

There is no doubt about the connection between child abuse and trauma, as highlighted by various studies (13-16). Abused children often experience a prolonged "chain of trauma" throughout their development. In our clinical work, we encounter many adults with post-traumatic symptoms stemming from childhood abuse. The psychological and physiological effects of trauma can persist throughout a person's lifespan. Bapolisi and colleagues demonstrated a link between trauma and high blood pressure in a population of adult men in Congo (17). Additionally, several studies have explored the potential correlation between child abuse and psychosomatic symptoms in both children and adults (18-20). Thus, abuse correlates with changes in the functioning of the immune system, brain, and DNA, accelerating the process of cellular aging. Stress induced by trauma can lead to deregulation of the hypothalamic-pituitary-adrenal axis and result in epigenetic effects.

Moreover, abused children are often diagnosed with multiple mental disorders, sometimes receiving several diagnoses, which complicates the assessment of trauma and the provision of effective help. Various authors, such as Blavier and Delhalle, have shown that a large number of abused children receive a variety of mental disorder diagnoses (21). Consequently, they may accumulate two, three, or even four separate diagnoses over their lifetime, sometimes even simultaneously. As Van der Kolk points out, it is not uncommon for "oppositional defiant disorder", depression, ADHD or separation anxiety to mask a traumatic situation related to a context of abuse (22). This complicates also the work of assessment and therapeutic intervention. There is a risk of a fragmented intervention strategy, which may overlook the traumatic trajectory in the development of young people.

The axes of intervention

While not exhaustive, we propose three axes of reference. The purpose is to support the professionals and help them overcome the challenges posed by these difficult situations (23).

The first axis emphasizes the need for a defined framework for intervention, tailored to the patient's complaint. We believe that a clear framework helps to avoid misunderstandings. It is important to remember that some psychopathological profiles specifically address the relationship to the framework, to the alterity and to the law (24). On the other hand, it is important to recognize and articulate the limits of our jurisdiction. It makes sense to determine one's area of knowledge and skills in the patient's best interest. Following this initial assessment, the objectives of the therapeutic intervention should be defined by exploring the explicit and implicit expectations of the person seeking help. The more precise we are in clarifying the details of the approach, the more we can avoid pitfalls that may lead to potential failure (25).

The therapeutic framework, a fundamental element of any intervention in the humanities, is challenged in situations of domestic abuse. Families with abusive dynamics are more likely to

challenge and confront the framework that, ideally, should protect the therapeutic relationship based on trust. However, violence inflicted on children can quickly contradict the prospect of providing caring support for family members. It jeopardizes the basic conditions for therapeutic bonding, which include an effective meeting, a project based on a clear plan, and a framework that encompasses both elements. For most professionals, the framework essentially includes a dimension of a paternal function. The latter refers to authority, which encompasses aspects such as sanctions (both negative and positive), limits, and organization. In the field of medical-psycho-social assistance, the notion of framework is closely tied to authority. It is both invoked and feared, as it serves to limit chaos and impose order, albeit at the risk of reducing freedom. Following Lebrun, we can consider that in our contemporary society, marked by the weakening of collective representation structures, the framework faces two main pitfalls (26). First, there is a loss of meaning due to a lack of benchmarks and rules, driven by the need for immediate gratification and impulsive actions. Second, the application of the framework can be either too rigid or overly adapted, leading to its ineffectiveness in fulfilling its functions. The child often finds themselves ensnared in a pre-existing system, established long before their conception, within a fantastical realm. Consequently, the second axis involves creating an intermediate space and a partnership envelope. Regardless, the child or adolescent inevitably exists within a network, a specific relational context. Among the theoretical-clinical benchmarks supporting the management of maltreating systems, the concepts of space-intermediary and partnership envelope form the foundation of work that mitigates the risks of malfunctioning. Any encounter, regardless of its format, serves as an intermediate space where knowledge, representations, and emotions are developed. This process is a co-construction, achieved through mutual listening, aimed at recognizing, understanding, analyzing, and developing to support resilience and modify inappropriate behaviors. This co-construction is facilitated by teamwork, as collaboration among various aid and healthcare actors, centered around the patient and their socio-family environment, ensures coherence in therapeutic approaches, preventing dissonance from contradictory interventions. In this intermediate space, professionals and/or teams create a 'partnership envelope.' This concept is inspired by Anzieu's observation that a group forms an envelope that holds individuals together (27).

Until that envelope is built, there may be a human aggregate, but not a cohesive cluster. The concept of the 'envelope of the group' in relation to the 'containment function' allows us to consider the weaving of attention necessary to contain the child's symptoms and the possible psycho-affective movements of the adult, whether depressive, aggressive, or otherwise. Welcoming someone necessitates creating an envelope system that allows for the expression of emotions, whatever they may be. For both individuals and groups, it can be essential to build an envelope that contains, delimits, and protects us while simultaneously facilitating exchange with the outside. Anzieu developed the concept of 'Moi-Peau' (28). In children, psycho-affective and cognitive development is intimately connected to sensorimotor experiences, which are primarily felt through the skin. What the toddler experiences physically during their initial experiments is reintroduced and contributes to the construction of their psychic apparatus. Similarly, the skin forms a boundary with others, its permeability filtering out tensions and emotions. The group is conceived as a living envelope with a double-sided membrane. One side is oriented towards the external, physical, and social reality, particularly towards other individuals or groups. This side of the group envelope constructs a protective barrier against external influences and, if necessary, functions as a filter for incoming information. The other side faces the inner reality of the group members, formed from the projections of their experiences and fantasies by professionals. Through this inner face, the group envelope facilitates the establishment of a 'trans-individual' psychological state, which Anzieu termed the 'self of the group.' In the context of a medical-psycho-social and educational team, this can be referred to as the 'self of the team,' where members share a group psychic reality and develop a sense of belonging to the system. This 'team self' acts as a protective container, allowing perceptions and emotions to flow between individuals. The concept of the 'partnership envelope' is also based on the work of Parret and Iguenane, highlighting functions such as building a container, protecting impulse movements ('arousal barrier'), and establishing a boundary between the inside and outside to ensure consistency of reality (29). The professionals' task is to create a psychic team envelope that can perform these functions to evaluate and treat the multiple impacts of abuse.

Metaphorically, the partnership envelope is the second skin that can help adults and minors whose self-image and self-esteem are affected by individual and/or systemic dysfunctions. This envelope, like the skin, benefits from being flexible, permeable, and continuous. It acknowledges the mobility and flexibility of the professionals who comprise it. Improvisation is embraced, and trial and error enriches everyone personally and collectively, fostering a stance of 'not knowing everything' about each other. With the protective wrap provided by the professionals, parents and children agree to dialogue, benefiting from the mirror effect offered by team members. The goal is to raise awareness of inappropriate behaviors and ways of being through the feedback that the support aims to provide. This general attitude is based on the creation of an envelope that includes all the partners involved and concerned by a specific situation, taking into account the logics and rules specific to each. This collective work helps to overcome judgments and stereotypes against patients, colleagues, partner services, and institutions. This constant and unifying process in family care seeks to avoid undermining the effectiveness of multiple interventions. It supports the development of solidarity links between professionals, enabling coordinated activities by accepting the complementarity of the constituent disciplines. By acknowledging the differences between stakeholders, we can welcome those of the families concerned and accompany them in understanding themselves and their environment. The aim of the partnership envelope is to provide institutional care for all professionals involved with a family. By organizing useful contact points and consultation meetings with and without family members, the envelope is built, each time singular and unique.

The third principle emphasizes the importance of working with the existing networks. Several categories of networks are defined based on the quality, function, and mandate of the professionals and/or structures that comprise them. Networks can be very tight or loose, more or less open or closed. Elkaim has developed applications of network practice, depending on the cultures involved and the type of work to be carried out, such as crisis situations or the presence of psychopathology in adults (30, 31). Responses are then introduced that are flexible, adaptive, and suited to the resources identified in the environment of a subject or a system in arrears. Families in socio-economic difficulties see around them the multiplication of assistance and protection interventions with the inherent risk of disqualification. Measures such as expertise, evaluation, specialized replacement care, and placement of children that follow one another over time contribute to this phenomenon. The larger and denser the network, the greater the risk of institutional abuse arising from configuration failures.

In general, network practice aims to stimulate the complex process of 're-functionalization' of a dispersed social field, which is fragmented or rendered impotent. Professional networks often need to be mobilized in situations of anomie, a state that generates exclusion and 'ghettoization.' Human systems labeled as 'problematic' typically induce and maintain ambiguous relationships with professionals who intervene in isolation, leading to exhaustion and dysfunction among the professionals themselves. Effective network practice avoids a reductionist approach by not considering the problem solely at an individual or family level. Instead, it aims

to create a context that integrates multiple components, enabling the generation of new hypotheses through shifts in perspective and elevation of understanding. This approach fosters collective intelligence, yielding original and unexpected insights. Network therapy is sometimes mentioned in this context. However, controversies within networks are not uncommon, as professionals working in their specific fields with defined mandates often find themselves in positions of mutual ignorance or rivalry, which can be very destructive to working relationships. These damaging positions result from macro-societal structural dysfunctions, due to the lack of social consensus and power challenges stemming from political, historical, and short-term reasons (32, 33). Moreover, the presence of conscious manipulations by patients or those involved in the field often reinforces the observation of system paralysis. Situations of abuse frequently generate frustration, exhaustion, a sense of helplessness, or even worthlessness. Our intention is to overcome this state by creating a dynamic of exchange based on respect for individuals, structures, and their missions. The tool for achieving this ambitious objective is consultation, which should be distinguished from negotiation and mediation. Consultation involves exchanges between multiple parties to agree on a common project, embracing confrontation, argument exchange, and clarification of viewpoints. Multidisciplinary should not be seen as merely the juxtaposition of competencies specific to each discipline, which could be perceived as 'constrained multidisciplinary.' This approach may necessitate reconciling or arbitrating different viewpoints inherent in the interests of each profession. We support the research and construction of business models based on consensual planning. Ideally, all interventions should be part of the human action, requiring a memory and a form of alliance around which professionals can come together to help and heal. Ideally, all interventions should be part of human action, requiring a sense of history and a form of alliance around which professionals can unite to help and heal. This consideration of history and the alliance established guarantee real concertation, providing coherence to the project of care and the resulting decisions (34).

Conclusion

Professionals involved in childhood and adolescence care often feel uncomfortable when they witness inappropriate parental behavior towards young people in need of identity and positive identification (35) (35). In the complexity of child abuse situations, professionals can improve their working comfort(environment) and efficiency by having clear benchmarks that define the scope of their intervention, allowing them to avoid dynamic duels(conflicts?) with family members. Ideally, in many situations, they will choose to work based on a multi-stakeholder model, supported by multidisciplinary team reflection and the possibility of referring to supervision sessions in any form.

Multi-stakeholder work forms the foundation of the 'partnership envelope.' Professionals constitute a living group with feelings and resentments, necessitating time to analyze the relationship between the relational dynamics within the multi-professional group and those within the family. Through multidisciplinary team meetings, this collective development is realized, experienced, and evolved. This multi-stakeholder practice emphasizes consultation and aims to prevent fragmentation in the care of families, particularly those with abusive interactions.

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En savoir plus ?

Multidisciplinary Assessment and Intervention in Sibling Maltreatment: Report of 4 Sibling Cases

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Keywords
Sibling maltreatment ; multidisciplinary assessment ; case report.

Abstract
This case report provides a detailed account of the experiences of a group of four siblings who were exposed to severe intrafamilial maltreatment. The children exhibited significant physical and psychological distress, with symptoms consistent with ADHD and autistic traits. A comprehensive medical and psychological assessment was carried out during their emergency admission to the paediatric ward. The case of these siblings demonstrates the importance of early identification of maltreatment, the need for multidisciplinary and interdisciplinary collaboration between professionals, and the provision of comprehensive care that includes both somatic and psychological dimensions. It highlights the challenges of achieving a balance between urgent measures to protect children and the mitigation of trauma during placement. It also underlines the importance of continuous post-treatment care to address both the immediate and long-term consequences for children who have been subjected to maltreatment.

Introduction

It is estimated that at least one in eight children are victims of child maltreatment before the age of eighteen. This phenomenon is a major public health concern. The manifestation of this phenomenon can take various forms, including neglect or physical, psychological and sexual abuse. These forms of maltreatment and neglect are widespread, under-reported and globally prevalent (1, 2). It is a well-documented fact that children who have experienced maltreatment may suffer long-term consequences, including physical and mental health problems, academic difficulties, as well as challenges in their professional lives and interpersonal relationships (3). Consequently, children who have been maltreated or neglected have been shown to have specific educational, health and social behavioural needs (4). These situations require special attention from health professionals, especially in paediatric settings, and call for a multidimensional and interdisciplinary approach (5). The objective of this article is to highlight the importance of such collaboration by drawing on the medical and psychological assessment of a group of siblings exposed to intrafamilial maltreatment.

Case report

Our case report concerns a group of four siblings who were admitted to the paediatric department as part of their emergency admission. The family consisted of Mia and Mason (aged 9, twins), James (aged 3) and Emma (aged 10 months). Two older children, Evelyn, 15, and Harper, 13, were not hospitalised. The children's fathers were not involved in the family's life. Only the youngest sibling, born in our maternity unit, had been known to our services since birth. Her perinatal medical record showed irregular antenatal care and poor maternal adherence to medical recommendations regarding pre-existing conditions. In addition, the mother had a pattern of alcohol and tobacco consumption during her pregnancy. This situation led to significant maternal complications in the postpartum period, requiring several days of intensive care and neonatal care for the newborn. However, the observations made by those involved during the mother-baby unit stay, the post-hospital paediatric consultation and the midwife follow-up at home did not reveal any concerns about the mother-baby relationship or medical care. The older siblings were monitored by the Youth Welfare Office and various outpatient and home help services had been set up. School absenteeism and repeated changes of school and residence made it impossible for the schools to collect data on the children.

The four youngest children of the sibling group were taken to the children's ward as part of their emergency placement. This was ordered by the juvenile court judge who found that the children were in a situation of grave danger. A team with expertise in assessing child maltreatment carried out an intervention with the sibling group to obtain the children's statements. The maltreatment appeared to have been chronic since birth and was primarily perpetrated by the subject's maternal grandmother, to whom the subject's mother regularly entrusted them, despite being fully aware of the circumstances. The documented cases of abuse included various forms of physical and psychological abuse, including strangulation to unconsciousness, prolonged

confinement in darkness, physical assault with belts, sticks or electric cables, deprivation of food, poisoning and the forced insertion of chilli peppers into various body orifices (nasal, genital, anal and eye).

On admission to the children's ward, a psychological assessment of the children was carried out and continued by the specialist child abuse team. In addition, the juvenile court judge requested a full medical assessment, including nutritional, ophthalmological, ENT, skeletal radiography, magnetic resonance imaging (MRI) of the brain, genital and dermatological examinations. The paediatric team made the following observations during the hospital stay.

Mason, 9 years old, shows significant signs of psychomotor agitation. These symptoms are related to his previous diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), but Mason is no longer taking his prescribed medication. His treatment has been resumed by the child psychiatrist consulted during his paediatric placement. Mason has difficulty with lateralisation, frequently bumps into objects, complains of pain in his feet and walks on the toes of his shoes. There were no injuries to his feet, but he was wearing shoes that were too small when he came to the ward. He hides episodes of urinary incontinence by discreetly changing in the toilet. He appears depressed and anxious and sometimes seems detached from reality. His medical examination revealed a cerumen plug and old scars on his face and body.

Mia, Mason's twin sister, shows no psychomotor agitation, expresses thoughts that are consistent with reality but displays anxious affect.. Within the sibling group, she appears to take on a maternal role, caring for her 10-month-old sister and relaying information about her twin brother's medication, despite a conflicted and violent relationship with him. An x-ray revealed a callus in the right medial malleolus, suggesting an old consolidated fracture, possibly related to abuse. The child also has scars and bruises all over her body, which she attributes to abuse by her grandmother.

James, aged three and a half years, had been diagnosed with a speech delay and autistic behaviours. The boy displays a marked reluctance to engage in interaction with others, exhibiting a withdrawn demeanour and an apparent inability to express emotions. He does not respond to vocalisations of his name, and has been observed engaging in repetitive object manipulation. Mason and Mia show aggressive behaviour towards James, which frightens him. James' medical examination reveals unexplained skin scarring.

Emma, the 10-month-old child, shows signs of depression, as evidenced by recurrent crying episodes and a state of inconsolability. She has difficulty initiating sleep due to increased levels of alertness. Mia reported that she was constantly carried and breastfed by their mother. The medical examination did not reveal any pathological conditions.

Following a fourteen-day period of hospitalisation, the sibling group was separated, with each child being placed in a different institution. Mia was placed in an emergency residential service for a maximum period of 40 days. Mason and James were placed together in a general residential service, where their placement could be extended into adulthood. Emma was transferred to a nursery.

Discussion

This case report underlines the crucial function of hospital placement processes in facilitating interdisciplinary coordination between professionals, both within and outside the hospital. This collaboration facilitates a comprehensive and detailed assessment of the child, ensuring a thorough evaluation within a single setting and timeframe. However, the length of hospitalisation must be limited, as the hospital environment does not provide adequate emotional, educational and physical needs of the child (6). The 15-day period was used to carry out a comprehensive medical examination in accordance with the instructions of the juvenile court judge. At the same time, assessment and psychosocial support were provided by the team specialising in child abuse, which had been involved prior to hospitalisation and remained involved throughout the stay. This continuity promoted a coherent and structured monitoring of the children and facilitated the coordination of the different actors involved in their care.

Within the hospital environment, effective communication between the various stakeholders (i.e. paediatricians, child psychiatrists, psychologists and social workers) is essential to ensure a comprehensive and coherent approach for each child. The regular convening of professionals is imperative for the dissemination of information and the coordination of care.

In addition, this case report underscores the pivotal role that hospitals are expected to play in cases of child maltreatment, particularly in times of crisis (7). As is well documented in the existing literature, children are known to experience significant psychological distress following disclosure of maltreatment. The subjects were removed from their family and school environment without prior authorisation to contact their mother, resulting in a sudden and abrupt weaning from breastfeeding for the youngest subject. In such cases, the provision of a supportive environment is particularly important, given the urgency and rapidity of hospital admission. It is thus imperative that paediatric services have adequate material and human resources to ensure the well-being of children, extending beyond the realms of medical, psychological, and social care (e.g., educators, teachers, etc.).

Separating abused children from their family environment is an essential step in ensuring their immediate safety. However, it is important to note that this process can also have long-term psychological consequences (8, 9). In this case, the fragmentation of families, due to placement of the siblings in different institutions because of a shortage of places, increases their level of distress. It is therefore vital to ensure that sibling bonds are maintained and that psychological follow-up is put in place to help the children overcome their trauma.

The management of child maltreatment cases invariably raises the issue of recognising signs of maltreatment. While the paediatrician's role encompasses a holistic vision of health and a professional mandate to ensure children's well-being and safety, conducting health assessments and preventive care to detect signs of child abuse in families with risk factors for abuse requires regular medical follow-up, which was lacking in the case of the siblings described (10). It is equally important for the paediatrician not to work alone and to mobilise both internal and external resources in order to provide comprehensive care.

Conclusion

This case report emphasises the imperative of a swift, collaborative, and multidisciplinary approach in child maltreatment cases. While urgent intervention ensures immediate safety, it also entails challenges, notably the psychological impact of abrupt separations and the fragmentation of a group of siblings. These factors emphasise the importance of ongoing psychological support that is tailored to address the unique needs of each child.

The early detection of maltreatment remains of crucial importance, as demonstrated by the necessity of regular medical follow-ups. Interdisciplinary collaboration is of pivotal importance in addressing both immediate and long-term consequences, while placement decisions should aim to minimise additional trauma and preserve sibling bonds wherever possible.

The delicate task of safeguarding children against potential harm while simultaneously mitigating the associated distress of institutional placement remains a multifaceted challenge. It is imperative to enhance prevention measures, optimise professional training, and ensure the provision of sustained psychological care to improve outcomes for children subjected to maltreatment. It is recommended that future research explore the influence of different intervention strategies on long-term well-being.

The authors have no conflict of interest to declare.

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who will?

81% van de ouders beschouwt hun arts als een primaire bron van informatie over vaccinatie voor hun kinderen. (n=800)[2]

BEXSERO
Meningokokken groep B-vaccin
(rDNA, component, geadsorbeerd)

BEXSERO is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B.[1]

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN: Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL:** Bexsero suspensie voor injectie in voorgevulde spuit. Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd), EU/1/12/812/001-EU/1/12/812/002-EU/1/12/812/003-EU/1/12/812/004. Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING: Een dosis (0,5 ml) bevat:** Recombinant Neisseria meningitidis groep B NHBAfusieeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B NadAeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B fHbpfusieeiwit[1,2,3]: 50 microgram • Buitenmembraanvesikels (BMV) van Neisseria meningitidis groep Bstam. NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat[2]: 25 microgram • [1] Geproduceerd in E. colicellen door recombinantDNAtechnologie - [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) - [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de volledige SPK. **FARMACEUTISCHE VORM:** Suspensie voor injectie. Melkwitte vloeibare suspensie. **KLINISCHE GEGEVENS: Therapeutische indicaties:** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door Neisseria meningitidis groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **Dosering en wijze van toediening:** Dosering: **Tabel 1. Samenvatting van de dosering: Leeftijd bij eerste dosis:** Zuigelingen van 2 tot en met 5 maanden[a]: **Primaire immunisatie:** Drie doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. - **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. • **Leeftijd bij eerste dosis:** Zuigelingen van 6 tot en met 11 maanden: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis:** Kinderen van 12 tot en met 23 maanden: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis:** Kinderen van 2 tot en met 10 jaar: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • **Leeftijd bij eerste dosis:** Adolescenten (11 jaar of ouder) en volwassenen*: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • [a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. - [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. - [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld. - [d] Zie rubriek 5.1 van de volledige SPK. - * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening: Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **Contraindicaties:** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **Bijwerkingen:** Overzicht van het veiligheidsprofiel: De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen: Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥ 1/10) - Vaak: (≥ 1/100, < 1/10) - Soms: (≥ 1/1.000, < 1/100) - Zelden: (≥ 1/10.000, < 1/1.000) - Zeer zelden: (< 1/10.000) - Niet bekend: (kan met de beschikbare gegevens niet worden bepaald). De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar):** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Voedings en stofwisselingsstoornissen: Zeer vaak: eetstoornissen. Zenuwstelselaandoeningen: Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn. - Soms: insulten (inclusief febriele insulten). - Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen: Soms: bleekheid (zelden na booster). - Zelden: ziekte van Kawasaki. Maagdarmstelselaandoeningen: Zeer vaak: diarree, braken (soms na booster). Huid en onderhuidaandoeningen: Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster). - Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar). - Soms: eczeem. - Zelden: urticaria. - Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: koorts (≥ 38 °C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid. Soms: koorts (≥ 40 °C). - Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). **Adolescenten (van 11 jaar en ouder) en volwassenen:** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Zenuwstelselaandoeningen: Zeer vaak: hoofdpijn. - Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen: Zeer vaak: misselijkheid. Huid en onderhuidaandoeningen: Niet bekend: huiduitslag. Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: myalgie, artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise. - Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België:** Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Afdeling Vigilantie - Postbus 97 - 1000 Brussel - Madou - Website: www.eenbijwerkingmelden.be - e-mail: adr@fagg.be. **Luxemburg:** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN:** GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië. **DATUM VAN DE GOEDKEURING VAN DE TEKST:** 26/04/2023 (v15). **AFLEVERINGSWIJZE:** Op medisch voorschrift.

References: 1. SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

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A Survey on the Knowledge of Clinical Signs of Child Maltreatment among Preschool and Primary School Teachers

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Keywords
Child abuse and neglect ; preschool and primary school teachers ; clinical symptoms and signs ; detection of abuse.

Abstract

Background
Child abuse and neglect are critical health issues with far-reaching physical, psychological, and social consequences. Teachers are uniquely positioned to identify signs of abuse due to their daily interactions with children. However, limited knowledge and training often impede effective identification and reporting of abuse. This study assesses the knowledge of preschool and primary school teachers in Flanders, Belgium, regarding the clinical signs of child abuse.

Methods
A prospective study was conducted using an online survey comprising 16 hypothetical cases. The cases, validated by pediatric and forensic experts, included both suggestive and non-suggestive scenarios of child abuse and neglect. Participants rated their level of suspicion using a Likert scale. Statistical analysis explored the relationship between socio-demographic factors and participants' ability to correctly identify cases.

Results
A total of 155 completed surveys were analyzed. Participants achieved a median accuracy of 75% overall, performing better on suggestive cases (87.5%) than on non-suggestive (62.5%). Sensitivity in identifying abuse was higher than specificity, with significant variability observed in non-suggestive case results. Prior training did not significantly improve scores, likely due to the superficial nature of existing training programs. Years of experience and prior exposure to suspected abuse cases also showed no significant correlation with performance.

Conclusion
While teachers demonstrated reasonable knowledge of child abuse and neglect, they sometimes struggle in recognizing non-suggestive cases and distinguishing abuse from mimickers. Further research is needed to evaluate the impact of standardized training programs on improving teachers' ability to detect and report child abuse and neglect effectively.

Introduction

Child abuse and neglect represent significant global health concerns, affecting children across all socio-economic backgrounds (1). Despite their impact, these issues often go underreported. Prevalence data stem from official reports, capturing only a fraction of affected children (2). A significant discrepancy exists between self-reported cases and official records (3).

The World Health Organization (WHO) defines child abuse and neglect as "all forms of physical and/or emotional ill-treatment, sexual abuse, neglect, and exploitation resulting in actual or potential harm to a child's health, development, or dignity." The four primary types are physical abuse, sexual abuse, psychological abuse, and neglect (4).

Child abuse and neglect have both immediate and long-term physical, psychological and social consequences (1). Victims often face lifelong mental-health issues, including high-risk behaviours and maladaptive coping strategies, as well as physical harm from the abuse itself. Recognizing early warning signs, or "sentinel injuries", such as minor bruises, can be life-saving and help prevent the long-term physical and psychological impacts of abuse (5). Overlooking early signs increases the risk of repeated harm, with up to 50% of affected children experiencing further abuse (6).

Physical abuse often manifests through visible signs. While bruises are common, their location, pattern, and number can indicate abuse. For example, bruises on the shins and foreheads are typically accidental, whereas those on the buttocks, cheeks, or thighs are more suspicious. Bruises on the neck, ears, and

genitalia are highly concerning (1). Other signs include bite marks, burns, and fractures, especially if injury explanations are inconsistent (1).

Beyond physical signs, school-aged children experiencing abuse often show emotional, behavioral, and cognitive symptoms (7). Studies indicate that neglected children display externalizing behaviors (e.g. aggression) and internalizing symptoms (e.g. anxiety, depression). They may exhibit ADHD-like symptoms, emotional dysregulation, and reduced cognitive abilities, affecting academic performance and social interactions (7,8).

Teachers play a key role in identifying abuse due to their daily interactions with children. They can observe changes in appearance, behavior, or academic performance that signal maltreatment. Furthermore, they build trusting relationships with their pupils which can encourage children to disclose maltreatment (2,7). Parent-teacher meetings offer additional insights into family dynamics. However, many teachers lack training in recognizing and reporting abuse, leading to underreporting (2). Identifying neglect is particularly difficult, with teachers often unsure about recognizing and reporting it (7).

In Flanders, Belgium, "Confidential Centers for Child Abuse" facilitate the reporting of abuse. In 2023, these centers recorded 7,541 reports involving 10,671 children. The reported cases included emotional abuse or neglect (36%), physical abuse (30%), sexual abuse (16%), and general risk situations (15%) (9).

Few studies have examined teachers' knowledge of child abuse and neglect. An Estonian study found that insufficient knowledge reduced the likelihood of reporting (10). Another study showed that training significantly improved teachers' ability to recognize and report abuse (11).

This study assesses preschool and primary school teachers' knowledge of clinical signs of child abuse and neglect in Flanders through an online survey using hypothetical case reports. We hypothesized that there is a gap in teachers' knowledge on this topic.

Methods

Study Design

This prospective study was conducted through an online survey and received approval from the Research Ethics Committee UZ/KU Leuven (MP028816). The study protocol was modeled on two prior investigations conducted by our research group but focused on a different population (12,13). Participation was voluntary, anonymous and required informed consent.

The survey consisted of two sections: a questionnaire gathering sociodemographic information and 16 hypothetical cases. The sociodemographic variables collected included gender, age, parental status, type of education (mainstream or special education), years of professional experience, prior exposure to potential cases of child abuse and neglect, province of residence and education regarding child abuse and neglect. The 16 fictional clinical cases (Table 1) presented scenarios of potential child abuse or neglect, accompanied by a clinical image showing signs of injuries or neglect as well as symptoms not related to abuse. All cases were situated within a school context.

Participants were asked to evaluate their level of suspicion regarding child abuse and neglect using a Likert scale with response options ranging from "not suspicious", "rather not suspicious", "neutral", "rather suspicious" to "highly suspicious". By offering gradations we aimed to reflect nuance that may occur in real life. The 16 cases were developed based on medical literature and validated by a panel of five experts in the field. Eight cases were designed to be non-suggestive of child abuse and neglect, while the remaining eight were suggestive of such instances. As the cases were never black/white with regards to the presence or absence of abuse or neglect, the expert answers did not always have to be perfectly consistent, but always had to concur regarding the direction of the suspicion (e.g. both "not suspicious" and "rather not suspicoious" could be used by the experts in their opinion of a specific case, but not "rather not suspicious" and "rather suspicious"). We dichotomized the correct answers after the survey was performed to allow for clearer statistical analysis of response accuracy. After completing the survey, participants received feedback on the cases.

The online survey was distributed via the platform 'LimeSurvey'. The survey was distributed on April 17, 2024. Data collection occurred from 17 April 2024 until 28 May 2024. Only fully completed questionnaires were included in the analysis.

Participants

Primary and secondary school teachers were recruited via email, which was distributed to school administrations in Flanders, Belgium. These email addresses were sourced from an official database provided by the Flemish government (14). The email contained a voluntary invitation to participate, along with a direct link to the survey. An information letter was attached, explaining the study's objective, methodology, implications, and outlining any potential risks and benefits of participation. Participation was entirely voluntary and fully anonymous, with informed consent obtained prior to the initiation of the survey.

Statistical analysis

Only questionnaires that were fully completed via LimeSurvey were included in the analysis. IBM SPSS software was used to perform all statistical analyses. Categorical variables were expressed as frequencies and percentages. For analysis purposes, responses were dichotomized: "unsuspicious" and "rather not suspicious" were grouped as "not suspicious," while "rather suspicious" and "highly suspicious" were categorized as "suspicious." The "neutral" option was consistently treated as incorrect.

Each case was reviewed by pediatric experts with clinical or forensic experience. Participant responses were then compared to these expert assessments, and an overall score was calculated for each participant, reflecting their ability to correctly identify potential cases of child maltreatment.

The proportion of correct answers for each case was calculated and visualized using a Likert plot. Normality of continuous variables was evaluated with the Shapiro–Wilk test. These variables are reported as mean (± standard deviation, SD) or median (± interquartile range, IQR), depending on the distribution. Categorical variables are expressed as frequencies and percentages. ANOVA tests were conducted to assess whether there were significant differences in overall scores between groups within each sociodemographic variable (such as gender, parental status, prior experience with child abuse cases, province of residence, type of education and education on child abuse and neglect). Pearson correlation tests assessed relationships between continuous sociodemographic variables (age and years of professional experience) and the overall score. Finally, linear regression was performed to determine if gender, age, parental status, years of professional experience, prior exposure to potential cases of child abuse and neglect, province of residence, type of education and education regarding child abuse and

TABLE 1: Case scenario description of the survey.

	Vignette	Image description	(Not) suggestive for child abuse and neglect
Case 1	**Bruises on lower legs**. Victor is an energetic 9-year-old boy in the third grade. He has trouble sitting still in class and often struggles to focus on the lesson. On the playground, he stands out as one of the more "active" kids. You notice his shins are covered in bruises. When you ask what happened, he says he's fallen several times while skating.	Clinical image of the lower legs of a child showing multiple ecchymoses on both shins.	Not suggestive
Case 2	**Fall from bicycle**. Noor, a 4-year-old girl in preschool, is currently in the second year of kindergarten. Her mother shared that Noor had a fall over the weekend while practicing riding her bike without training wheels. This happened while she was staying with her grandparents. Concerned about her injuries, Noor's grandparents took her to the general practitioner, where her scrapes were carefully treated. Fortunately, aside from a few bruises and scrapes, Noor did not sustain any serious injuries.	Clinical image of a child with multiple superficial abrasions on the face, predominantly on the forehead and right cheek.	Not suggestive
Case 3	**Bruise on ear**. Liam, a 4-year-old boy, is in your preschool class. He is quiet and shy. During a coloring activity, you notice a bruise on his ear. When you ask him about it, Liam does not want to say how it happened. After school, you decide to ask his mother. She explains, "His older sister was jumping rope with a plastic rope yesterday, and Liam got hit on the ear." Liam's mother is a single parent who has been struggling financially since her divorce.	Clinical image of a child's ear showing an ecchymosis located at the antihelix and scapha. The remainder of the ear appears normal.	Suggestive
Case 4	**Bedwetting**. Sofia, a cheerful and lively 5-year-old girl in her final year of preschool, has seemed quieter and less enthusiastic over the past two weeks. She cries more often and shows less engagement during classroom activities. Notably, she has wet herself twice in the past week, which had not happened before. Concerned about these changes, you speak with her father at the school gate. He explains that Sofia's mother, An, gave birth to a baby boy a month ago. Things have been very hectic at home, and they realize that Sofia is struggling with this major change. He appreciates your concern and thanks you for bringing it up. He says he will discuss with his wife what they can do to help Sofia feel better again.	Image of a young girl standing alone, visibly crying.	Not suggestive
Case 5	**Naevus on the back**. During a school trip to a water park, you notice that Charlotte has a blue mark on her back. Since this area is usually covered by clothing, it's the first time you've seen it. Charlotte is an 8-year-old, very enthusiastic girl. You ask if she had a fall, but she explains that she has had this mark since she was very young.	Clinical image of a congenital nevus measuring approximately 2x3 cm. The macula has a flat surface and appears reddish in color with irregular borders.	Not suggestive
Case 6	**Cigarette burn**. Timo is a somewhat hyperactive boy in the fifth grade of elementary school. He has ADHD and is often very difficult to keep under control. Despite his efforts, he has had to repeat a year, and his academic performance doesn't seem to be improving this year either. You have the impression that his parents provide him with little support and leave him to handle things on his own. Today, he enters the classroom with a round wound on his forearm that, at first glance, resembles a burn. Timo says he bumped into something and quickly hides the wound under his sleeve.	Clinical image showing a circular second-degree burn wound, approximately 0.5cm in diameter, caused by a cigarette. The wound is surrounded by an erythematous border.	Suggestive
Case 7	**Burn**. Sofian, a fourth-grade student, arrives several hours late to class today with a bandage on his right forearm. His mother apologizes and explains that Sofian spilled hot tea on his arm this morning. They went straight to the emergency room, and fortunately, it is only a superficial second-degree burn, so they were allowed to go home quickly. She politely asks if Sofian could skip gym class today.	Clinical image of a boy with his right arm resting on his leg, wrapped in a bandage. His left hand supports the right arm.	Not suggestive
Case 8	**Bite wounds on thighs**. During gym class, you notice that Merel has a wound on the inside of her thigh, which resembles a series of bite marks. The girl herself says that her cat bit her. Merel is 10 years old and part of a family with five children. Since her family has only been at the school for a few weeks, you don't know her parents yet. However, a colleague mentioned on the playground that the family lives in social housing near the canal and that both parents are currently unemployed.	Clinical image showing the inner thigh of a child with three reddish lesions. The lesions have a bite-like pattern, with a size and shape consistent of an adult's dentition.	Suggestive

	Vignette	Image description	(Not) suggestive for child abuse and neglect
Case 9	**Bite wound on the cheek**. Oliver and Noah are twins in the final year of kindergarten. Noah has a bite mark on his cheek. He says, “My brother did that.” Oliver later confirms the story. This doesn’t surprise you, as the brothers often have rough fights. Their mother did not mention this incident this morning, likely because she always seems rushed to get to work on time.	Clinical image of a young child with a circular, red lesion on the cheek. The lesion has the shape of child’s dentition and appears as a small, superficial bite wound.	Not suggestive
Case 10	**Poorly treated wound**. Just before the Easter break, Lina fell on the playground while playing tag, resulting in quite a large scrape. The wound was immediately taken care of. Now, two weeks later, Lina is back in your class. The wound looks quite concerning, with yellow crusts and a red edge. You decide to clean it thoroughly and put a bandage on it. Lina mentions that her dad didn’t think a bandage was necessary, believing it would heal on its own. After school, you inform her father that you think the wound might be getting infected. His response is brief, emphasizing that he knows how to care for a scrape.	Clinical image of a knee of a child with an abrasion covered by a yellowish, purulent crust. The wound margin appears red and inflamed.	Suggestive
Case 11	**Cold and few clothes**. It is February, and the weather has been very cold for several weeks. Milan, a 7-year-old boy, comes to school without a coat for the third time this week. His clothing is clearly not suitable for this cold weather. While supervising the playground, Milan comes over to you, shivering, and says, "Teacher, when is the break over? I’m very cold." He explains that he simply forgot to put on his coat. This reminds you about the fact that he has forgotten his lunchbox several times this school year.	Clinical image of a boy standing outside, wearing only a sweater. He visibly appears cold, with flushed cheeks.	Suggestive
Case 12	**Behavioral regression**. Finn is a 7-year-old boy in the first grade. He is slightly behind his classmates, but with a bit of extra help, he manages to keep up with the material. However, you’ve noticed a significant change in Finn's behavior over the past week. He appears withdrawn and barely wants to talk. It almost seems as if he has forgotten everything he learned over the past few months. At the school gate, you observe his father responding to Finn in a noticeably cold manner. When Finn tries to talk about his day, his father ignores him.	Image of a young boy walking hand in hand with his father towards the school exit.	Suggestive
Case 13	**Vegan diet**. Jebbe is starting is starting his first day of kindergarten today. His parents explain that they are raising him with a strong emphasis on ecological awareness. The family follows a vegan diet (excluding all animal products), but this is done in consultation with their doctor to ensure that Jebbe receives all necessary nutrients and vitamins. The parents kindly request that the school takes this dietary preference into account. While reviewing Jebbe's medical information, you notice that he has only received the mandatory polio vaccinations.	Image of a young girl serving her plate from a bowl filled with various vegetables.	Not suggestive
Case 14	**Bruises upper arm**. Mila is a 10-year-old girl. Her parents divorced a year ago, and she now lives with her mother and stepfather. The transition has been particularly challenging for her, especially given her mild form of autism. Today, you notice several bruises on her upper arm. She tells you that she fell during gym class. Concerned, you ask the gym teacher if they saw anything, but he did not see Mila fall during the sport lesson.	Clinical image of a girl’s left upper arm showing multiple ecchymoses. The bruises are scattered across the upper arm and have a pattern suggestive of finger grip marks.	Suggestive
Case 15	**School absence**. Simon, a 9-year-old boy, has already missed school 8 times this year. Even though the school year has only been underway for two months. A few absences were accompanied by a doctor’s note, but the majority remain unexplained. This pattern of absence is starting to take a toll, as Simon is struggling to keep up with his peers. Simon himself is a reserved child with few friends in the class. Additionally, his mother is at home dealing with depression, and his father works as a laborer in a construction company.	Image of a boy sitting on the corner of a bench, looking down at the ground. He appears lonely and sad.	Suggestive
Case 16	**Pulled elbow**. In the morning, Ella's father approaches you. While playing with her father, 4-year-old Ella injured her elbow, which became dislocated. They went straight to the emergency room, where she was diagnosed with a "pulled elbow". Fortunately, the elbow was successfully repositioned. Ella is still experiencing some discomfort in her elbow. Her father kindly asks if you could keep an eye on how Ella is doing.or other abnormalities. Despite this, Sofie appears happy and does not seem to have any other issues.	Clinical image showing a girl in a hospital emergency bed. Her left arm rests straight at her side, while her right arm is in use.	Not suggestive

TABLE 2: Socio-demographic characteristics of the participants.

	N = 155	%
Gender		
Male	9	5.8
Female	146	94.2
Age		
19-35 years	51	32.9
36-50 years	61	39.4
>50 years	43	27.7
Children of their own		
Yes	122	78.7
No	33	21.3
Numbers of years of work experience		
1-5 years	26	16.8
6-10 years	20	12.9
11-25 years	64	41.3
> 25 years	44	28.4
Been in contact with suspected child maltreatment		
Yes	113	72.9
No	42	27.1
Training for recognizing child abuse		
Yes	26	16.8
No	129	83.2
Type of education		
Mainstream education	128	82.6
Special education	27	17.4
Province of residence		
	N=155	%
Antwerp	32	20.6
Brussels	18	11.6
Limburg	25	16.1
East Flanders	26	16.8
Flemish Brabant	30	19.4
West Flanders	24	15.5

* per 100.000 residents in Flanders.

neglect could predict participants' overall scores. Statistical significance was defined as a p-value of less than 0.05.

Results

Participants

A total of 231 respondents participated in the survey, of whom 155 completed the questionnaire. Only fully completed questionnaires were included in the analysis. Table 2 provides an overview of the socio-demographic characteristics of the participants. The sample was predominantly female (94.2%). Among the participants, 17.4% worked in special education. The respondents had a mean age of 42 years old (IQR: 33-51). On average, participants had 18.7 years of work experience (IQR: 8-27), with only 16% having fewer than five years of experience, indicating a largely experienced cohort.

In addition, 70% of participants reported having previous contact with suspected cases of child abuse and neglect, highlighting the prevalence of this issue. However, only 16.8% of the participants had received training on recognizing the signs of child abuse and neglect.

Overall score

The overall median score of all the participants (n=155) on the 16 cases (compared to the categorization provided by the experts) was 75% (IQR: 68.75-81.25), corresponding to a median of 12 out of 16 correct responses (IQR: 11-13). Only 12 participants (7.7%) scored 8 or fewer out of 16. The lowest score observed was 43.75%, achieved by 2 respondents, while the highest score of 100% was achieved by 4 participants.

We analyzed the sub-scores for the cases suggestive of child abuse and neglect and the non-suggestive cases. In the analysis of the suggestive cases, the median accuracy was 87.5%, indicating higher sensitivity in identifying potential child abuse and neglect. Participants generally performed better on these cases. In contrast, the median accuracy for non-suggestive cases was 62.5%, reflecting the specificity of the participants in correctly identify cases not indicative of child abuse and neglect.

The proportion of correct answers per case is represented in table 3, while figure 1 A-B visualizes the proportion of correct answers using a Likert plot. The highest accuracy among the non-suggestive cases was for identifying bruises on the lower legs (78.1% correct), whereas the most challenging case involved a vegan diet (40.0% correct). Among the suggestive cases, participants achieved the highest accuracy in the scenario involving thin clothing in cold weather (97.4% correct), while the lowest accuracy was observed in the case involving a bruise on the ear (61.3% correct).

Relationship between participant characteristics and overall score

An ANOVA test was conducted to explore potential relationships between categorical sociodemographic characteristics and the overall score. The analysis found no significant differences between the mean scores of the different groups of the variables gender, parental status or previous contact with suspected child maltreatment. Similarly, there were no significant differences between the mean scores of the different groups based on training for recognizing child abuse, type of education or province of residence. The Pearson correlation analysis revealed non-significant correlations between the continuous variables (age and years of work experience) and the overall score. Finally a linear regression analysis was performed (table 4). None of the included variables were significant predictors of the overall score.

Discussion

Focusing on preschool and primary school teachers working in Flanders, Belgium, this study aimed to assess their knowledge of the clinical signs of child abuse and neglect and identify the contributing socio-demographic factors.

The majority of participants were women (94.2%) which is in line with the actual gender distribution among pre-school and primary school teachers in Flanders (87.2% female in 2024) (14). However, due to this distribution, we could not analyze the influence of gender on the overall score. Additionally, there was a slight overrepresentation of teachers working in special education compared to the 2024 average (17.4% versus 10% in Flanders)

(14). The sample demonstrated a balanced distribution across the different provinces in Flanders. There was a slight oversampling from the provinces of Limburg (25 teachers, 2.8/100.000 residents) and Flemish-Brabant (30 teachers, 2.5 per 100.000 residents). It is important to note that only Flemish-speaking schools in Brussels were contacted, which may explain the apparent underrepresentation of the Brussels region, as French-speaking schools were not included. Overall, this sample can be considered representative, comprising experienced teachers (averaging 18.7 years of work experience) relatively well distributed across all provinces in Flanders.

Overall, our results indicate that participants performed well on the questionnaire, with a median score of 75%, indicative of strong overall knowledge. A significant difference emerged when comparing scores on 'suggestive' versus 'non-suggestive' cases. Participants demonstrated a higher accuracy in identifying suggestive cases, with a median score of 87.5%, compared to 62.5% for non-suggestive cases. This suggests that sensitivity in identifying child abuse and neglect cases was higher than specificity. Additionally, we observed a greater variation in the results of the non-suggestive cases, indicating that participants found these cases more challenging. This discrepancy may stem from potential bias, as participants were aware that the study focused on child abuse and neglect, possibly heightening their sensitivity to such cases. While high sensitivity is crucial to ensure that no cases are overlooked, an understanding of clinical signs that mimic abuse or neglect is equally important. For instance, a congenital naevus, often mistaken for a sign of abuse, was misidentified by 40.6% of the participants. Another example of a mimicker is bullous impetigo, a skin infection that causes erosions that can resemble cigarette burns (6). Distinguishing between inflicted injuries and similar-looking medical conditions or accidental trauma is crucial to avoid wrongful accusations against parents, which could damage trust between teachers, children, and caregivers. Therefore, training programs should not only emphasize detection but also address common mimickers of abuse to improve diagnostic accuracy among preschool and primary school teachers. A study by our research group involving general practitioners and pediatricians in training also showed that suggestive cases were identified more accurately (12). However, a study with daycare workers found no significant difference between suggestive and non-suggestive cases (13).

TABLE 3: Proportion of correct answers: per case.

Cases suggestive for child abuse and neglect		Cases not suggestive for child abuse and neglect	
Title	**Correct answers (%)**	**Title**	**Correct answers (%)**
Cold clothes	97.4	**Bruises on lower legs**	78.1
Burn cigarette	96.1	**Bike fall**	77.4
Bruises upper arm	95.5	**Pulled elbow**	70.3
Behavioral regression	95.5	**Burn hot tea**	64.5
Bite trauma upper legs	89.7	**Naevus**	59.4
School absence	89.7	**Daytime wetting**	55.5
Infected wound	76.8	**Bite trauma face**	43.9
Bruise on ear	61.3	**Vegan diet**	40.0

FIGURE 1A: Cases suggestive for child maltreatment: best to least adequately solved.

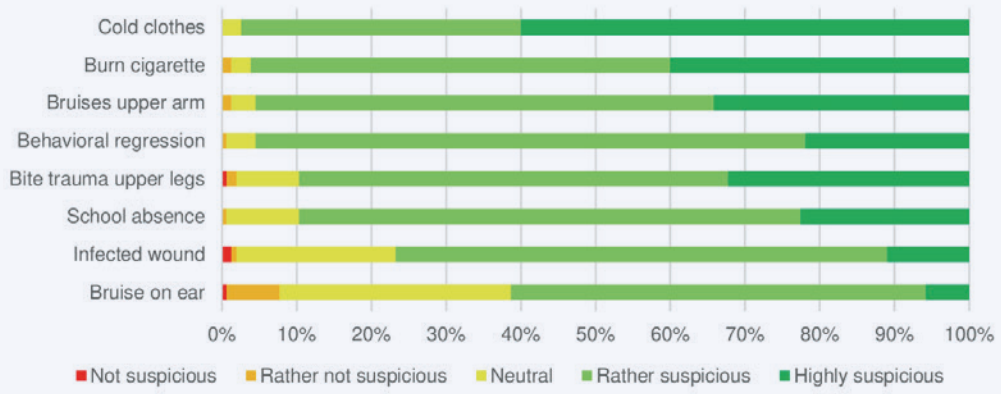
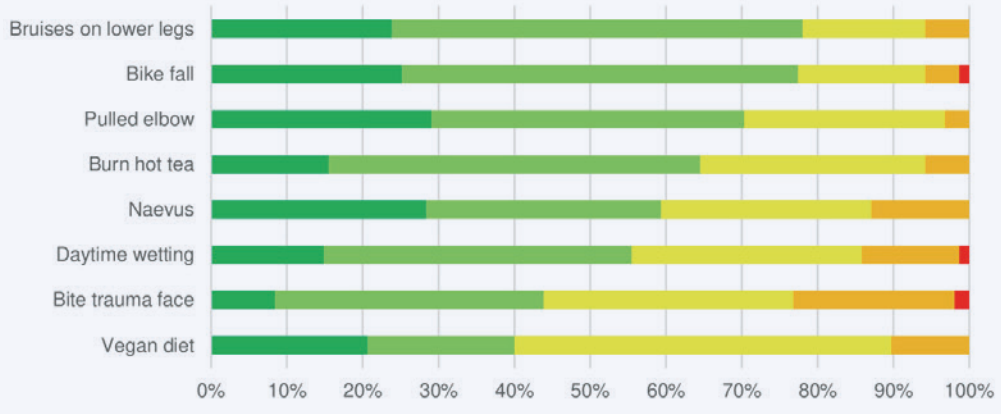


FIGURE 1B: Cases not suggestive for child maltreatment: best to least adequatelysolved.



It should also be noted that teachers can primarily play a role in the early detection and signaling of possible child abuse or neglect, based on observed clinical signs and behavioral changes. As previously mentioned, missing an early indicator increases the risk of repeated harm (6). In this context, a high sensitivity, even at the expense of some specificity, aligns with their preventive role. Further evaluation could be carried out by healthcare professionals. In Flanders, the school physicians of the CLB (Centre for Pupil Guidance) serve as an

TABLE 4: Linear regression analysis: influence of sociodemographic variables on overall score

Socio-demographic variable		Standardized coefficients beta	p-Value
Gender	**Male**		
	Female	-0.027	0.758
Age		0.099	0.630
Years of work experience		-0.192	0.347
Children	**No**		
	Yes	0.110	0.235
Been in contact with suspected child maltreatment	**Yes***		
	No	0.064	0.469
Training for recognizing child abuse	**Yes***		
	No	0.054	0.521
Type of education	**Special education***		
	Mainstream education	-0.019	0.843

* For categorical variables, the category marked with an asterisk (*) is the reference group in the regression model. The reported beta coefficients represent the difference in score compared to this reference group.

essential link between education and healthcare context allowing teachers to refer concernsn while the physicians should consider the differential diagnosis and the level of suspicion regarding child abuse (15). This underscores the importance of raising awareness among teachers, not only about the signs of abuse, but also about how and where to access appropriate support.

In comparison to similar research on childcare workers, participants in this study achieved higher overall scores, with an average score of 75% compared to 67.8% (13). This difference may be partly explained by the design of the hypothetical cases used in the current research, which included direct quotes and statements from children. These verbal indicators likely offered additional context, facilitating the recognition of signs of abuse and neglect. The inclusion of such information could have contributed to the relatively high scores observed in our study. In contrast, young children in daycare settings are often pre-verbal, limiting the available information for assessment. It is also necessary to realize that the two surveys were not matched for level of difficulty, so any variation there could also contribute to the difference in overall scores.

We hypothesized that previous training would have a positive effect on participants' scores. However, we found no significant difference between participants who had received training on child abuse and neglect and those that had not. This may be due to the often superficial nature of training, with many participants describing their training as a one-time session. Such brief training sessions may be insufficient for addressing this complex issue. More in-depth, high-quality training could yield better results, as supported by findings in other studies where extensive training has shown a positive impact. A study with Turkish teachers showed that after a training on the clinical signs of abuse, the scores on a case-based survey about child abuse and neglect were higher than before the training (11). A meta-analysis also indicated higher knowledge levels among professionals working with children after training, though the evidence quality was low, necessitating further rigorous research (16). Research from Ireland highlights the suboptimal knowledge of teachers in training in recognizing child abuse and neglect, emphasizing the critical importance of incorporating pre-service training (17). Finally, there is also a need for regular reeducation, as research indicates that knowledge levels tend to decline over time following a single training session (18).

Interestingly, greater work experience did not correlate with higher scores. This may be due to the relatively rare nature of child abuse cases, which present in diverse and often subtle ways. Even with years of experience, professionals may not encounter the full spectrum of signs associated with child abuse. This underscores the importance of proper training, as experience alone cannot replace the depth of knowledge gained through targeted education. An Australian case-based study supports the finding that teaching experience does not significantly improve scores on a case-based questionnaire. However, it does indicate that more experienced teachers are more likely to report suspected cases (19). Moreover, experienced teachers may less likely recognize signs of child abuse and neglect, as years of teaching experience could theoretically lead to increased tolerance and a reduced sensitivity to the issue (18). Furthermore, we did not observe higher scores among teachers who had previously encountered cases of child abuse during their careers. This could be explained -as mentioned above- by the large spectrum of abuse and neglect manifestations. Therefore, we suggest that training should focus on the diverse presentations of child abuse and neglect to improve overall detection.

Limitations

This study did not identify significant predictors for the overall score, likely due to the relatively small sample size (155 participants). Larger-scale research could provide more robust conclusions. Additionally, the survey's reliance on hypothetical cases may not fully replicate real-life scenarios, where teachers have access to broader contextual information, such as ongoing interactions with the child and insights from caregivers. The survey's explicit focus on child abuse and neglect may have heightened participants' vigilance, potentially influencing their responses. Moreover, the voluntary nature of participation could introduce selection bias. The variable quality and format of prior training among participants also made it challenging to draw firm conclusions regarding its impact. Future studies should prioritize systematic and comprehensive training to assess its effects on improving recognition of child abuse and neglect. Another limitation is that we did not investigate teachers' knowledge of reporting pathways or available sources of guidance when evaluating such situations.

Implications

This study provides a snapshot of current knowledge levels regarding child abuse and neglect among preschool and primary school teachers. It underscores the need for further research to identify the various factors contributing to this knowledge. Future studies should prioritize evaluating the impact of comprehensive and standardized training to determine how it might enhance detection accuracy and awareness. Expanding research in this field could lead to more targeted interventions that effectively help teachers and other professionals working with children to better recognize and respond to signs of abuse and neglect.

Conclusion

This study provides valuable insights into the knowledge of preschool and primary school teachers in Flanders regarding the clinical signs of child abuse and neglect. Although teachers generally performed well on the survey, a gap was observed in recognizing non-suggestive cases.

No significant predictors for knowledge levels were identified, and the influence of work experience or prior exposure to child abuse cases was limited. This highlights that good knowledge in this area requires the ability to recognize and interpret the wide spectrum of manifestations of child abuse and neglect.

We did not find evidence that prior training effectively increased knowledge levels. However, we hypothesize that a well-designed, standardized training program focusing on recognizing both clear and subtle indicators of abuse could bridge this gap, especially given prior studies that demonstrated the positive effects of training. Such training could also address the complex mimickers of abuse, which are often mistaken for signs of maltreatment, hereby reducing the risk of misidentification and false accusations.

Given the limitations of this study's case-based assessment and its relatively small sample, future research should aim for larger, more diverse populations to validate and expand upon these findings. Exploring the factors that influence teachers' knowledge and their understanding of how to report concerns could lead to more effective interventions ultimately providing educators and other professionals working with children with the skills needed to accurately detect and report cases of child abuse and neglect and finally strengthening child protection and welfare.

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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INFORMATIONS ESSENTIELLES – DENOMINATION DU MEDICAMENT Enterol 250 mg, poudre pour suspension buvable. Enterol 250 mg, gélules. *Saccharomyces boulardii* CNCM I-745 – COMPOSITION QUALITATIVE ET QUANTITATIVE Enterol 250 mg, poudre pour suspension buvable : Chaque sachet-dose de poudre pour suspension buvable contient 250 mg de *Saccharomyces boulardii* CNCM I-745 sous forme lyophilisée (soit au minimum 6 x 10^9 cellules reviviscentes au moment de la fabrication et 1 x 10^9 cellules lyophilisées reviviscentes à la date de péremption). Enterol 250 mg, gélules : Chaque gélule contient 250 mg de *Saccharomyces boulardii* CNCM I-745 sous forme lyophilisée (soit au minimum 6 x 109 cellules reviviscentes au moment de la fabrication et 1 x 10^9 cellules lyophilisées reviviscentes à la date de péremption). Excipient(s) à effet notoire (voir rubrique 4.4 du RCP) : Enterol 250 mg, poudre pour suspension buvable : fructose, lactose monohydraté, sorbitol. Enterol 250 mg, gélules : lactose monohydraté. Pour la liste complète des excipients, voir rubrique 6.1 du RCP. FORME PHARMACEUTIQUE Enterol 250 mg, poudre pour suspension buvable : Poudre pour suspension buvable. Enterol 250 mg, gélules : Gélule. DONNEES CLINIQUES **Indications thérapeutiques** • Prévention de la diarrhée associée à l'antibiothérapie à large spectre chez des sujets prédisposés à développer une diarrhée à Clostridium difficile ou rechute de diarrhée à Clostridium difficile. • Traitement des diarrhées aiguës chez les enfants jusqu'à 12 ans, en complément de la réhydratation orale. **Posologie et mode d'administration** Posologie : Adulte : 2 à 4 gélules ou 2 à 4 sachets-doses par jour, en 2 prises. Population pédiatrique Enfant : 2 gélules ou 2 sachets-doses par jour, en 2 prises. Mode d'administration : Gélules : avaler avec un peu d'eau. Sachets-doses : diluer la poudre dans un verre d'eau. Précautions à prendre avant la manipulation ou l'administration du médicament En raison d'un risque de contamination aéroportée, les sachets ou gélules ne peuvent pas être ouverts dans les chambres des patients. Les professionnels de la santé doivent porter des gants durant la manipulation de probiotiques en vue de leur administration, puis les jeter immédiatement après usage et se laver les mains avec soin (voir rubrique 4.4 du RCP). Durée du traitement : Prévention des récurrences ou rechute de diarrhée à Clostridium difficile : 4 semaines. Traitement de la diarrhée en complément à la réhydratation orale chez l'enfant : 1 semaine. Contre-indications : • Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP. • Patients porteurs d'un cathéter veineux central, patients dans un état critique ou immunodéficients en raison du risque de fongémie (voir rubrique 4.4 du RCP. Mises en garde et précautions particulières d'emploi). • Allergie aux levures, spécialement *Saccharomyces boulardii* CNCM I-745 Effets indésirables : Les effets indésirables sont classés ci-dessous par système-organe et par fréquence comme définies ci-après : très fréquents (≥ 1/10), fréquents (≥ 1/100, < 1/10), peu fréquents (≥ 1/1.000, < 1/100), rares (≥ 1/10.000, < 1/1.000), très rares (< 1/10.000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Classes de systèmes d'organes Fréquence Infections et infestations Très rares : Fongémie chez des patients porteurs d'un cathéter veineux central, et chez des patients dans un état critique ou immunodéficients (voir rubrique 4.4 du RCP), mycose à *Saccharomyces boulardii* CNCM I-745. Fréquence indéterminée : Sepsis chez les patients de réanimation ou immunodéprimés (voir rubrique 4.4 du RCP) Affections du système immunitaire Très rare : choc anaphylactique. Affections vasculaires Très rare : choc anaphylactique. Affections respiratoires, thoraciques et médiastinales Très rare : dyspnée. Affections gastro-intestinales Très rares : constipation, épigastralgies, météorisme abdominal (épigastralgies et météorisme abdominal ont été observés lors d'études cliniques). Affections de la peau et du tissu sous-cutané Très rares : prurit, exanthème, Œdème de Quincke. Troubles généraux et anomalies au site d'administration Très rares : soif. Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration. Belgique – Agence fédérale des médicaments et des produits de santé Division Vigilance – Avenue Galilée 5/03 – B-1210 Bruxelles Site internet: www notifieruneffetindesirable.be – e-mail: adr@afmps.be Luxembourg/Luxemburg – Direction de la Santé – Division de la Pharmacie et des Médicaments – 20, rue de Bitbourg – L-1273 Luxembourg-Hamm Site internet: www.guichet.lu/pharmacovigilance e-mail: pharmacovigilance@ms.etat.lu TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE BIOCODEX Benelux NV/SA – Boulevard de l'Humanité 292 – 1190 Bruxelles – Belgique – Tél : 0032(0)23704790 NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE Enterol 250 mg, poudre pour suspension buvable : BE269026, LUX 2011041132. Enterol 250 mg, gélules en flacon en verre : BE269035, LUX 2011041131. Enterol 250 mg, gélules en plaquette: BE397896, LUX 2011041131 MODE DE DELIVRANCE Délivrance libre DATE DE MISE A JOUR DU TEXTE Mise à jour : 04/2023 – Approbation : 09/2023

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20	19,36 €	20	19,36 €	20	19,36 €
50	38,96 €				

BIOCODEX Benelux

Love is not Enough... The Need for Adapted Parenting

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Keywords
Child neglect ; Parenting ; Rickets ; Developmental delay ; Children's rights.

Abstract
Parental maltreatment due to inadequacy is a form of inappropriate parenting that leads to emotional, educational, and/or neglect-related deficiencies with severe consequences for a child's physical and psychological development, though it is not necessarily intentional abuse. This constitutes a violation of the fundamental rights established in the United Nations Convention on the Rights of the Child.

We present the case of a two-and-a-half-year-old boy who was brought to the emergency department by the police. He was severely malnourished, which resulted in nutritional rickets and developmental delay. He had been fed almost exclusively breast milk. His parents had a profoundly distorted perception of his needs. This case is discussed from paediatric, child psychiatric, and legal perspectives.

Introduction

Rickets, a growth disorder caused by severe nutritional deficiencies, is still observed in industrialized countries and serves as a warning sign of serious deficiencies in the care of a child (1).

When these deficiencies result from parental maltreatment due to inadequacy, the situation becomes even more concerning, as it involves neglect of the child's fundamental needs. Though often unintentional, this form of maltreatment has devastating physical and psychological consequences, that jeopardize the child's overall development. According to the United Nations Convention on the Rights of the Child (UNCRC), every child has the right to adequate nutrition and medical care, and to an environment that fosters their well-being (2). Failure to meet these basic needs can result in developmental delays, cognitive and emotional impairments, and long-term health issues.

This article explores the connections between inadequate parenting, parental psychiatric disorders, attachment issues, rickets, and violations children's rights, emphasizing the need for collective vigilance to safeguard vulnerable children.

Clinical Case

In late August 2024, a 2.5-year-old boy, was brought to the emergency department by the police due to suspected malnutrition. He had been reported to child protection services by maternal family members. Following an initial evaluation, the juvenile court ordered emergency protective custody.

The boy was an only child was living with his parents. He had irregular medical follow-ups with different doctors from the age of 6 months old, and there were no consultations between the ages of15 months and 2.5 years. He had only received the polio vaccination (the only mandatory vaccine in Belgium), and his parents chose, not to offer vitamin D supplementation from birth, despite medical advice. At admission, the boy's weight was below the third percentile (Gomez classification < 60%), indicating severe protein-energy malnutrition. His growth curve showed a marked decline starting at six month. He had been on an exclusively milk-based diet since 20 months of age and had a complete food aversion.

Clinical evaluation revealed signs of severe malnutrition, including pallor, rickets, and skeletal deformities such as genu varum, bowed femurs, and wrist deformities. Laboratory tests indicated iron deficiency anaemia (Hb: 6.2 g/dL [N 12.0]), severe vitamin D deficiency (5 ng/mL [N > 20]), and severe hypophosphatemia (0.55 mmol/L [N 1.00-1.95]), responsible for severe rickets confirmed by radiographs of the leg, knee, wrist, and pelvis. Secondary hyperparathyroidism was also present, with elevated alkaline phosphatase levels (3.094 U/L [N 100-320]), indicating increased bone remodelling.

Developmentally, he exhibited motor delay (walking acquired at 21 months) and limited language skills, still presenting jargon at the age of 30 months.

His immediate medical management included nasogastric feeding with a whey-based extensively hydrolysed formula, iron, vitamin D, and phosphate supplementation, alongside gradual introduction of meals outside his hospital room without parental presence. Child psychiatric intervention was initiated in a day hospital setting while staying in the paediatric hospitalisation unit at night. He presented as severely withdrawn and absorbed in his own world. He responded only with fixed smiles and exhibited repetitive and stereotyped movements. He also used very few words.

The parents displayed a partly involuntary non-compliance with medical recommendations, particularly with regard to dietary diversification from six months of age onwards. Continuing exclusive breastfeeding was not their deliberate choice. After an initial introduction of spoon-feeding and solid foods at around 12 months of age, they were unable to manage his progressive

and then absolute refusal to diversify his diet. They reported not realising the profound impact of this regression on his physical and psychological health and development.

Despite demonstrating affection and concern for their son's well-being after five months of hospitalisation (child psychiatric day care and paediatric night care), the parents continued to deny their role in his severe health condition. Their ongoing questioning of paediatric and psychiatric interventions and their lack of collaboration further delayed the child's progress and full recovery. Parental and family interventions proved ineffective, as discussions were limited to interrogating the medical team and pointing out its inefficacy in getting the child to eat. Due to the parents' persistent hampering of the treatment and their lack of adjustment to the child's health and developmental needs, the healthcare team sought judicial intervention to limit parental presence, particularly at night.

Since these protective measures were implemented by the juvenile court, the child has shown significant progress in domains of motor skills, language, emotional and relational skills. He now shows signs of developing an emerging, individualised sense of self, with increasing engagement with others, some playfulness and shared pleasure (3, 4).

Nutritional therapy has addressed deficiencies, yet feeding remains a therapeutic challenge as the boy continues to refuse to consume solid foods orally. A multidisciplinary approach is essential to support his motor, linguistic, emotional, and social development, as well as addressing legal considerations, and requires continuous adjustments. This treatment still needs to be administered in day and night hospitalization since his parents are unable to provide good enough medical and psycho-educational care to the child outside his day care hours.

Discussion

Child abuse manifests in various forms, including physical, psychological, and sexual abuse, as well as neglect. The mission of the SOS Enfants teams is to prevent and deal with situations of child abuse. These teams are skilled in understanding problematic situations and supporting families. They intervene in situations involving physical, psychological, sexual or institutional abuse, as well as situations of risk or neglect. According to data from SOS Enfants in 2021, 26% of calls received concerned physical and 26% concerned sexual abuse, while 19% concerned psychological abuse. 17% of calls involved children exposed to repeated domestic violence and nearly 12% concerned severe neglect (5).

Parental inadequacy as a form of child maltreatment in young children is characterised by a failure of parents or legal guardians to meet the child's fundamental needs. Although often unintentional, this form of maltreatment has severe consequences for the child's physical and psychological development and constitutes a violation of their fundamental rights as established by the United Nations Convention on the Rights of the Child (UNCRC) (6).

In this clinical case, the lack of age-appropriate cognitive and motor stimulation resulted in intellectual and psychomotor developmental delays (e.g., poor language acquisition), thus violating the child's right to education (Article 28 of the UNCRC). An inadequate and insufficient diet resulted in nutritional deficiencies and rickets, breaching the right to health and adequate nutrition (Article 24 of the UNCRC). A lack of medical care (only six medical visits in three years, fragmented follow-up by three different paediatricians and incomplete vaccinations) compromised the child's right to proper healthcare (Article 24 of the UNCRC). Finally, the absence of social interactions (no schooling, an isolated home environment, and difficulties forming relationships) restricted the child's right to socialisation and personal development (Article 31 of the UNCRC).

His parents lived in an isolated nuclear family unit and did not seek advice or help from professionals or relatives regarding their son's feeding difficulties. Their vulnerabilities regarding attachment and personality appear to have resulted in a lack of epistemic trust (7). They relied exclusively on their own beliefs and convictions about nutrition and child-rearing. This beliefs were neither widely shared nor validated by society, and were medically and psychologically harmful.

Moreover, the parents had a distorted perception and interpretation of their child, his intentions, and his needs. Fonagy termed their "tendency to elaborate models of internal states in the absence of relevant evidence" as "hypermentalising", and more specifically "intrusive pseudo-mentalising" (7). They harboured an idealised view of their child believing him to be highly intelligent and having the maturity to make independent choices about his nutrition, clothing, and screen time. The parents insisted that his lack of verbal communication was a deliberate decision on his part; not due to developmental delay. They firmly believed that their child could self-regulate and self-sustain without external intervention, and that parent-child interactions should be courteous and conflict-free.

We hypothesise that the emergence of their son's subjective self between the ages of 7 and 15 months was intolerable for his parents (3). Until the judicial authorities intervened, the child existed in a symbiotic fusion with his mother, without a transitional space, thus preventing the separation and individuation processes necessary for psychological birth (4, 8) When confronted with their son's emerging autonomy and independent desires, the parents were unable to adopt a mature mentalising stance and failed to engage in healthy negotiations around his needs. Instead, they unconsciously resorted to denial of their child's individuality and induced a regression to an oral-symbiotic phase, reinforcing a mother-child fusion through prolonged exclusive breastfeeding.

At the child psychiatric day hospital, parental intervention and engagement in therapy remains unfeasible. The parents continued to deny their role in and responsibility for their child's condition. During parental consultations, they failed to engage in mentalising their difficulties in their relationship with their son and refused to engage in therapeutic reflection. It appears narcissistically unbearable for them to acknowledge their shortcomings and to accept that medical professionals might be more competent in feeding and nurturing their son than they were. Consequently, on an unconscious level, they may have signalled to their son that accepting food from us posed a vital risk to his psychological stability. The only intervention the parents valued was the parent-child interaction workshops, where, through play and movement, we worked to enhance parent-child interactions, help parents interpret their son's meaningful expressions, and guide parents in adjusting to their child's psychological movements.

Some reflections for therapeutic support

As clinicians, we should be aware of relational knots, dead ends and "pathways" that the family systems can create to circumvent the therapeutic process. It is certainly a clinical risk, primarily for the children involved. Traumatized, the boy had to alienate part of himself to exist, to feel somewhat loved. Professionals can also be threatened with wanting to "act quickly and well," not respecting enough the child's rhythm, forcing individual and relational dynamics, blinding themselves as the process reaches its limits and generates a "secondary trauma". The professional posture is so solicited, engaged, that we allow ourselves to call it, in a metaphorical way, "therapeutic funambulism". By funambulism, we must understand the ability, the virtuosity allowing us to play around with difficulties, to be able to determine the solutions. By this term, we emphasise the multidirectional caring attitude that must be adopted even if our primary patient is the child. The

balance must constantly be found between questions, support, connotation, reframing, ... and stopping, if necessary (9).

To adequately accompany the family, we favour a logic of network intervention that is based on the work of medical, psycho-social and legal gridding. The mesh can be understood as a system that contains, assists, monitors and cares, the first level of which certainly concerns child protection, from the onset of the intervention. There may indeed be a real, current and serious danger to the child. Not so much the incapacities of the adult, but rather the detrimental effects of his functioning on the child, sometimes necessitates a distancing from the child. Some, however, advocate maintaining contacts in a supervised setting to respect filial loyalty and connection. The term "mesh" illustrates the intersection of help and care in several directions. Each link in the mesh represents a point of contact, a meeting. The mesh is gradually built , with its weft evolving, tightening or relaxing depending on the risks and on the evolution of the postures of each person involved. Multi-stakeholder intervention also enhances the chances of building trust with the protagonists in complex settings such as high parental conflicts, situations where there is a risk of loss of parental bonds, in which the relational dynamics are based on the complementarity of the rigid type with abrupt oscillations between fusion and rejection.

In the light of these considerations, it seems important to grant an actual place to the adult who is speaking to the professional about his child. It is a matter of welcoming and accompanying this parent, by offering him an adjusted listening, of allowing him to speak, of trying to join him in what he says, in what he expresses about his child. This caring professional attitude, which aims to help and care by ensuring the right amount of protection and respect for integrity, requires to be comfortable with the "funambulism" mentioned above. Understanding without judgement is the first step in any intervention. The prospect of relevant support for the parent, the child and the family requires, in advance, the most accurate assessment possible of the relational context and the history of a family. To do this, it is an asset to intervene with several professionals or even with several services, so much so that the intersecting viewpoints are complementary in a respectful and adequate understanding.

A factor in the establishment of a significant network is mutual trust between services, a state of mind that contributes to the basic serenity conducive to high-quality collaborative work. Without a modicum of calm, rivalries and disqualifications would prevail. Trust can only be gained through continuous reflection on one's practice, a good knowledge of the status of the network, its evolution, the various services of which it is composed, and certainly through the maintenance of respectful interpersonal relationships. It is not a question of opting for single mode of thinking or of reinforcing each other's interpretations of the families, but rather of establishing platforms for discussion and reflection, fuelled by each other's specific work. No one can claim to "know" about a family's functioning by patronizing another person's opinion. We should intervene certainly with our emotions but mostly in terms of hypotheses by welcoming the opinion of others, possibly opposed to ours, as a complement of comprehension and observation, without necessarily seeing it as a disqualification of what we have understood. How many families show themselves differently from one place to another, depending on the interpersonal stakes of alliance and coalition? It should be noted that if a family displays a positive evolution, it is regularly attributed to the resources of the family system, whereas in the case of a negative change, the responsibilities are essentially placed on the professionals (10).

There are a number of factors that determine the operational dimension of a network. It is not a question of making mental and relational functioning more cumbersome by putting forward administrative frameworks and controlling attitudes, but rather of supporting creativity. It should be emphasized that trying to bring about change without respecting the time needed to understand the reasons for the modes of operation is to neglect each singular creation of a family and its multiple meanings. In the same way, it is necessary to know the context in which a network is set up, as well as the awareness of the network by its protagonists as a structure on itself.

In the same vein, let us be vigilant not to be alienated, nor to alienate colleagues in the "next door" service. Concretely, being alienated implies letting oneself think what the other wants us to think; in situations of child abuse, the prudence of experience teaches us the need to be authentic with ourselves, that is to say, to confront our elaboration with the real, avoiding being led to think in another way (11).

In the same way, let us be careful not to become alienated, nor to alienate our colleagues in the service «next door». In concrete terms, being alienated means allowing ourselves to think what the other wants us to think. In situations of child abuse, the prudence of experience teaches us the need to be authentic with ourselves, that is, to confront our elaboration with the real, avoiding to be led to think in a different way (11).

Conclusion

This case illustrates a severe form of paediatric malnutrition, resulting in rickets and developmental delay, a rare occurrence in industrialized countries. It highlights the severe consequences that inadequate paediatric follow-up and dysfunctional parenting can have on a child's health.

This case underscores that love alone is not sufficient and that appearances can be misleading. As clinicians, we may be misled by loving parents whose behaviours is critically inappropriate for their child's fundamental needs. The case emphasises the need for heightened vigilance among healthcare professionals in cases of irregular consultations, symptom minimisation, or refusal of medical recommendations.

A proactive approach combining structured paediatric follow-up, early screening of family vulnerabilities, tailored communication, and parental guidance is essential to prevent similar cases (12). When necessary, reporting to child protection authorities is imperative.

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Vulvar Lesions in a 5-Year-old Girl

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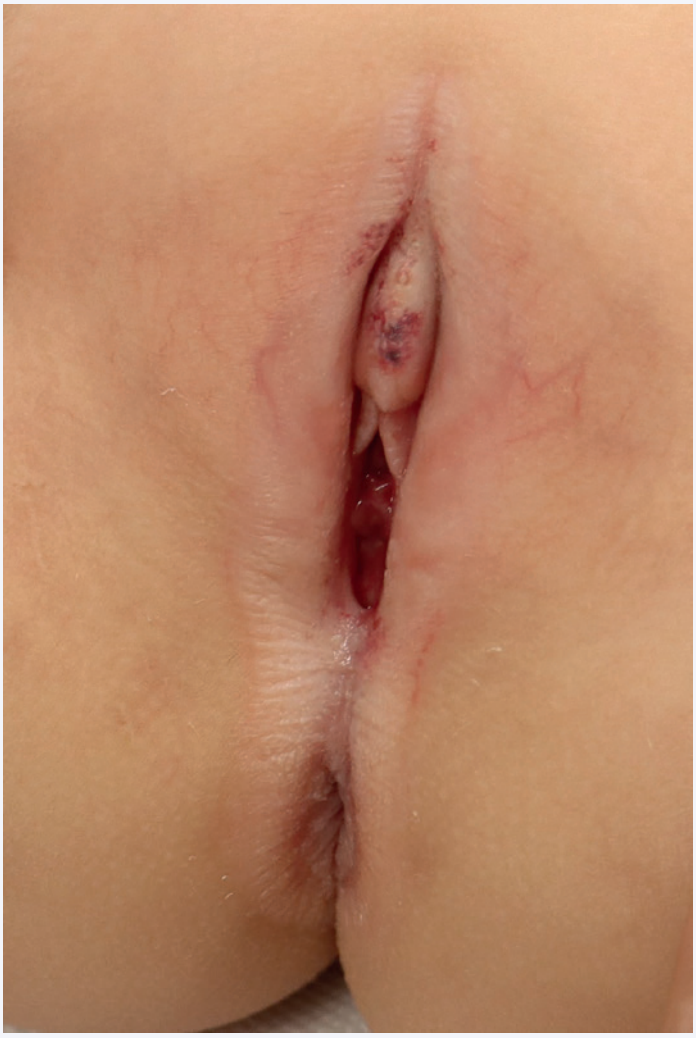
Keywords
Child sexual abuse ; genital lesions ; case report.



Case report

A 5-year-old girl presented to the Sexual Assault Center of Antwerp (SAC). A SAC is a center that provides multidisciplinary care to victims of sexual violence and advice and help to their support circle. This care is offered in one place by a team, consisting of specially trained nurses, physicians and psychologists. The girl was referred by a physician because of genital injuries suspected for sexual abuse. According to the mother, a single parent, there were no known suspicious contacts. The mother could not provide an explanation for her daughter's genital injuries, although she described an incident in which the child was accidentally kicked in the vulvar region when she was three years old. According to the mother there were no problems with the child's behavior, either at home or at school. The girl's development was normal, sleeping behavior was normal for her age. Physical examination revealed small hematomas around the preputium and labia, with lacerations at the fourchette and around the anus. There was hypopigmentation of the skin around the vagina and anus (Figure). The hymen was normal. What is the diagnosis?

Diagnosis

The vulvar lesions in this girl are caused by lichen sclerosus (LS), a chronic autoinflammatory disease. It can present in a number ways and is often initially misdiagnosed with an average diagnostic delay of 1 to 2 years. Because of the genital lesions, sexual abuse is suspected in 14% - 70% of children with LS (1).

LS is more prevalent in females than males with a bimodal age distribution affecting both premenarchal and postmenopausal women. It is most commonly diagnosed in postmenopausal women. However, approximately 5–15% of cases occur in childhood, typically from ages 4 to 6 (1). The prevalence is estimated at 1:900 in premenarchal girls, but because of underdiagnosis of this condition the true prevalence numbers are unknown (2).

Clinical presentation

Typical for LS are ivory white and rose-colored patches forming a hypopigmented area around the vulva. This area can spread to the perianal region forming a classic "figure of eight" or "key-hole" shape. The patches may be atrophic and shiny or thickened due to hyperkeratosis caused by repeated excoriations from scratching. Repeated excoriations from scratching can lead to ecchymoses, subepithelial hemorrhage, superficial erosions, fissures and telangiectasias. Subsequently, these skin changes may progress to genital scarring which can result in adhesion of labia and clitoral hood, narrowing of the vaginal introitus and loss or attenuation of labia minora (2). These architectural changes are more frequently present in adolescents (3). Also, melanotic macules and nevi can emerge as a result of melanocytic proliferations (2,3).

Complaints associated with LS in children are mostly vulvar irritation and pruritus. Other significant symptoms include pain, bleeding due to skin fissures, constipation and dysuria (2,3). Vulvar irritation and pain may be more present at night (2,4). Adolescents can report dyspareunia and are less likely to complain of pruritus (3). Extragenital LS occurs in 18% of cases and emerges mostly on the trunk and extremities, less frequently in the mouth (2).

Diagnosis is based on history and clinical examination. In some cases, the lesions remain asymptomatic and may be discovered incidentally. Performing a biopsy is rarely necessary for the diagnosis in the pediatric population, although it can be warranted in case of treatment failure or when the lesions are atypical and the diagnosis is unclear. In postmenopausal women vulvar biopsies are more frequently performed because of the increased risk of vulvar squamous cell carcinoma (2).

Differential diagnosis

Lichen sclerosus presents in a variety ways and may mimic other conditions, such as trauma or sexual abuse. Children who have been victims of sexual abuse will generally show no or subtle injuries on examination (5). If there are lesions in girls due to sexual abuse, lacerations of the labia, perineum, posterior fourchette or vagina can be seen in the acute phase. Also, bruising, petechiae and lacerations or abrasions of the hymen can be seen. Although early recognition of LS is important to counter unnecessary worries about sexual abuse and to initiate appropriate treatment of the condition, it should be noted that LS and sexual abuse can of course coexist. LS is diagnosed in 4% of cases of confirmed sexual abuse (1). If sexual abuse is suspected, a trained healthcare professional should evaluate the child. In Belgium, such care is available at ten SACs spread throughout the country. In the future 3 more SACs will be opened, which means that each province of Belgium will have its own SAC. SACs provide comprehensive multidisciplinary support to individuals affected by possible sexual violence and their families. This includes medical and psychological care, but also forensic evaluation and assistance with initiating legal proceedings, including the possible filing of a police report (6).

Other differential diagnoses to consider include vitiligo, lichen planus, psoriasis, atopic dermatitis, eczema or candidiasis. Although vitiligo is also characterized by hypopigmentation, it is sharply demarcated with a patchy distribution. It is asymptomatic and is not associated with vulvar atrophy or structural changes. Lichen planus in prepubertal girls is extremely rare; when it presents in the vulvar region, mucosal involvement is possible, whereas this is not seen in LS (2).

Pathogenesis

The pathogenesis remains uncertain but LS is considered an autoimmune disorder. In children it is related to other autoimmune disorders like thyroiditis, pernicious anemia, psoriasis, vitiligo, morphea and alopecia areata. An unspecified genetic contribution is suspected, as 25% of girls with LS have a first-degree relative with autoimmune disorder. In addition, there is a higher prevalence of HLA class II antigen DQ7 in children with LS. Patients with Turner syndrome, who are at risk for autoimmune disorders, have a higher prevalence of LS. The role of other factors such as connective tissue alterations, sex hormone factors and trauma, remains unclear (1,2).

Treatment

The primary goal of treatment is not only to relieve symptoms but also resolve atrophic changes and prevent scarring. First-line treatment is with high-potency topical corticosteroids (class IV). Although there can be considerable side effects, such as thinning of the dermis, these outweigh the risk of untreated or undertreated LS. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) are considered second-line treatment. These immunomodulators are as efficient as corticosteroids, have fewer systemic effects and a lower risk of atrophic changes. However, they are not the first choice treatment given the long-term safety is not yet warranted. After initial treatment with high-potency corticosteroids for at least 4 weeks, maintenance therapy with low/medium-potency corticosteroids is warranted to prevent relapse. Supportive measures, such as good vulvar hygiene, cool compresses and hypoallergenic topical emollients are encouraged to relieve discomfort. In addition, vulvar pruritus may be treated with antihistamines (2).

LS is a chronic condition. Continued monitoring into puberty and adulthood is recommended due to considerable risk of relapse. Winfrey et al. reported that childhood disease persists into adolescence in approximately 40% of patients (3). Consequently, periodic follow-up is important to prevent long-term sequelae including anatomic changes that can significantly impact quality of life and sexual function (2–4).

Conclusion

Lichen sclerosus typically presents with genital injuries that may raise concerns of sexual abuse. Recognition of LS is important to initiate timely and adequate treatment, resolve symptoms and prevent long-term sequelae. Diagnosis may also prevent unnecessary concerns of sexual abuse. However, LS and sexual abuse can coexist and referral to a trained health care professional is warranted in case of concern of sexual abuse. In Belgium, 10 different sexual assault centers are easily accessible for specialized care.

A written permission for the publication of the figure has been given by the parents.

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The Paediatrician: The Bridge between Help, Safety and Trust in a Family in the Event of (Suspected) Child Abuse or Neglect

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Keywords
Child abuse ; health inequities ; adverse childhood experiences ; child advocacy.

What is child abuse?

Child abuse is defined as any harmful act or omission by an adult whom the child depends on, which can result in serious physical or psychological harm. This often happens at home and is referred to as domestic violence. Children and their parents often do not spontaneously report when there are problems at home. They depend on others who may or may not recognize these signals.

All parents strive for the best for their children. Parents who are involved in abuse or neglect of their children often do not act intentionally or with the intention to harm. Usually this is the result of an accumulation of problems within a situation of powerlessness and the lack of prospect of positive change. These parents often struggle with psychological problems or serious addiction issues. Additionally, parents who have been mistreated, neglected, or abused in their own childhood are more likely to continue these behaviours. In addition, some parents may have insufficient parenting skills or fall short in their knowledge of what children need to develop healthily.

Emotional abuse and neglect rare the most commonly reported forms of child abuse (1).

Emotional neglect

Emotional neglect occurs when caregivers fail to meet a child's emotional needs, such as providing love and support (2). This can result in problems such as attachment disorders, behavioural problems, and increased vulnerability to depression. The child may also experience a sense of great shame and try to satisfy the parent by performing well (3). Emotional neglect is often accompanied by physical neglect and is more common in boys than in girls.

Emotional abuse

Emotional abuse involves caregivers belittling, ridiculing, or frightening children. This can greatly undermine children's self-confidence. Growing up in an environment of systematic humiliation and rejection can cause deep emotional wounds that may not become apparent until years later (4, 5).

Child abuse in Belgium

Child abuse is also a serious social problem in Belgium that can have a deep and lasting impact on a child's development and well-being. Sometimes up to adulthood.

In 2024, there were 10,913 children in Flanders and Dutch-speaking Brussels who were reported to the centres, an increase of more than 20 percent compared to 2018 (6).

In 2022, there were 6,511 reports in Wallonia and French-speaking Brussels (7).

The reports mainly concern emotional abuse or neglect (37 percent in Flanders; 30.4 percent in Wallonia), physical abuse or neglect (28 percent in Flanders; 26.5 percent in Wallonia), sexual abuse (15 percent in Flanders; 25.7 percent in Wallonia) and general risk situations and processing problems (16 percent in Flanders; 17.4 percent in Wallonia). Of all reported children, the age group 12 to 14-year-olds was the largest.

Emotional abuse and neglect remain the most commonly reported forms of child abuse.

The reporting person was mainly someone from a school-related facility, health care or the child's primary environment.

The increase in the number of reported children indicates a growing willingness of professionals to identify and discuss their concerns about the safety of children.

Child abuse and children's rights

Children have the right to grow up safely. Physical, emotional or sexual abuse, as well as neglect, to witness domestic (partner) violence constitute violations of the fundamental rights of the child, as enshrined in the International Convention on the Rights of the Child (UNCRC), adopted by the United Nations in 1989. This convention, signed by almost all countries in the world, states in Article 19 that every child has the right to protection from abuse and neglect, and guarantees their access to health care and support (8).

Article 19, International Convention on the Rights of the Child:

1. *States Parties shall take all appropriate legislative, administrative, social and educational measures to protect the child from all forms of physical or mental violence, injury or abuse, neglect or negligent treatment, maltreatment or exploitation, including sexual abuse, while in the care of parent(s), legal guardian(s) or any other person who has the care of the child.*
2. *Such protective measures should, as appropriate, include effective procedures for the establishment of social programmes to provide necessary support for the child and for those who have the care of the child, as well as for other forms of prevention and for identification, reporting, referral, investigation, treatment and follow-up of instances of child maltreatment described heretofore, and, as appropriate, for judicial involvement*

Lifelong impact of child abuse

Children who are victims of child abuse have an increased risk of experiencing violence later in life. This can manifest itself in the use of violence themselves or in an abusive relationship.

About a third of children who grow up with violence later use violence against their own children. Possible causes include the lack of a good example, a lack of trust due to insecure attachment, unprocessed traumas and emotional problems, and difficulty balancing autonomy and connection with their partner (9).

Child abuse not only has physical consequences but can also cause long-term damage (10). Examples are post-traumatic stress disorder and dissociative disorders such as memory loss. Child abuse also leads to various psychological problems, including anxiety and depression. Social problems manifest themselves, for example, in withdrawn or aggressive behaviour.

Child abuse affects brain development and epigenetics. This is shown by research into Adverse Childhood Experiences (ACEs). For example, these children have a higher chance of developing serious health problems in the long term and even a life expectancy that is 20 years shorter.

Keeping families stable, safe and together

Child safety comes first. However, assistance focuses primarily on keeping families stable, safe and together. After all, the health effects of family separation are lifelong (11).

Alternative care rarely provides more stability for children than staying with their parents. If it is not possible to leave children with their parents, the UN Guidelines for the Alternative Care of Children give priority to placement with close relatives (12).

Role of the paediatrician

Paediatricians play a key role and bridging role in identifying, treating and preventing child abuse. Their medical expertise enables them to recognize the physical and psychological signs of abuse, such as unexplained injuries, malnutrition, or severe anxiety symptoms. In addition, they can form a bridge between the child, the parents, support agencies and the legal authorities, so that children receive the protection and care they need in a timely manner.

Paediatricians also have an educational and preventive function. By providing education to parents and caregivers about safe parenting methods and the importance of a healthy, supportive environment, they can contribute to reducing risk factors. In addition, they can advocate for policies that help combat child abuse, such as better reporting procedures and specialized care programs.

To take on this role as a paediatrician, it is important to have a good overview of the care and assistance landscape in the event of child abuse.

The website on Family Problems of the Federal Government brings together the various per community and region. After all, 'child abuse' is a competence of the federated entities at the policy level (13).

The link between child abuse, the International Convention of the Rights of the Child and the paediatrician is important: the treaty provides an international framework for children's rights and paediatricians play a role in safeguarding these rights. Through prevention, identification and intervention, paediatricians help to realise the principles of the convention and contribute to the future of children worldwide.

More information

Flanders and Brussels: Vlaams Expertisecentrum Kindermishandeling (VECK): Vlaams Expertisecentrum Kindermishandeling - VECK

Wallonia and Brussels: SOS Enfants – ONE : Les équipes SOS Enfants - Professionnel - Office de la naissance et de l'enfance

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Short Term Mortality and Morbidity in Extremely Preterm Babies Born Before 27 Gestational Weeks: Comparison Between Two Birth Cohorts (1999-2003 and 2010-2016) in a Belgian Third Level NICU

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Keywords
Extremely premature ; mortality ; morbidity.

Abstract

Purpose
To compare mortality and morbidity in a third-level neonatal intensive care unit in 2010-2016 in order to assess changes in outcomes since 1999-2003 and to evaluate possible intervention improvement.

Methods
We retrospectively analyzed data collected between 2010 and 2016 on 109 patients born before 27 gestational weeks among infants hospitalized at the Cliniques Universitaires Saint Luc in Brussels. We compared them with a previous internal study cohort of 75 patients of the same age born between 1999 and 2003. We compared mortality and morbidity at unit discharge between the two periods.

Results
The overall mortality rate of extremely preterm infants decreased by 4% from 1999-2003 to 2010-2016. This is not statistically significant (p=0,66). Neonatal deaths occurred earlier in the period 1999-2003. Between 1999 and 2003 deaths were most often attributed to multiorgan failure. In the 2010-2016 period deaths were most frequently attributed to severe central nervous system injury.

The overall prevalence of survivors without major morbidities decreased by 2% from the 1999-2003 to the 2010-2016 period (p=0,78), also not statistically significant.

Conclusions
Our findings corroborate previous studies suggesting that improved outcomes for infants born before 25 weeks of gestation might be achieved by considering resuscitation before 24 weeks. In order to obtain more statistically significant data, future research should compare the Belgian EPIBEL 1999-2000 cohort with a more recent Belgian cohort, potentially clarifying the impact of advanced interventions and care strategies on mortality and morbidity rates in extremely preterm infants.

Introduction

Very extreme prematurity, considered here as birth before 27 gestational weeks, remains nowadays a huge challenge in terms of mortality and morbidity.

Significant advances were made in the nineties with the generalization of the use of antenatal corticosteroids and surfactant (1 - 3).

In France a large cohort study, EPIPAGE 2, revealed that survival without morbidity for preterm babies born between 25 and 27 gestational weeks has still improved over a 15-year period (1997-2011), but not for babies born at 24 weeks (4). This difference for the infants born at 24 weeks of gestation is linked to the general habit in France of choosing not to reanimate preterm babies before 24 weeks.

A cohort study, made in the U.S., where neonatologists generally intervene from 22 weeks, showed an increase in the rate of survival without neurodevelopmental impairment from 2000 through 2011 in preterm babies born at 23 and 24 weeks, but not for those born at 22 weeks (5).

The aim of the present study was to compare babies born extremely preterm in the Cliniques Universitaires Saint Luc (CUSL) in Brussels between 1999 and 2003 to those born between 2010 and 2016 at the same institute. We wanted to see whether there has been an improvement in terms of morbidity and mortality between the two periods. As in France, the policy of the institution during those years was not to intervene before 24 gestational weeks. This study will be useful to identify possible improvements in the interventions with preterm babies. It will also guide the staff to give a better information to parents facing a preterm birth.

Methods

Study population and definitions

This single center retrospective study at CUSL includes very extremely preterm babies, considered here as babies born before 27 gestational weeks, from 1st January 1999 to 31st December 2003 (75 patients selected), compared to those born from 1st January 2010 to 31st December 2016 (109 patients selected). The data from the first cohort (1st January 1999 to 31st December 2003) were derived from a previous non-published internal study. Consequently, we first analyze the second cohort (1st January 2010 to 31st December 2016) using the same criteria that were used for the first study. In a second time we compared the two cohorts.

We used the neonatal department registry to select patients born before 27 gestational weeks and hospitalized in the third level neonatal center in CUSL. Gestational age was established as the best obstetric estimate based on the last maternal menstrual period date and/or antenatal ultrasonography data.

Patient data were retrospectively collected from the discharge summary.

The primary outcome was infant mortality, defined as the number of children who died before discharge from the department. We also analyzed the cause and timing of death. The secondary outcome was severe neonatal morbidity at discharge. It was defined as one or more of the following outcomes: severe central nervous system (CNS) injury considered as grade III or more intraventricular hemorrhage, according to the Papile et al. classification; periventricular leukomalacia defined as persistent parenchymal hyper echogenicity; severe bronchopulmonary dysplasia (BPD), according to the Jobe and Bancalari definition; stage 3 or higher retinopathy of prematurity with laser treatment, according to the international revisited classification (6 - 8).

As this is a retrospective cohort study, it does not include any personal data of the patients, therefore informed consent was not asked to the parents or guardian of the children. No data can be directly linked to the patient themselves.

Research ethics board agreement has been given by the hospital-faculty Ethics Committee of Cliniques Universitaires Saint Luc on 27th may 2024.

Statistical analysis

For our statistical analysis and creation of graphics, we used Graphpad Prism (V 10.2.1).

We compared the overall and cause-specific mortality and morbidity rates (number of events per total number of patients) and the proportionate mortality and morbidities (relative percentage contribution) for the coded causes of death and neonatal short-term morbidity among infants born in two birth-year periods. We selected a larger second period to ensure a total number of patients greater than 100, aiming to more significant results.

We compared all population characteristics between the two periods using the chi-square test. For the groups where there was at least one N ≤ 5, we used the Fisher's exact test with Graphpad Prism (V 10.2.1). We considered the differences between the two cohorts as statistically significant if p≤0,05.

As we did not have precise gestational age for each patient in the first cohort, we used a nonparametric Mann-Whitney test to compare gestational age in the two cohorts.

We also used the chi-square test and the Fisher's exact test, with the same criteria, to compare the mortality and morbidity rates in our population with those of some national cohort studies, acknowledging the known statistical limit due to the differences in the size and characteristics of the populations studied.

Results

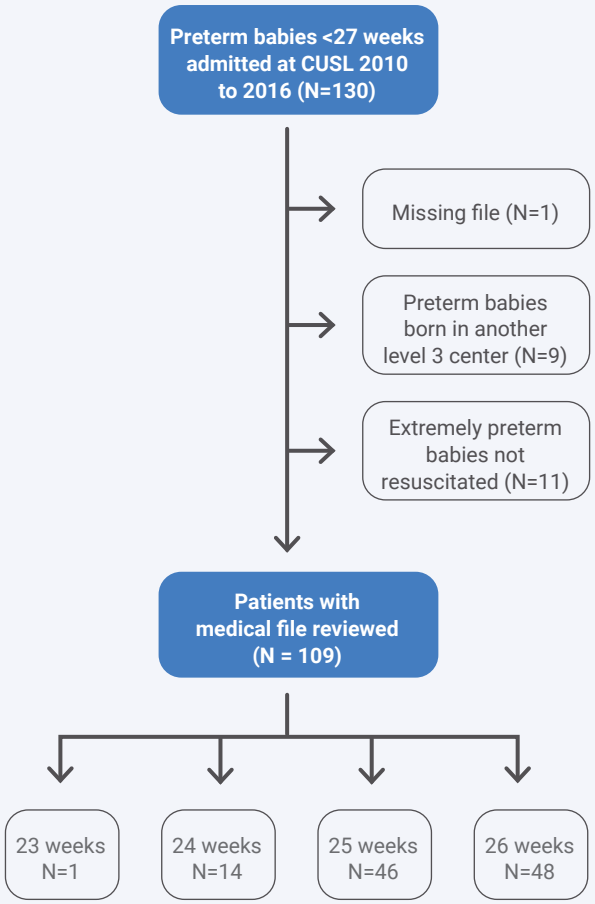
Characteristics of the two cohorts

We initially had 130 patients, one patient was excluded because the report was missing. Nine patients were excluded because they were born and initially hospitalized in another third level neonatal center. They were transferred to the department for ophthalmologic or otorhinolaryngologic advice. Finally, we excluded 11 patients that were not actively reanimated at birth and who received palliative care. These patients were all born before 25 gestational weeks: 8 of them were born before 24 weeks and were not reanimated due to the general policy in the department during our study, while 3 others were born between 24 and 24 weeks 6/7, all of them in a context of chorioamnionitis, and received palliative care in agreement with the parents (Figure 1).

75 extremely preterm babies (24 to 26 6/7 weeks of gestation) that meet the inclusion criteria were born in our center from January 1st, 1999, to December 31st, 2003, and 109 from January 1st, 2010, to December 31st, 2016. Among these infants 51 (68%) survived to discharge in the first cohort and 78 (72%) survived to discharge in the second cohort.

Mean birthweights were similar in the two groups, but there were more infants considered extremely small for gestational age from the point of view of birthweight (20% vs 6% p=0,007) and birth length (19% vs 6%, p=0,006) in the first group compared to the second one. (Table 1). This difference is mainly due to the different growth chart used for the two populations: Usher and McLean growth curves were used for the first group and Fenton preterm growth chart for the second one (9, 10).

FIGURE 1: Flow chart of inclusion criteria.



Gestational age and sex were similar in the two groups, with the only difference that the second cohort included a 23 weeks' gestation patient (Table 1).

There was a small and non-significant difference in the overall age at birth (babies were younger in the cohort 1 (25,2 +/- 0,8 vs 25,5 +/- 0,9). There was no difference in the age at birth of the survivors 25,9 +- 0,7 in the two cohorts (Table 1).

There were less multiple gestations in the first group than in the second one (24% vs 30%) but siblings in the first cohort tend to be younger than in the second one (55% born at 24 gestational weeks vs 12%) (Table 1).

Regarding obstetrical problems as chorioamnionitis, eclampsia and metrorrhagia, there was no significant difference between the two populations (Table 1).

Between the two periods we detected a significant increase in the percentage of women who delivered by cesarean section (from 51% to 78%, p=0,001) (Table 1). There was also a significant decrease in the number of women not receiving antenatal corticosteroids at all (24% in the first period and 10% in the second period, p=0,01). However the number of women that underwent a complete course of antenatal corticosteroids was not significantly different (52% vs 62% p=0,22) (Table 1).

Finally, during the second period there was a significant increase of intubated neonates in the delivery room (from 69% to 89%, p=0,006) and of neonates that underwent surfactant therapy (from 20% to 86%, p<0,001). Mean APGAR score at 1, 5 and 10 minutes was similar in the two groups (Table 1).

TABLE 1: Characteristics of the two cohorts.

	1999-2003	2010-2016	p value
	(N=75)	(N=109)	
Gestational age (GA) - weeks	25,13 +/- 0,8	25,29 +/- 0,8	0,177
23 weeks – no. (%)	0	1 (1)	
24 weeks – no. (%)	19 (25)	14 (13)	
25 weeks – no. (%)	27 (36)	46 (42)	
26 weeks – no. (%)	29 (39)	48 (44)	
Birth weight – g (median +/- standard deviation)	762 +/- 167	759 +/- 166	
Extremely small for GA (<P3) – no. (%)	15 (20)*	7 (6)¶	0,007
Birth length – cm (median +/- standard deviation)	33 +/- 3 cm	33 +/- 2	
Extremely small for GA (<P3) – no. (%)	14 (19)*	6 (6)¶	0,006
Head circumference – cm (median +/- standard deviation)	23 +/- 2	23 +/- 2	
Extremely small for GA (<P3) – no. (%)	3 (4)*	5 (5)¶	1
Male sex – no. (%)	44 (59)	66 (59)	
Multiple gestation – no. (%)	18 (24)	33 (30)	
Mother received prenatal glucocorticoids		N= 106	
None – no. (%)	18 (24)	11 (10)	0,01
Incomplete course – no. (%)	18 (24)	27 (25)	0,91
Complete course – no. (%)	39 (52)	68 (62)	0,22
Chorioamnionitis – no. (%)	33 (44)	39 (36)	0,3
Pre-eclampsia/HELLP/Eclampsia – no. (%)	14 (19) §	16 (15)	0,46
Metrorrhagia – no. (%)	31 (41)	39 (36)	0,48
Premature rupture of membrane – no. (%)	27 (36)	38 (35)	0,88
Inborn – no. (%)	65 (87)	102 (94)	0,2
Cesarean section – no. (%)	38 (51)	85 (78)	0,001
Intubated in delivery room – no. (%)	52 (69)	97(89)	0,006
Surfactant therapy no. (%)	15 (20)	94 (86)	<0,001
Apgar score			
1 min – median (+/- standard deviation)	4 (2)	3 (2)	
5 min – median (+/- standard deviation)	6 (2)	7 (2)	
10 min – median (+/- standard deviation)	7 (2)	7 (2)	
Length of stay – mean +/- std.dev (median)	82+/-27 (79)	103+/-33 (94)	
Term at discharge (weeks)	37,7+/-3,8	40,5+/-4,5	
Return home – no./total no. survivors (%)	28/51 (55)	63/78 (81)	0,07
Post-term return home > 40 gestational weeks	10/28 (36)	19/63 (30)	0,62
Post-term return home > 44 gestational weeks	4/28 (14)	5/63 (8)	0,71

* Usher and McLean growth curves (16); ¶ Fenton preterm growth chart (17);
§ N=74: data missing for one patient.

Hospital stay

The median length of stay in hospital and the term at discharge among survivors increased from the 1999-2003 period (82 +/- 27 days and 37,7 +/- 3,8 weeks) to the 2010-2016 period (103 +/- 33 days and 40,5 +/- 4,5 weeks). Meanwhile the transfer in other departments of CUSL or in a first or second level neonatal center decreased. Overall post-term discharge home, considered as a return home after 40 gestational weeks, decreased in the second population compared with the first one (Table 1). All these differences are not statistically significant.

Trends in mortality

The overall in hospital mortality rate of the extremely preterm babies decreased by 4% in the CUSL from 1999-2003 to 2010-2016, but this is not statistically significant (p=0,66). In the cohort 2010-2016 the mortality decreased especially in babies born at 24 gestational weeks (from 63% to 43%, p=0,32), and also in babies born at 25 gestational weeks (from 32% to 30%, p=0,9). Mortality seems to increase slightly in babies born at 26 gestational weeks (from 16% to 21%, p=0,55). Nevertheless all these differences are not statistically significant (Table 2 and Figure 2). The only reanimated 23 weeks of gestation baby died at 6 days of life.

The mortality rate among babies born of multiple pregnancies from 1999 to 2003 was higher than from 2010 to 2016 (61% vs 15% p= 0,001). For babies with antenatal chorioamnionitis, eclampsia or premature rupture of membrane there was no significant difference in the mortality rate between the two groups (Table 2).

Neonatal deaths occurred earlier in the 1999-2003 period compared with the 2010-2016 period. 66% of babies died before 48 hours in the first group compared with 18% in the second group (p<0,001). 79% of babies died before 72 hours in the 1999-2003

TABLE 2: Mortality rate comparison.

	1999-2003	2010-2016	p value
Mortality – no. deaths /total no. (%)	24/75 (32)	31/109 (28)	0,63
23 weeks – no. deaths /total no. (%)	-	1/1 (100)	-
24 weeks – no. deaths /total no. (%)	12/19 (63)	6/14 (43)	0,34
25 weeks – no. deaths /total no. (%)	8/27 (30)	14/46 (30)	1
26 weeks – no. deaths /total no. (%)	4/29 (14)	10/48 (21)	0,55
Origin of the baby			
Inborn – no. deaths /total no. (%)	19/65 (29)	29/102 (28)	0,91
Outborn – no. deaths /total no. (%)	5/10 (50)	2/7 (29)	0,62
Number of babies per pregnancy			
Singleton – no. deaths /total no. (%)	13/57 (23)	26/76 (34)	0,18
Multiple pregnancies – no. death /total no. (%)	11/18 (61)	5/33 (15)	0,001
Chorioamnionitis§			
No chorioamnionitis – no. deaths/total no. (%)	17/41 (41)	20/70 (29)	0,19
Proved chorioamnionitis – no. death/total no. (%)	6/33 (18)	11/39 (28)	0,35
Premature rupture of membrane			
No premature rupture of membrane – no. deaths/total no. (%)	14/47 (30)	20/71 (28)	0,86
Premature rupture of membrane – no. deaths/total no. (%)	9/27 (33)	11/38 (29)	0,72
Pre-eclampsia, HELLP or eclampsia			
None – no. deaths/total no. (%)	20/60 (33)	27/93 (29)	0,6
Pre-eclampsia, HELLP or eclampsia – no. deaths/total no. (%)	3/14 (21)	4/16 (25)	1
Antenatal corticosteroid use Δ			
None – no. deaths /total no. (%)	8/18 (44)	6/11 (55)	0,71
Incomplete course – no. deaths/total no. (%)	7/18 (39)	8/27 (30)	0,55
Complete course – no. deaths/total no. (%)	9/39 (23)	16/68 (24)	0,96
Other ◊ corticosteroids – no. deaths/total no. (%)	0	1/3 (33)	1

§ Data unknown for one death patient in the 1999-2003 cohort; Δ Betamethasone complete course = 2 doses at 24 h distance; ◊ Dexamethasone initially used as treatment of HELLP syndrome.

period compared with 35% in the 2010-2016 period (P=0,002). In the second period, most babies died between 3 and 7 post-natal days (35% vs 4% in the first period, p=0,007) (Figure 3).

Between 1999 and 2003, deaths were most frequently attributed to multi-organic failure (MOF) that represented 42% of deaths against only 10% during the 2010-2016 period (p= 0,009). In contrast, between 2010 and 2016, deaths were most frequently attributed to severe CNS injury (32% against 8% in the first period, p=0,048). There was no significant difference between the two periods in the other mortality causes as pulmonary or cardiac failure (Figure 4).

Neonatal morbidity

Strikingly, the overall prevalence of survivors without major morbidities decreased by 2% from the 1999-2003 period to the 2010-2016 period, but this is not statistically significant (p=0,78) (Table 3, Figure 5). This prevalence decreased for patients surviving without CNS bleeding (from 92% to 88%, p=0,56), but increased for those surviving without severe BPD (from 73% to 80%, p=0,43) or without severe retinopathy of prematurity, considered here as retinopathy needing a laser treatment, (from 83% to 92%, p=0,23) (Table 3).

Of all extremely preterm babies that where initially reanimated, 60% in the 1999-2003 cohort and 52% in the 2010-2016 cohort (p=0,09) survived without CNS lesions (bleeding and/or permanent hyper echogenicity). 45% vs 48% (p=0,84) survived without CNS lesions and without chronic lung disease. Finally 45% vs 43% (p=0,78) survived without any severe condition.

FIGURE 2: Mortality rate for babies born before 27 weeks (% of total patients).

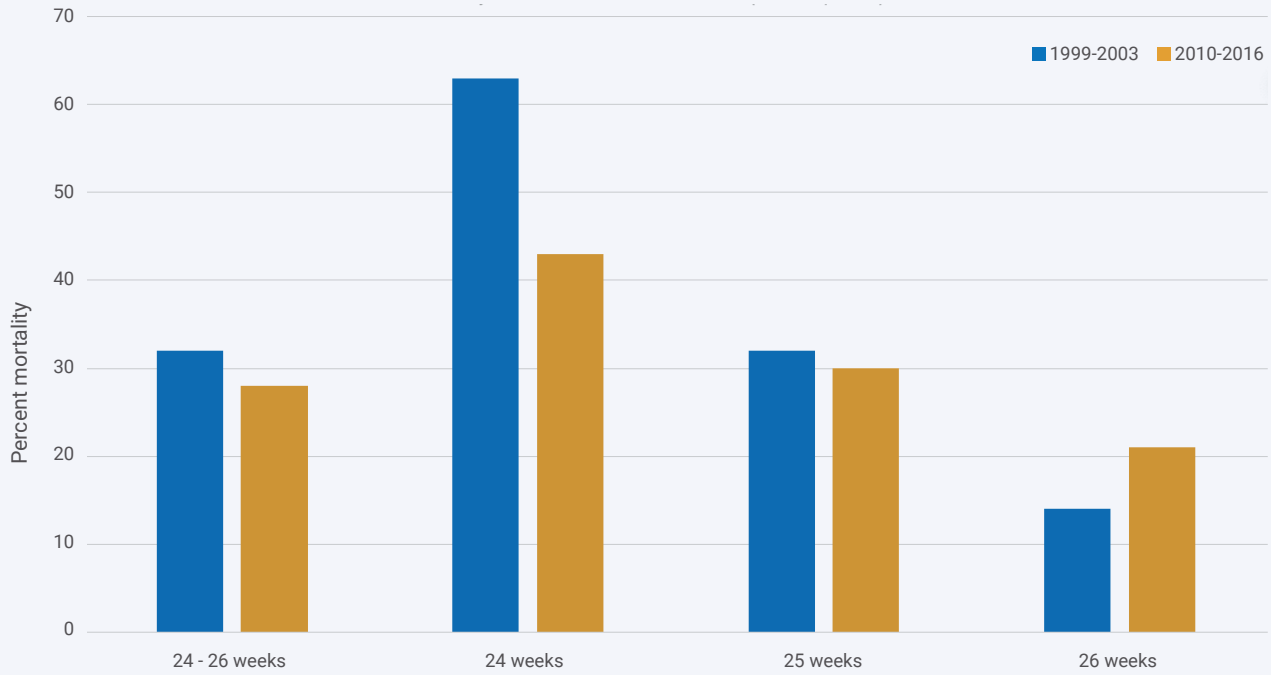


FIGURE 3: Timing of death comparaison.

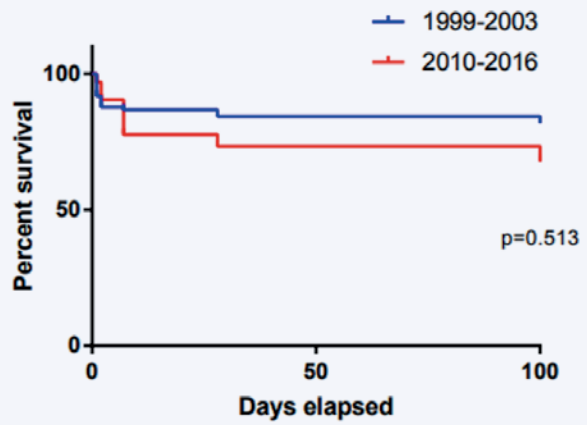
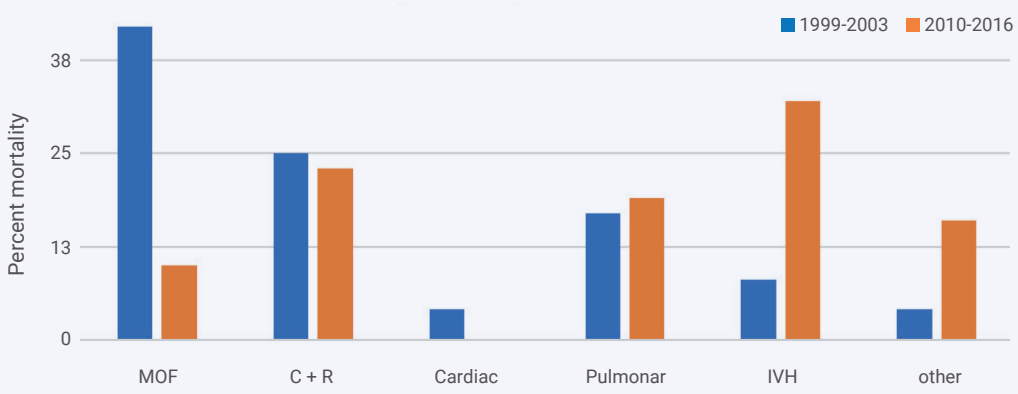
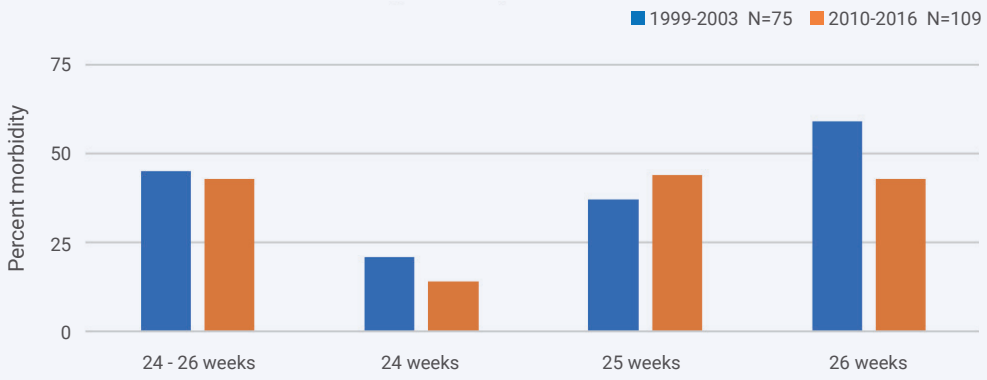


FIGURE 4: Principal causes of death (% of total dead patients).



MOF = Multiple Organ failure; C + R = Cardiac and respiratory failure; IVH = Intraventricular Hemorrhage; Other reason of death: dysmaturity, digestive failure and severe sepsis.

FIGURE 5: Survival without major morbidity (% total patients).



Discussion

Considering gestational age, morphology, obstetrical history, there is no significant difference in the characteristics of the two population studied. There seems to be a difference in the number of extremely small for birthweight and birth length infants. This is probably due to a different growth chart used in the two periods.

Overall, we do not observe any significant difference in the mortality and morbidity rates between the two populations studied. This is probably explained by the small size of the analyzed populations, especially when divided in subgroups by gestational age. Furthermore, we suppose that the lack of difference is also due to the fact that our populations are separated only by 7 years from the end of the first period (2003) to the beginning of the second period (2010). Moreover during such a period there has not been any major advance in neonatal medicine. Nevertheless, we observe a significant increase in the use of surfactant therapy and in the number of patients intubated in the delivery room in the 2010-2016 cohort. We can correlate it to a decrease in the severe bronchopulmonary dysplasia at 36 gestational weeks, but these data are not significant. Furthermore, the decrease in BPD can also be linked to the protective ventilation strategies developed in recent years (11). These data are not shown in the current study.

The other significant difference in the mortality rate between the two groups concerns a decrease in the mortality of babies born from multiple pregnancies. This is probably due to the fact that in the 1999-2003 cohort there was a larger number of siblings born at 24 gestational weeks compared to the 2010-2016 cohort. Moreover 8 of them were triplets in the first group while in the second one they were all twins.

Finally, we found a significant difference in the time of death: preterm babies died earlier in the first cohort than in the second one (Figure 3). This is probably due to the more aggressive reanimation at birth in the 2010-2016 period with an increase in intubation and surfactant therapy in the delivery room. Due to this more aggressive reanimation, the causes of death were significantly different in the two groups. Babies in the first cohort died mainly of multiple organ failure, while in the second one of severe CNS bleeding. Similar data on change of causes and timing of death were already reported in an American cohort study in 2015 (12).

In contrast with the Epipage 2 study in France, we do not observe any significant improvement in mortality rate over time (4). However the survival rate in our first cohort was already considerably higher compared to what is described in that study. The required number of patients to evidence some differences between the two cohorts of our study should have been approximately 2050 children per group, based on our observations (survival difference of 4%, p at 0,05 and power at 0,8). Indeed, our figures are closer to what has been observed in the Epicure English cohort in 2006, but they are still far off from the Australian, Japanese and Swedish figures (Table 4) (13 – 16). The main difference we can observe with these countries

is that they start to reanimate babies born before 24 gestational weeks. Therefore, as the authors of the Epipage 2 study concluded, if we want to improve mortality and morbidity of extreme preterm babies we should probably change the institutional policy and start to reanimate babies before 24 weeks of gestation (4).

Moreover, another difference we noticed is a slight increase in the length of hospital stay in the second group that was probably due to a smaller number of transfers to other departments as the overall discharge to home time decreased in the second cohort. Anyway, the median hospitalization length, 95 days, in the 2010-2016 cohort was similar to the 111 days reported in the EPICURE cohort study for their 2006 population (13).

Conclusion

Our study shows that, in absence of major technical or medicinal advance, it is difficult to improve mortality and morbidity in extreme preterm babies. The countries with the best results are those who reanimate babies from 23 weeks of gestation, with potential extension to 22 weeks, based on favorable conditions.

To improve mortality and morbidity rates in neonatal intensive care units (NICU), especially for babies born before 25 gestational weeks, we should start to reanimate from 23 gestational weeks. The policy at CUSL nowadays considers resuscitating preterm babies from 23 weeks of gestation.

Future studies, including a comparison with a more recent CUSL NICU cohort and the realization of an "EPIBEL 2" study, are planned to assess the impact of these changes on mortality, morbidity, and long-term outcomes of extremely preterm newborns. These efforts aim to contribute to the ongoing debate on peri-viability and to refine parental guidance on resuscitation and survival expectations for extremely premature infants.

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

TABLE 3: Morbidity rate comparison.

	1999-2003	2010-2016	p value
Survival without major morbidity – no. /total no. survivors (%)	34/51 (67)	47/78 (60)	0,52
24 weeks – no./total no. survivors (%)	4/7 (57)	2/8 (25)	0,31
25 weeks – no./total no. survivors (%)	10/19 (52)	20/31 (65)	0,46
26 weeks – no./total no. survivors (%)	17/25 (68)	25/39 (64)	0,78
Survival without major morbidity – no. /total no. (%)	34/75 (45)	47/109 (43)	0,78
24 weeks – no./total no. (%)	4/19 (21)	2/14 (14)	0,31
25 weeks – no./total no. (%)	10/27 (37)	20/45 (44)	0,46
26 weeks – no./total no. (%)	17/29 (59)	25/49 (51)	0,78
Intraventricular hemorrhage			
Absence of severe CNS bleeding* – no./total no. (%)	58/69 (84)‡	82/106 (77)§	0,37
Survival without severe CNS bleeding* – no./total no. survivors (%)	47/51 (92)	69/78 (88)	0,56
24 weeks – no./total no. survivors (%)	6/7 (86)	6/8 (75)	1
25 weeks – no./total no. survivors (%)	18/19 (95)	27/31 (87)	0,64
26 weeks – no./total no. survivors (%)	23/25 (92)	36/39 (92)	1
Survival without severe BPD at 36 gestational weeks ¥ – no./total no. survivors (%)	32/44 (73)†	64/80 (80)	0,43
24 weeks – no./total no. survivors (%)	4/6 (67)	4/7 (57)	1
25 weeks – no./total no. survivors (%)	11/15 (73)	26/31 (84)	0,45
26 weeks – no./total no. survivors (%)	17/23 (74)	34/42 (81)	0,57
Survival without laser treatment for retinopathy** – no./total no. survivors (%)	39/47# (83)	67/73# (92)	0,23
24 weeks – no./total no. survivors (%)	6/7 (86)	4/7 (57)	0,56
25 weeks – no./total no. survivors (%)	13/17 (76)	28/30 (93)	0,17
26 weeks – no./total no. survivors (%)	20/23 (87)	36/37 (97)	0,15

* Severe CNS bleeding considered as a stage ≥ 3 of Papile classification (6)
‡ CNS ultrasonography not performed for 6 patients (death before 24 hours)
§ CNS ultrasonogrphy not performed for 3 patients (death before 24 hours)
¥ Severe bronchopulmonary dysplasia (BPD) according to Jobe and Bancalari definition (7)
† Data missing for 7 patients transferred in another hospital before 36 gestational weeks
** Retinopathy classification according the international revisited classification (8)
# Data missing for 4 patients in the cohort 1 and 5 patients in the cohort 2

TABLE 4: Comparison to international literature figures.

	CUSL 2010-16	EPIPAGE 2 (4)
Mortality 23-26 weeks – no. deaths /total no. (%)	31/109 (28)	444/996 (45)
23 weeks – no. deaths /total no. (%)	1/1 (100)	88/89 (99)
24 weeks – no. deaths /total no. (%)	6/14 (43)	128/186 (69)
25 weeks – no. deaths /total no. (%)	14/46 (30)	126/308 (41)
26 weeks – no. deaths /total no. (%)	10/48 (21)	102/413 (25)

	CUSL 2010-16	EPICURE (13)
Survival without major morbidity 24-26 weeks – no. /total no. (%)	34/75 (45)	407/972 (42)
24 weeks – no./total no. (%)	4/19 (21)	52/178 (29)
25 weeks – no./total no. (%)	10/27 (37)	133/346 (38)
26 weeks – no./total no. (%)	17/29 (59)	222/448 (50)

	CUSL 2010-16	Australia 2005 (14)
Mortality 23-26 weeks – no. deaths /total no. (%)	31/109 (28)	71/178 (40)
23 weeks – no. deaths /total no. (%)	1/1 (100)	25/32 (78)
24 weeks – no. deaths /total no. (%)	6/14 (43)	21/43 (49)
25 weeks – no. deaths /total no. (%)	14/46 (30)	15/46 (33)
26 weeks – no. deaths /total no. (%)	10/48 (21)	10/57 (18)
Survival without major morbidity 23-26 weeks – no. /total no. (%)	31/76 (41)	225/492 (46)
23 weeks – no./total no. (%)	0/1 (0)	9/53 (17)
24 weeks – no./total no. (%)	4/19 (21)	30/96 (31)
25 weeks – no./total no. (%)	10/27 (37)	75/167 (45)
26 weeks – no./total no. (%)	17/29 (59)	111/176 (63)

	CUSL 2010-16	Japan 2003-05 (15)
Mortality 24-25 weeks – no./total no. (%)	20/60 (33)	139/737 (19)

	CUSL 2010-16	EXPRESS 2009 (16)
Mortality 23-26 weeks – no. deaths /total no. (%)	31/109 (28)	125/617 (20)
23 weeks – no. deaths /total no. (%)	1/1 (100)	28/81 (35)
24 weeks – no. deaths /total no. (%)	6/14 (43)	36/132 (27)
25 weeks – no. deaths /total no. (%)	14/46 (30)	33/200 (16)
26 weeks – no. deaths /total no. (%)	10/48 (21)	28/204 (14)
Survival without major morbidity 23-26 weeks – no. /total no. (%)	31/76 (41)	225/492 (46)
23 weeks – no./total no. (%)	0/1 (0)	9/53 (17)
24 weeks – no./total no. (%)	4/19 (21)	30/96 (31)
25 weeks – no./total no. (%)	10/27 (37)	75/167 (45)
26 weeks – no./total no. (%)	17/29 (59)	111/176 (63)

Comparison to be considered taking into account the limits due to the differences in size and characteristics of the populations studied

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Growth delay in infants: ensuring optimal care

Faltering growth in infants and young children under the age of two is a common concern in clinical practice. This condition is associated with various adverse health and developmental outcomes, highlighting the importance of implementing strategies to promote catch-up growth when indicated. However, some healthcare professionals may be reluctant to intervene optimally, often due to the misconception that addressing faltering growth could lead to excessive growth acceleration. Challenging these misconceptions and promoting an evidence-based approach are therefore essential to ensuring the healthy development of affected children.[1-4]

Faltering growth in infants is characterized by a slower-than-expected weight gain relative to age, sex, and current weight. According to the World Health Organization (WHO) criteria, it is defined as a decrease of ≥ 1.0 in the weight-for-age z-score. Experts recommend assessing such a decrease over a period of at least one month.. This definition excludes the first two weeks of life, during which physiological weight loss is expected.[2,3]

Standard management is typically focusing on nutritional support and behavioral guidance to enhance overall energy intake and ensuring an appropriate protein-to-energy ratio. Essential anthropometric measurements - including weight, length, and head circumference - are fundamental for tracking a child's growth trajectory. Screening tools such as STRONGkids, PYMS, STAMP, and iNEWS aid in the identification and assessment of children at risk.[4]

Faltering growth can have immediate consequences on a child's health and may indicate an underlying medical condition. It is therefore crucial for healthcare professionals to identify and appropriately manage growth concerns. Routine growth monitoring, along with parental or professional observations, plays a key role in early detection.[2]

Consequences of faltering growth: a socioeconomic perspective[1,2]

Faltering growth in early childhood can have significant and lasting consequences, both in hospital settings and beyond. In high-income countries, malnutrition in hospitalized children has been associated with increased risk of complications, longer hospital stays, and higher vulnerability to infections. Even when not linked to an underlying disease, growth faltering may negatively affect cognitive development and academic performance. Behavioral and communication difficulties are also more common in these children, including a higher prevalence of attention deficit disorders and hyperactivity. In the long term, faltering growth has been associated with a smaller adult stature and potential socioeconomic disadvantages.

Over time, the effects of early-life growth faltering can persist into adulthood. These include reduced physical work capacity, impaired educational attainment, and lower earning potential — ultimately contributing to a cycle of social disadvantage and diminished human capital. Without timely and adequate intervention, faltering growth can entrench health and economic inequalities across generations, particularly in contexts where access to healthcare and nutrition is limited.

Nutritional management of faltering growth: considerations for infants[1,2,5]

The nutritional management of faltering growth, whether associated with an underlying medical condition or not, requires a balanced intake of energy, proteins, and micronutrients to support optimal catch-up growth. According to WHO recommendations, an adequate protein-to-energy ratio, ranging from 8.9% to 11.5% of total energy intake, is advised to ensure effective and safe recovery without compromising metabolic balance.

Breastfeeding should be encouraged in all cases, ensuring that appropriate techniques are used to provide adequate intake. In specific cases where additional support is needed, fortification, cup feeding, or mixed feeding strategies may be considered.

For infants receiving formula, ready-to-use, high-energy and appropriate protein-energie ratio, medically specialized nutritional products with proven efficacy should be used whenever available. Locally available powdered formulas with appropriate nutritional composition can be utilized, following WHO hygiene guidelines for reconstitution.

The use of modular additives consisting solely of fats and carbohydrates should be avoided, as they increase energy intake without a corresponding increase in protein, thereby lowering the protein-to-energy ratio. This can lead to excess fat gain rather than balanced growth, which ideally consists of approximately 70% lean mass and 30% fat mass.

A structured catch-up growth plan should be integrated into the nutritional strategy, with progress monitored at an appropriate rate, as determined by healthcare professionals. The level of medical supervision and intervention should be tailored to the severity of the growth delay and the healthcare resources available.

Evolution of nutritional management of hospitalized children in Belgium: comparison 2014-2021[6,7]

In Belgium, the nutritional management of hospitalized children has evolved over the past decade, but certain challenges persist. A 2014 survey revealed that only half of pediatric departments conducted nutritional screening (39.5% Flemish speaking and 71.4% Walloon speaking). The main methods used were weight and height measurement (92.7%) and clinical assessment (74.7%), while more specific tools, such as mid-upper arm circumference measurement or skinfold thickness assessment, were rarely employed (19.7%). Furthermore, 60.5% of Flemish-speaking and 28.6% of French-speaking departments had no established protocol for managing malnutrition. The primary barriers to systematic screening were lack of training (46.9%), lack of awareness of nutritional screening tools (42.2%), and time constraints (29.7%).

By 2021, some progress had been made. A dietician was present in 80.3% of all responding units compared to 46.5% in the 2014 survey. However, systematic nutritional screening remains limited to 30.4% of Flemish-speaking and 40% of French-speaking centers, marking a decline from 2014 levels. In French-speaking centres, a positive screening result most often led to referral to a dietitian (86.7%), whereas in Flemish-speaking centers it more frequently resulted in a discussion with the paediatrician about nutritional management (54.3%) than referral to a dietician (34.8%). Post-discharge nutritional follow-up is still primarily handled by a physician with or without a dietician (95.1%) rather than a dietitian alone (3.3%).

Despite these advancements, barriers to nutritional management have remained largely unchanged since 2014. Time constraints (59%), lack of knowledge on the subject (47,5%) and lack of staffing (42,6%), continue to be major obstacles for conducting nutritional screening. Malnutrition treatment barriers included «no barriers» (50.8%), lack of knowledge (34.4%), lack of reimbursement (24.6%) and lack of time (24.6%).

While awareness, paramedical resources, and more systematic screening practices have improved since 2014, nutritional screening remains inconsistently implemented across Belgian pediatric hospitals, and overall, the barriers identified a decade ago persist.

Fast Facts - Infant Faltering Growth: discover the accredited online training for physicians and dietitians, available in English, French and Dutch

Given the persistent challenges in nutritional screening, continued professional education is crucial. More training and awareness are needed to improve the recognition, detection and treatment of malnutrition.

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- **Explain the consequences** of faltering growth on patients and their communities
- **Identify** faltering growth, accelerated growth, and catch-up growth using growth charts
- **Apply** evidence-based recommendations for the nutritional management of faltering growth

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Bridging the gaps: a call for action on faltering growth

Faltering growth in infants remains a widespread clinical concern with significant long-term consequences. Early identification and nutritional intervention are essential but remain inconsistently applied, particularly in hospital settings. While some progress has been made in Belgium over the past decade, persistent barriers such as lack of time, training, and resources continue to hinder systematic screening. Ongoing professional education and structured protocols are key to improving the quality of care and outcomes for affected children.

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The Belgian Pediatric Clinical Research Network (BPCRN): Pediatric Trial Facilitation During and Beyond Conect4children

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Keywords
Clinical trials ; network.

Abstract

Objective
The Belgian Pediatric Clinical Research Network (BPCRN) aims to promote pediatric clinical research by enhancing collaboration among stakeholders and facilitating high-quality trials. This manuscript outlines BPCRN's growth, its role in the Innovative Medicines Initiative 2 conect4children (c4c) project, and its contributions to pediatric drug development in Belgium.

Methods
Summary of BPCRN's activities since 2018, including its role in the c4c project. Data were collected from progress reports, internal databases, and interviews with investigators. The analysis highlights BPCRN's operational activities, trial facilitation, governance structure, and collaborations with international partners.

Results
BPCRN now includes 15 pediatric study sites across Belgium, utilizing a single-point-of-contact model for efficient communication. The network supported six commercial and non-commercial trials under the c4c project and facilitated over 20 additional studies through collaborations with global partners like I-ACT for Children. A new governance framework was introduced, including an Advisory Board and Steering Committee to guide future growth and sustainability.

Conclusion
BPCRN evolved to become a key contributor to pediatric clinical research in Belgium, overcoming barriers like recruitment difficulties and methodological challenges. The network's collaborative model and strategic governance will enable its continued expansion, ensuring that children have access to innovative and safe treatments. BPCRN's success positions Belgium as a leading hub for pediatric clinical trials and addresses the unmet needs of pediatric patients.

Introduction

Therapeutics prescribed for children must demonstrate both effectiveness and safety (1). To ensure this, medicines and medical devices must undergo rigorous evaluation through well-designed and properly conducted clinical trials that include participants from all relevant age groups (2). However, conducting clinical trials in a pediatric setting poses significant challenges for all stakeholders involved. These challenges include not only methodological complexities and ethical considerations, but especially recruitment difficulties, administrative burdens, and financial constraints (3,4).

A key strategy to address the persistent inequities in access to therapeutics for children is the promotion of collaboration and capacity-building and -sharing among pediatric study sites (4). Strengthening sites enhances the feasibility and success of clinical trials, thereby facilitating the timely development and delivery of innovative, evidence-based therapies to this vulnerable population. To support the development and maintenance of the high-quality standards essential for conducting pediatric clinical trials at a local level, (inter)national networks have been established (5,6). These networks have demonstrated significant benefits across various stakeholders, including patients, investigators, study sites, regulators, governments, and sponsors.

In Belgium, the Pediatric Clinical Research Network (BPCRN) was established in 2009 as a working group within the national pediatric society, the Belgische Vereniging voor Kindergeneeskunde-Société Belge de Pédiatrie (BVK-SBP), under the auspices of the late Prof. Dr. José Ramet (7). The primary goals were to map the pediatric research landscape in Belgium and to improve communication among key stakeholders. Since 2018, the BPCRN has been an active partner in the Innovative Medicines Initiative 2 conect4children (c4c) project, a collaborative project between academic and private sectors that includes 35 academic and 10 industry partners, as well as more than 50 third parties and around 500 affiliated partners (8). During c4c, BPCRN has evolved into a fully operational and collaborative research network, focusing on the high-quality and efficient execution of pediatric clinical trials in Belgium. This report outlines BPCRN activities since 2018 and provides an early outlook on the network beyond conect4children project funding.

Methods

This manuscript provides an overview of BPCRN activities and achievements since joining the conect4children project in 2018. It highlights the operational activities that have contributed to the network's capacity building and growth into its current structure. Data for this analysis was collected from progress reports and internal databases documenting clinical trials conducted during and beyond the conect4children project funding period. Additionally, qualitative insights were obtained through interviews with investigators from the coordinating centre and participating study sites.

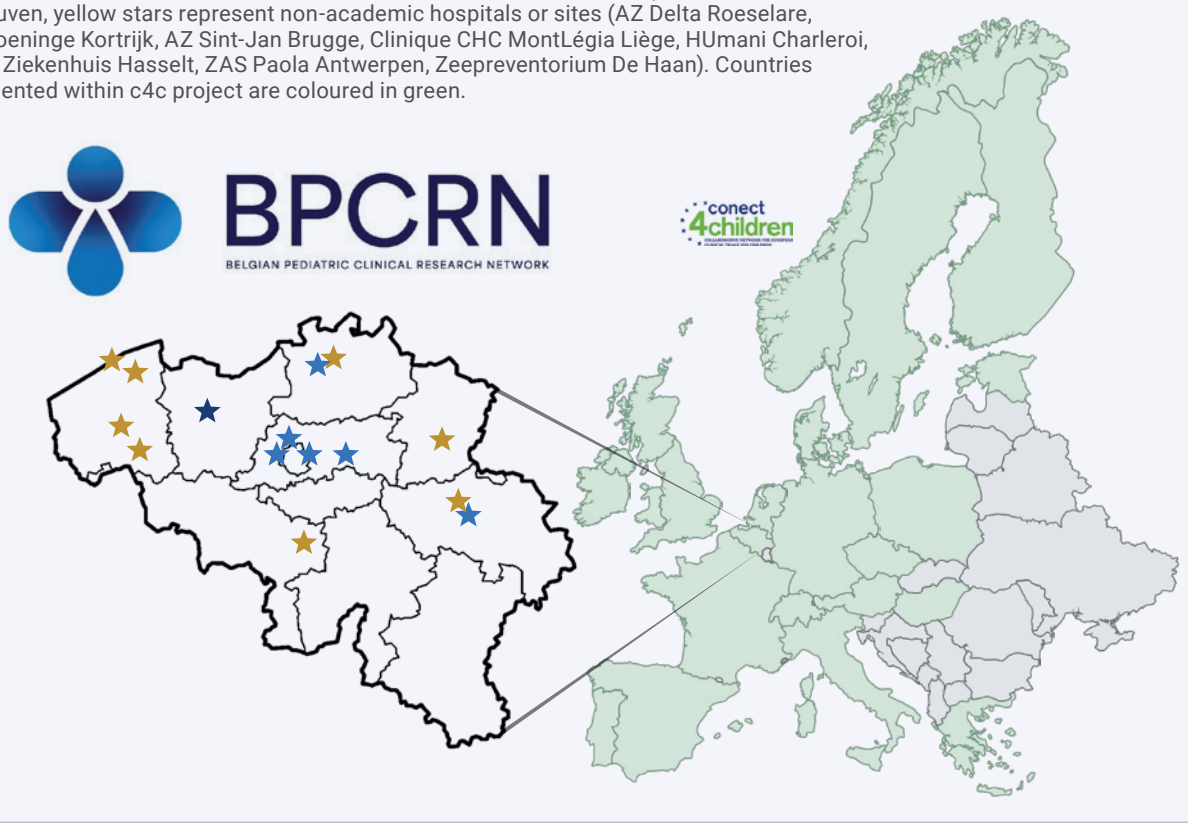
The historical context of the BPCRN, including its establishment in 2009 and activities prior to 2018, has been previously described (7).

Results

Status of the network

BPCRN comprises 15 pediatric study sites, including all seven Belgian university hospitals, seven large regional hospitals, and one pediatric rehabilitation center (Figure 1). The network is open to expanding its membership to other pediatric healthcare institutions interested in contributing to pediatric clinical research. These institutions may include academic and non-

FIGURE 1: The structure of the Belgian Paediatric Clinical Research Network (BPCRN), as developed during conect4children (c4c). Dark blue star represents the BPCRN headquarter (UZ Gent), light blue stars represent academic hospitals (CHU de Liège, Cliniques universitaires Saint-Luc, H.U.B.-HUDERF Bruxelles, UZ Antwerpen, UZ Brussel, UZ Leuven, yellow stars represent non-academic hospitals or sites (AZ Delta Roeselare, AZ Groeninge Kortrijk, AZ Sint-Jan Brugge, Clinique CHC MontLégia Liège, HUmani Charleroi, Jessa Ziekenhuis Hasselt, ZAS Paola Antwerpen, Zeepreventorium De Haan). Countries represented within c4c project are coloured in green.



academic hospitals, residential treatment centers, ambulatory clinics, and research facilities.

The national coordination of BPCRN activities is managed by an Operational Team based at Ghent University Hospital, which is in close contact with the network sites through a single point of contact (SPoC) model. To underscore its nationwide scope, BPCRN has been integrated into the scientific task force of the Belgian Academy of Paediatrics (BAoP)—the national umbrella organization for pediatrics that brings together the former BVK-SBP and regional medical associations with active scientific working groups, such as the Vlaamse Vereniging voor Kindergeneeskunde (VVK) and the Groupement Belge des Pédiatres de langue Française (GBPF). Through active involvement in international initiatives and collaborations with global partners, BPCRN has established itself as a key stakeholder internationally. Accordingly, in 2024, BPCRN achieved recognition as a Category 1 European Network of Paediatric Research by the European Medicines Agency (Enpr-EMA).

Clinical trial facilitation

During the conect4children (c4c) project (2018-2025), BPCRN actively supported site identification, feasibility assessment, start-up and conduct of two academic and four industry-sponsored trials by taking up the role and responsibilities of a national coordinator (Table 1). These trials included interventional studies sponsored by academic institutions targeting pediatric populations with Kawasaki disease and preterm neonates with patent ductus arteriosus, and commercial studies recruiting patients with multiple sclerosis, chronic kidney disease and ulcerative colitis. In total, nine different Belgian sites opened for recruitment for at least one of the studies.

The network's added value was evident through its proactive communication with sponsors and study sites, facilitating site identification and streamlining feasibility assessments. BPCRN's trial support included strategies to boost recruitment, streamline trial-team coordination, pre-fill site feasibility questionnaires, and to provide guidance during the submission process. For academic trials, central and local ethical committee submissions in Belgium were executed by BPCRN. These submission packages were based on essential documents from the international sponsor and were supplemented with local documents and translations, fully supported by BPCRN. These trial support efforts relieved workload from BPCRN sites, enhanced trial efficiency, and improved feasibility outcomes.

Beyond its involvement in clinical trials under the c4c project, BPCRN established collaborations with the United States-based Institute For Advanced Clinical Trials (I-ACT) for Children, enabling further capacity building and alignment with global pediatric research efforts (9). Through collaboration with I-ACT for Children and independent direct contact with sponsors, BPCRN performed facilitation surveys for over 20 other pediatric clinical trials.

BPCRN aims to broaden its role beyond patient recruitment by providing methodological input, reviewing trial protocols, and coordinating feasibility assessments through clinical experts. While these contributions are valuable across all phases of clinical research, BPCRN particularly strives to engage with sponsors early in the trial lifecycle. In addition, the network is exploring harmonized approaches to site budgeting and contract templates, actively gathering input from both sites and sponsors to align expectations and streamline processes, with the goal of reducing start-up timelines.

Communication within and outside the network

To enhance communication and operational efficiency, BPCRN employs a single point of contact (SPoC) model for academic, industrial, and hospital stakeholders. Site-level SPoCs consist out of (at minimum) a physician and a study coordinator. They are responsible for facilitating efficient handling of requests within their respective hospital team members or departments, ensuring reliable and timely deliverables, and providing consistent bilateral feedback to the Operational Team.

To strengthen the network, roadshow meetings were conducted in 2023 and 2024. In-person visits to the sites allowed for an in-depth assessment of network involvement, trial progress follow-up, and evaluation of site-specific needs. These equally allowed for an in-depth exploration of one of the network's key strengths, namely its multidisciplinary engagement, including the involvement of the principal investigator, research coordinator, data manager, and sub-SPoCs.

In the coming years, the Operational Team plans regular visits to existing network sites and introducing new sites involved in pediatric clinical research activities that are interested in joining the network.

In addition to gathering input from the sites, BPCRN aimed to learn from similar networks in other countries. Knowledge, skills and connections of the BPCRN have significantly increased by actively participating in meetings of the National Network of Networks (hosted by c4c) and by seeking support from networks represented in Enpr-EMA. To reflect upon common challenges, BPCRN representatives engaged in close communication with similar national networks such as PedMed-NL (the Netherlands), PEDSTART (France), DanPedMed (Denmark) and NorPedMed (Norway).

Supporting activities

Besides establishing and maintaining the network and facilitating clinical trials in itself, BPCRN has been able to develop various activities that have added value to conducting high-quality and meaningful research.

One of the key priorities for BPCRN has been the explicit integration of **experts** within the network to stimulate broader participation. Expert involvement remains critical, which is why this aspect will be further emphasized to encourage engagement from relevant professionals. The growing database of national experts is consultable for academic and commercial stakeholders and accessible through the BPCRN.

Another essential initiative has been the development of a **clinician-scientist platform**. This platform serves to bridge clinical practice and academic research by creating structured opportunities for shared learning, joint project development, and methodological support. As recently highlighted(10), structured clinician-scientist programs are essential to sustain translational research capacity across Europe. These programs aim to train and retain talented medical doctors by offering protected research time, strong mentorship, and clear career pathways at the interface of care and science. In addition to scientific and clinical training, they provide institutional support for long-term career development, promote interdisciplinary collaboration, and actively involve patients in the research process. BPCRN and its Dutch counterpart, PedMed-NL were among the key instigators of this initiative.

This platform serves to bridge clinical practice and academic research by creating structured opportunities for shared learning, joint project development, and methodological support. As recently highlighted in *Nature Medicine*, structured clinician-scientist programs are essential to foster sustainable careers at the intersection of care and research. These programs typically include protected research time, mentorship, dedicated infrastructure, and access to interdisciplinary collaboration, allowing clinicians to address unmet medical needs with clinically

informed research questions. BPCRN and its Dutch counterpart, PedMed-NL, were among the initiators of such an initiative within the conect4children project.

In addition, BPCRN has prioritized **patient engagement**, collaborating closely with the European Young Person's Advisory Group Network (eYPAGnet), and set up a pilot project to involve young patients in shaping research priorities, study design, and clinical trial training programs. These efforts led to the initiation of a Pediatric Nephrology Youth Advisory Council on Clinical Trials and Training which has provided valuable insights to further develop a broader and more inclusive advisory group for children (link).

Approximately 75% of **rare diseases** manifest in childhood. BPCRN has actively contributed to research exchange initiatives aimed at aligning European Reference Networks (ERNs) with c4c (11). Given that many Belgian sites demonstrate a high level of ERN participation—some achieving the highest average site involvement in Europe—this represents a significant area of contribution and ongoing efforts for BPCRN.

conect4children beyond Innovative Medicines Initiative (IMI)-funding

During the conect4children (c4c) project, BPCRN contributed to key work packages on trial execution (WP2, WP7), sustainable network models (WP3), and data standardization (WP5). As the project concludes in May 2025, BPCRN remains actively involved in advancing data integration, supporting expert panels, providing training for study teams, and coordinating the Young Investigator Community (YIC).

Following the completion of the grant, the c4c project transitioned into a nonprofit organization, c4c Stichting, administratively headquartered in the Netherlands. BPCRN played a pivotal role in providing insights from a national network perspective to support the development of this sustainable model, formally established in May 2024.

As of 2024, BPCRN continues to serve as an active member of c4c Stichting, contributing to clinical trial facilitation and expert consultations. The shared mission of both c4c Stichting and BPCRN is the advancement of better medicines for children. From a national perspective, this involves conducting the maximum number of relevant clinical trials across a well-curated selection of Belgian sites to ensure innovative treatments are accessible to the pediatric population.

While many activities during the c4c project were primarily focused on clinical drug development, BPCRN is currently exploring how, through the involvement of the same key stakeholders—along with an expansion to university and other research partners—it can also provide support for preclinical and translational research in children, including initiatives under the umbrella of the European Paediatric Translational Research Infrastructure (EPTRI). The engagement of multiple sites and their established networks represents a logical extension of the EPTRI consortium and is expected to positively impact the development of meaningful pediatric research, whether related to medicines or other health interventions.

As part of the continued maturation of the network, BPCRN is exploring connections with established European research infrastructures such as the European Clinical Research Infrastructure Network (ECRIN), with the aim of strengthening its international collaboration capacity and avoiding duplication of efforts. In this context, BPCRN's expertise and site-level capacity could also contribute to initiatives focused on making network data available for the establishment of international disease registries supporting registry-based randomized clinical trials (such as the Trials Within Cohorts [TWICs] approach), or the coordinated conduct of pediatric vaccine studies—both in healthy and immunocompromised children (e.g., through platforms such as Vaccelerate). These are high-priority areas of unmet medical need, particularly within pediatric and rare disease research, and BPCRN could serve as a valuable partner in setting up such initiatives in close collaboration with its existing stakeholders. Engaging with these European infrastructures offers an opportunity to further position the Belgian network within the broader European clinical research landscape and to contribute meaningfully to the coordination of national and cross-border pediatric trials.

BPCRN beyond conect4children

To support future collaboration and strategic growth, BPCRN proposed a new governance structure in 2024, formally introduced during a kick-off meeting held in Ghent at September 6, 2024. This restructuring led to the establishment of the BPCRN Advisory Board, comprising representatives from all network sites and relevant national stakeholders.

The Advisory Board includes voting members responsible for guiding the network's overall direction. These members represent study sites (SPoCs and heads of pediatric departments), the national pediatric organization BAoP, as well as patient advocacy groups like RaDiOrg. Non-voting members provide expert advice based on their involvement in the pediatric clinical trial ecosystem in Belgium. These include representatives from regulatory bodies (Federal Agency for Medicines and Health Products (FAGG/AFMPS)), industry associations (pharma.be, BeCRO), and pediatric associations.

The Advisory Board also endorsed the formation of a Steering Committee, comprising volunteer experts from network sites. The primary role of the Steering Committee is to oversee the activities of the Operational Team and ensure alignment with the strategic objectives of the BPCRN. This governance framework aims to foster robust collaboration, accountability, and effective management within the network.

Under the guidance of the Advisory Board, the BPCRN Steering Committee is actively pursuing both research and networking opportunities to advance the network's mission. The Steering Committee developed a BPCRN Roadmap, which outlines the network's strategic direction, including the definition of its mission and vision. This roadmap also established key principles and provided the foundational steps necessary to ensure the long-term financial sustainability of the BPCRN.

In addition to its focus on academic initiatives, BPCRN is engaging with commercial stakeholders, including (but not limited to) contract research organizations (CROs) and pharmaceutical companies. These discussions aim to identify existing gaps within the pediatric clinical trial landscape that BPCRN could address, as well as to explore potential collaborative partnerships to drive innovation, including devices, medical technologies, and diagnostics, and enhance the impact of pediatric clinical research.

Discussion and conclusion

This manuscript provides a comprehensive overview of the BPCRN, highlighting its evolution during its involvement in the c4c project and beyond. Since its participation in c4c, BPCRN has substantially enhanced its capacity to conduct pediatric clinical trials (7,9,12), thereby contributing to the broader pediatric research landscape and improving access to novel therapies and new technologies for children in Belgium.

The need for more pediatric medicines has prompted the implementation of necessary international legislation over the years. Notably, the European Union (EU) introduced the

Pediatric Regulation in 2007, aiming to promote the development and authorization of pediatric medicines (13). The regulation established the Paediatric Committee (PDCO), which determines the requirement for pediatric studies under pediatric investigation plans (PIPs) and provides incentives to support their execution. The European Commission's ten-year review of the regulation highlighted an increase in the availability of pediatric medicines; however, progress has been limited in certain areas, particularly for rare diseases and conditions that primarily affect children (14–16). Despite these efforts, up to 50% of pediatric clinical trials do not achieve successful completion, highlighting the enduring challenges within the field of pediatric research (17–20). Moreover, several of these initiatives at the European level may be at risk due to upcoming regulatory changes. It is evident that emerging European regulations will further shape the current landscape, underscoring the importance of having stable national actors to ensure the continuity of clinical studies in Belgium.

BPCRN's collaborative approach has significantly contributed to overcoming barriers to pediatric clinical trials. By supporting site identification, streamlining site initiation processes, enhancing recruitment strategies, and improving coordination among study sites, BPCRN has demonstrated the advantages of national networks in addressing key challenges in pediatric research. Moreover, BPCRN's efforts in data standardization, integration of real-world data, and building of an expert network database have strengthened the quality and efficiency of pediatric clinical trials, ensuring consistency across studies and facilitating data sharing among stakeholders. A concrete outcome of these efforts is the availability of a specific CDISC Pediatric User Guide (21), which is now online and ready for use. Additionally, BPCRN has established a broad network of experts who can be consulted for pediatric clinical and trial-associated inquiries, further supporting the development and execution of high-quality pediatric research.

Through its national SPoC structure and regular operational contacts, BPCRN collaborates closely with clinical trial units embedded in university hospitals and regional centers, promoting harmonization of processes and fostering knowledge exchange. From the perspective of participating sites, the national expert network coordinated by BPCRN is available for consultation, enabling access to targeted clinical and methodological expertise. Other potential benefits for sites include streamlined feasibility procedures, support in ethics and regulatory submissions, opportunities for training and capacity building, as well as increased visibility for national and international study opportunities.

The success of BPCRN can largely be attributed to its robust partnerships with academic institutions, medical associations, industry, and regulatory bodies. A key development in this regard has been the establishment of a governance framework, which includes an Advisory Board and a Steering Committee. This structure has enabled BPCRN to align its objectives with the network's long-term strategy, ensuring transparency, accountability, and effective decision-making. The BPCRN Roadmap, developed by the Steering Committee, outlines strategic priorities, including securing sustainable funding and fostering relationships with commercial partners to ensure continued growth and innovation. These novel developments were presented and approved by the Advisory Board at the BPCRN kick-off meeting in Ghent at Sept 6th, 2024.

Despite these accomplishments, several challenges remain. Recruitment, particularly for rare diseases, continues to be a major obstacle, as do methodological complexities, such as the design of age-appropriate studies and adherence to ethical guidelines (4). Cross-disciplinary collaboration is essential, not only between centers but also among EU-recognized ERN units within Belgium and across broader EU infrastructures, such as ERDERA. While rare diseases affect both pediatric and adult populations, Belgium currently lacks a dedicated BPCRN counterpart for adult patients, representing a critical unmet need. Additionally, a major emerging challenge in clinical trials is the increasing regulatory requirements set by the European Medicines Agency (EMA) for medical devices in children. Addressing these regulatory demands will be crucial to ensuring continued innovation and accessibility of pediatric medical technologies.

Addressing these challenges requires ongoing optimization of clinical trial planning, recruitment strategies, involving patients and public, and site coordination. Additionally, financial constraints remain a significant barrier to expanding the network and ensuring the sustainability of pediatric clinical trials. As such, continued collaboration with industry and securing both public and private funding will be crucial for the network's long-term viability. Clear agreements with private partners and internal stakeholders are essential to ensure that industry funding never compromises the integrity of the network—a principle that will ultimately benefit all parties in the long run.

The future success of BPCRN will depend on its ability to expand both local and international collaborations. Strengthening these partnerships, alongside efforts to secure long-term financial support, will be critical to sustaining the network's growth. As BPCRN continues to evolve, its role in advancing pediatric drug development and improving access to novel treatments for children in Belgium and beyond will remain indispensable.

Conclusion

BPCRN's progress in conducting pediatric clinical trials and its commitment to collaboration have significantly advanced pediatric clinical research in Belgium. While challenges persist, BPCRN's robust governance model, strategic partnerships, and ongoing capacity-building efforts will aid to firmly establish Belgium as a leading hub for pediatric clinical trials. In doing so, BPCRN will help address the unmet needs of pediatric patients by enhancing access to safe and effective therapies for children.

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Posterior Urethral Valves: The Spectrum of Radiological and Clinical Presentations

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Keywords

Urethral obstruction ; prenatal diagnosis ; ultrasonography ; renal failure.

Abstract

Objective

Posterior urethral valves (PUV) are the most common cause of congenital lower urinary tract obstruction (LUTO) and kidney failure with renal replacement (KFRT) in boys. They are suspected on prenatal ultrasound (US) showing bilateral ureterohydronephrosis, megabladder and posterior urethral dilatation. PUV presents with variable clinical severity and radiologic appearance. This study aims to review PUV cases in our center, describe imaging aspects, and assess renal and bladder outcomes of prenatally and postnatally diagnosed cases.

Methods

We reviewed the medical records of all boys who underwent PUV ablation at HUDERF between 2006 and 2021. We recorded prenatal and perioperative US, age and symptoms at diagnosis, cystourethrogram, outcome of renal and bladder function. Prenatal and postnatal diagnosed patients were compared.

Results

We include 50 boys treated for PUV with available antenatal data. Thirty-one patients (62%) had abnormal fetal screening: 90% had the classic antenatal presentation of PUV: bilateral ureterohydronephrosis and megabladder. Three patients had an unusual fetal presentation with unilateral (uretero)hydronephrosis. Nineteen (38%) were diagnosed postnatally with a median age of 9 months. The most common postnatal clinical presentations were urinary tract infection (84%) and voiding disorders (11%). 34% of patients, with similar proportions between antenatally and postnatally diagnosed, reached CKD grade 2-4; 6% progressed to KFRT, all prenatally diagnosed.

Conclusion

This study demonstrates an improvement in fetal screening for PUV. Most fetuses had the classic antenatal presentation, but 10% had unilateral dilatation without signs of LUTO. Children diagnosed antenatally had the worst prognosis in terms of renal and bladder function.

Introduction

Posterior urethral valves (PUV) are tissue leaflets fanning distally from the prostatic urethra to the external urethral sphincter. This pathology is the most common cause of congenital lower urinary tract obstruction (LUTO) affecting 1 in 4,000 male births and it is the leading cause of kidney failure with renal replacement (KFRT) in boys (1-3).

PUV are commonly suspected on prenatal ultrasound (US) revealing bilateral hydroureteronephrosis, bladder wall thickening and proximal urethral dilatation taking the aspect of a keyhole (4, 5). In severe cases, PUV cause a complete bladder obstruction, with oligohydramnios and renal dysplasia (6).

At birth, the elective radiological exam to perform is the voiding cystourethrogram (VCUG), and the diagnosis is confirmed by the presence of proximal urethral dilatation with often a trabeculated bladder and bilateral vesicoureteral reflux (VUR) (4).

PUV may however present with a broad clinical and radiological spectrum with variable severity ranging from early renal failure to late mild picture such as minor lower urinary tract symptoms and recurrent urinary tract infection (UTI).

The aim of this study is to review the PUV cases that occurred in Queen Fabiola Children Hospital, Brussels, in the last 15 years and describe the imaging aspects including uncommon and challenging presentations. The secondary aim is to assess and compare the renal and bladder outcome of children prenatally and postnatally diagnosed of PUV.

Materials and methods

In this descriptive retrospective observational study, we reviewed the medical records of all male patients under 16 years of age who underwent PUV ablation at the Queen Fabiola Children Hospital, Brussels, between January 2006 and March 2021. The following

data were extracted: prenatal US findings, age and symptoms at postnatal diagnosis and preoperative imaging (US and VCUG).

After birth, diagnosis of PUV was based on the VCUG images and reflux, if present, was graded according to the International Reflux Study Committee classification (7). We recorded the age, height and serum creatinine level of the patients 5 years after PUV ablation and at the last follow-up. Renal function was estimated by calculating the glomerular filtration rate (GFR) in ml/min/1.73 m² using the Schwartz formula (8). Renal function was classified according to the KDIGO guideline stages of chronic kidney disease (CKD) (9). KFRT was defined as a stage 5 of CKD (GFR < 15 ml/min/1.73 m²) requiring dialysis or renal transplantation. Renal function 5 years after PUV ablation and at the last follow-up was compared between prenatally and postnatally diagnosed cases. In all children older than 5 years of age, supposedly already fully toilet trained, the presence of voiding disorders (urinary incontinence and urgency, poor urinary stream, or the need of clean intermittent catheterization) was recorded. Categorical variables were compared using chi-square test. A p-value <0.05 was considered statistically significant. The study protocol was reviewed and approved by the Ethics Committee of our institution (reference CEH 30/20).

TABLE 1: Children (Group 1) with abnormal imaging findings at antenatal US screening (N=31).

	No. (%)
Classical presentation	**28 (90%)**
Bilateral ureterohydronephrosis and megabladder	24
Unilateral ureterohydronephrosis, megabladder and keyhole sign	2
Isolated ruptured megabladder with urinary ascites	2
Uncommon presentation	**3 (10%)**
Unilateral hydronephrosis	2
Unilateral ureterohydronephrosis	1

Results

A total of 57 patients with PUV were diagnosed and surgically treated at the pediatric uro-nephrology department of our tertiary center between January 2006 and March 2021. Antenatal data were available for 50 patients (88%), seven patients (12%) with missing data have been excluded from the analysis. The included patients were classified according to their antenatal US findings. Group 1 included 31 patients (62%) with abnormal fetal urinary tract US (Table 1). Group 2 included 19 patients (38%) who had a normal antenatal screening.

Patients with abnormal antenatal screening (Group 1, n=31)

Classical PUV antenatal imaging

28/31 (90%) patients had a classical PUV antenatal imaging (Table 1). Most of them showed a bilateral hydroureteronephrosis associated with a megabladder. Two patients had a major unilateral hydroureteronephrosis with a large bladder and a dilated urethra taking the appearance of a keyhole sign. Two patients presented with a ruptured bladder and urinary ascites. The first patient showed an isolated megabladder at the US of 23 weeks of gestational age. A week later ascites developed secondary to a urinary leakage from the bladder. There was no hydroureteronephrosis, renal dysplasia nor oligohydramnios. A fetal MRI confirmed the US images and showed a megabladder with posterior urethral dilatation appearing as a keyhole sign as well as a large amount of urinary ascites (Figure 1). After birth VCUG confirmed the presence of PUV with bilateral high-grade VUR. The renal function progressed favorably with a plasma creatinine of 0.89 mg/dL at 17 years of age. The second patient showed at the 22nd week of gestational age a severe bilateral hydroureteronephrosis, oligohydramnios and urinary ascites, and at the fetal MRI pulmonary compression by diaphragmatic dome inversion secondary to significant ascites. At birth, the US confirmed the severe bilateral hydroureteronephrosis with renal cortical hyperechogenicity and megabladder, and the VCUG revealed the presence of a stricture in the posterior urethra without VUR (Figure 2). Surprisingly, the patient showed a favorable outcome in terms of both respiratory and renal function with plasma creatinine of 0.73 mg/dL at 13 years of age. Both patients with antenatal urinary ascites progressed favorably also in terms of bladder function and became fully toilet trained before the age of 5 without any medication.

Uncommon PUV antenatal imaging

Three patients (10%) did not present antenatally as a classical PUV (Table 1). One had a unilateral hydroureteronephrosis and two patients presented a unilateral isolated pelvis dilatation.

FIGURE 1: Sagittal fetal magnetic resonance imaging scan. Urethral valve with mega-bladder, keyhole sign and urinary ascites.

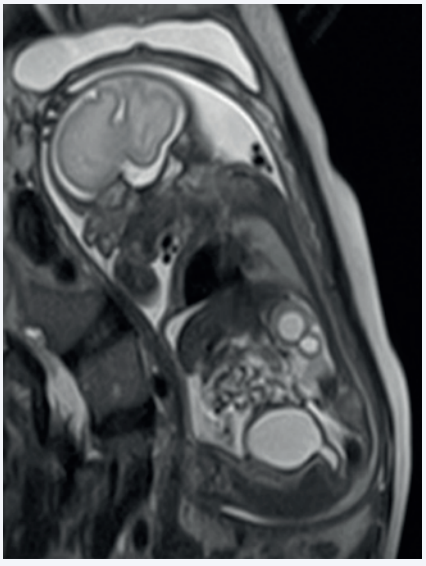
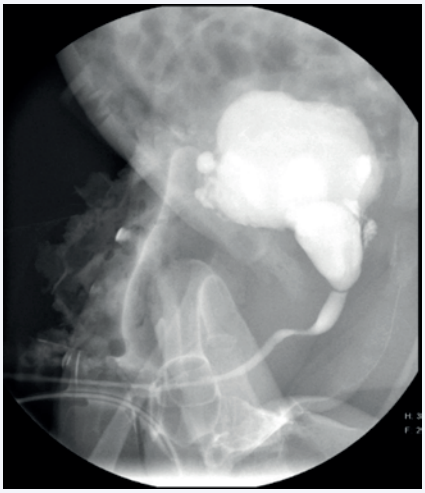


FIGURE 2: Voiding cystourethrogram showing dilatation of the posterior urethra associated with posterior urethral valves, trabeculated bladder and no vesicoureteral reflux.



In the three cases, VCUG after birth surprisingly revealed a PUV. One of these infants rapidly developed a particularly severe clinical outcome with a progressive abdominal distention within the first 10 days of life. US showed a large amount of ascites, left unilateral hydroureteronephrosis and perirenal urinoma. VCUG revealed a dilated posterior urethra, a large trabeculated bladder, high-grade VUR on the left side with peritoneal extravasation of contrast medium.

Patients with normal antenatal screening (Group 2, n=19)

Nineteen patients (38%) had a normal antenatal US. They were diagnosed of PUV during the imaging work-up of urinary tract infection (UTI) in 16 patients (84%) and voiding disorders in 2 patients (11%). One patient was fortuitously discovered during prematurity imaging investigations. Median age at diagnosis was 9 months (IQ range: 3 months to 6 years). Preoperative urinary tract US were normal in 6 children (32%), while different grades of hydronephrosis were found for the remaining 13 patients (68%). The diagnosis of PUV was confirmed by VCUG in all patients and VUR detected in 9 cases (47%).

Long term renal and bladder function

Renal function at last follow-up is reported in Table 2. Median follow-up was 8 years (IQ range 3 to 13 years). A total of 29 patients (58%) had a normal renal function, with the same proportion in Group 1 and 2 (p-value 1). A total of six patients (12%) reached a GFR < 60 ml/min/1.73m², and three children progressed to KFRT, all from Group 1 (p-value 0.07).

The presence of voiding disorders (such as urinary incontinence and/or urgency, poor urinary stream or the need of clean intermittent catheterization), was found in 19 patients (61%) out of the 31 children investigated whom this information was available (20 from Group 1, 11 from Group 2).

In Group 1, 14/20 (64%) children had a voiding disorder: 10 urinary incontinence, 2 poor urinary stream and 2 intermittent catheterization.

In Group 2, 5/11 (45%) children presented a voiding disorder such as urinary incontinence and/or urgency.

Although children in Group 1 tend to have more frequently a voiding disorder as compared to children in Group 2, the difference is not statistically significant.

TABLE 2: Renal function at last follow-up.

1999-2003	Total (n=50)	Group 1 (n=31)	Group 2 (n=19)	p-value
Normal renal function	29 (58%)	18 (58%)	11 (58%)	1
CKD grade 2	15 (30%)	7 (23%)	8 (42%)	0.2
CKD grade 3	2 (4%)	2 (6%)	0	0.07
CKD grade 4	1 (3%)	1 (3%)	0	
RRT	3 (6%)	3 (10%)	0	
Follow-up, median (IQ range)	8 years (3 to 13)	8 years (4 to 13)	8.5 years (3 to 12)	

CKD = chronic kidney disease; GFR = glomerular filtration rate; RRT = renal replacement therapy; £CKD grade 2 (GFR < 90 ml/min/1.73m²); CKD grade 3 (GFR < 60 ml/min/1.73m²); CKD grade 4 (GFR < 30 ml/min/1.73m²).

Discussion

PUV represent the most common cause of congenital lower urinary tract obstruction in boys (1, 2). This pathology constitutes a clinical spectrum ranging from early presentation with severe renal dysplasia to late diagnosis due to mild lower urinary tract symptoms and recurrent UTI (3, 4) .

PUV are commonly suspected on routine prenatal screening US. The classical findings are bilateral hydroureteronephrosis, with enlarged bladder and, occasionally, a dilated posterior urethra taking the aspect of a keyhole (4-6). The prognosis is often relatively easy to predict in severe cases, such as antenatal presentation before 24 weeks, with oligohydramnios and increased cortical echogenicity (10). In those situations perinatal death often occurs secondary to pulmonary hypoplasia and renal failure (6). In partial obstruction, the outcome is less predictable. Fetal urinary electrolytes and β-2 microglobulin are the most used biological markers to predict post-natal renal function. Raised urinary osmolality and a β-2 microglobulin greater than 4 mg/L suggest the worst case scenario (11). The ongoing European ANTENATAL study has been designed to validate fetal urine biochemistry such as proteomics and metabolomics in order to predict postnatal renal function in fetuses with PUV (12). The results of this large multi-centric study are pending.

In developed countries, approximately one-third to one-half of PUV cases are identified by antenatal US (1, 2). A 2014 prospective national cohort study in the UK reported that about one third of PUV cases were diagnosed antenatally, and two third afterwards. Although it was expected that antenatal diagnosis would increase over time, the authors observed that the proportions remained mostly unchanged in the last 30 years (1). In our cohort more than 60% of PUV patients were diagnosed in utero. This better figure of antenatal diagnosis rate is potentially explained by the fact that in Belgium pregnancies are followed with minimum 3 antenatal US.

While the classic antenatal presentation of PUV is bilateral hydroureteronephrosis with enlarged bladder, the proportion of patients showing different images is far less described.

In our cohort, unsurprisingly 90% of antenatally diagnosed cases presented classically.

Noteworthy, two of them presented with bladder rupture and extravasation of urine resulting in urinary ascites. This phenomenon due to the high pressure in the urinary tract has been reported in about 15% of neonates with PUV and is considered a protective pop-off mechanism (13-15). Although we report only two patients, in line with the literature, they both progressed satisfactorily in terms of renal and bladder function after more than 12 years of follow-up.

Moreover, our study shows that 10% of patients had an uncommon antenatal presentation. They were not suspected of PUV as they presented with a unilateral upper urinary tract dilatation without any other signs of LUTO. One of them rapidly developed a major complication soon after birth and before the programmed postnatal US scan.

In our tertiary care center, PUV patients with normal fetal scans represent nearly 40% of the cases. This figure is in accordance with an Australian report (2). However, although UTI was the leading

presentation for 80% of our patients postnatally diagnosed, it only represented 50% in the Australian cohort.

Delayed PUV cases usually present less severe obstructions with minimal impact on the urinary tract and may therefore remain silent for years (3). Brownlee et al. demonstrated that cases diagnosed postnatally have smaller hydronephrosis and less renal dysplasia when compared to antenatally diagnosed obstructions (1).

The median follow-up in our cohort is 8 years. In accordance with a North-American study with a similar median follow-up, the number of patients with normal renal function and very mild CKD, were not significantly different between the antenatally and postnatally diagnosed groups (16). However, when we look at the most severe CKD, the figures are different. In the first group, almost 20% of children reached a GFR < 60 ml/min/1.73m², and 10% progressed to KFRT. During the same follow-up period, none from the postnatally diagnosed group reached a CKD grade 3. Our data are consistent with the literature which shows that about 20% of patients with PUV reach KFRT sometimes even decades after the initial presentations (3). According to Engel et al, patients with later diagnosis progress to KFRT in 10% of cases (17).

In literature, the incidence of bladder dysfunction in PUV patients varies widely, from 13% to 38% and may be suspected in cases of recurrent UTI and/ or voiding dysfunction (4). Infants with valve bladders have detrusor hypertrophy. This will cause poor bladder compliance and detrusor overactivity, reducing functional bladder capacity and causing incontinence. In the more favorable scenario, bladder capacity increases with age and overactivity disappears (18).

In the least favorable scenario, secondary bladder outlet obstruction due to bladder neck hypertrophy will lead to elevated residual bladder volumes and increased storage pressures. This will ultimately lead to myogenic failure (19).

In our cohort, more than 60% of children older than 5 years of age, whom this information was available, presented voiding disorders, slightly more in those diagnosed antenatally. This could be explained by the fact that children diagnosed postnatally have less severe obstructions with minimal impact on the urinary tract.

Conclusions

With 60% of PUV cases diagnosed antenatally, this study shows an improvement in fetal screening for this condition. Although most of those fetuses showed the classic antenatal presentation, 10% presented a unilateral dilatation without any sign of LUTO. While the number of patients with normal renal function and mild CKD did not differ between the antenatally and postnatally diagnosed groups, one fifth of the children in the first group achieved a GFR < 60 ml/min/1.73m² with ten percent of them needing renal replacement therapy. During the same follow-up period, none from the postnatally diagnosed group reached a CKD grade 3. Children diagnosed antenatally showed the most severe prognosis in terms of both renal and bladder function.

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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Acute Motor Axonal Neuropathy with Bulbar Symptoms- Case report

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Keywords
Acute severe motor axonal neuropathy ; Guillain-Barré syndrome ; Paralysis- Bulbar- Pediatric.

Abstract
Acute motor axonal neuropathy (AMAN), a rare variant of Guillain-Barré Syndrome (GBS) presents with rapid paralysis. A 14-year-old boy exhibited bulbar symptoms alongside limb weakness. Clinical examination revealed positive Gowers's sign and inability to walk on toes. Sensory function was normal, with intact reflexes and sphincter control. Investigations including cerebrospinal fluid, viral serology, and magnetic resonance imaging of the brain and spinal cord yielded no abnormalities. Electromyography confirmed motor axonal polyneuropathy. Treatment with intravenous immunoglobulin led to symptom regression within two weeks. AMAN, lacking sensory involvement, often follows a severe course, necessitating consideration of IVIg due to hyperreactive humoral response.

Introduction

Acute motor axonal neuropathy (AMAN) is classified among the axonal variants of Guillain-Barré syndrome (GBS) (1-3). GBS typically manifests as a rapidly progressive ascending paralysis of the lower extremities resulting in a tetraplegia and is characterized by an albumin-cytological dissociation in the cerebrospinal fluid (1, 3, 4). Clinically it is subdivided into motor, sensory, sensorimotor, autonomic involvement and Miller Fisher syndrome (4, 5). Neurophysiological study can define different GBS variants, such as an acute motor axonal neuropathy (AMAN), an acute motor sensory axonal neuropathy (AMSAN) and acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (4). AMAN is the pure motor variant without sensory or autonomic nerve involvement.

The etiopathogenesis of AMAN remains unclear. Autoimmune mechanisms leading to axonal degeneration are taught to be involved (1, 5). *Campylobacter jejuni* infection may precede muscle weakness but is only observed in a third of cases (6). Molecular mimicry is widely accepted in explaining the pathogenesis of axonal degeneration in Guillain-Barré syndrome (3). The best-known example of this mechanism is *C. jejuni*. Ganglioside-like epitopes on the lipopolysaccharide (LPS) and the lipo-oligosaccharide (LOS) of this bacteria are recognized by the innate immune system. Antigen presenting cells recognize these epitopes and activate B cell and T helper cell proliferation. B cells develop into plasma cells and produce anti-ganglioside antibodies. These antibodies attack the invader but also destroy sodium channels at the nodes of Ranvier (3, 4, 6). As anti-ganglioside IgM and IgG can be detected in patients with AMAN, this suggests the condition is an autoimmune disease of the peripheral nervous system (3). In AMAN, anti-GM1b and anti-GD1a antibodies are directed against GM1-like and GD1a-like LOS of *C. jejuni*. Electrophysiological studies reveal a reversible conduction block, reversible conduction failure (RCF) or decreased compound muscle action potential (CMAP) amplitudes with normal sensory conduction. These abnormalities become apparent mainly 3-6 weeks after the acute phase and can differentiate AIDP from AMAN. Today, there is no consensus on the electrophysiological criteria. Intravenous immunoglobulin IVIG and plasma exchange are the most commonly used therapies. IVIG inhibits macrophage activation and prevents antibody and complement binding. 1 out of 4 AMAN patients have a rapid recovery after IVIG therapy, in the paediatric population the results are more favourable (3).

Case report

A 14-year-old boy was admitted to the emergency room with reduced muscle strength mainly in lower limbs. Initially the weakness was mainly noticeable at the left side. Over the past four days, he was unable to keep up with his basketball teammates, necessitating him to pull himself toward on the banister to climb the stairs. Additionally, parents reported he choked during feedings the last few days.

Recently, he had no respiratory or gastrointestinal symptoms. Apart from allergic rhinitis, there was no significant medical history. There were no known muscle or neurologic diseases in the family, and his siblings were in good health. Born in India, he had been residing in Belgium for the past five years. On physical examination he could stand supported but couldn't walk on his toes, Gowers's sign was positive. Sensory examination was normal, tendon reflexes and sphincter control were present. There was no respiratory distress. Heart rhythm and oxygen saturation were normal.

Investigations

Laboratory tests were within the normal range for blood cell count, C reactive protein, creatine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), thyroid stimulating hormone, lead, cyanocobalamin, thiamine, pyruvate kinase and creatine kinase. The erythrocyte sedimentation rate (25 mm/hour

[N < 15 mm/hour]) was mildly elevated and albumin was high-normal (47.2 g/L [N 35,0 – 52,0 g/L]). Serological test for *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, cytomegalovirus, Epstein-Barr Virus and varicella-zoster virus were negative. Unfortunately, anti-ganglioside antibody determination was not feasible in our hospital. Urine toxicology screening was also negative. Stool culture was negative for *Campylobacter jejuni*. The cerebrospinal fluid protein level was within the normal range and no cells were detected. Magnetic resonance imaging of the brain and spinal cord revealed no abnormalities. Electromyography was consistent with a motor axonal polyneuropathy affecting all four limbs. The motor nerve conduction study at the level of the 4 limbs shows reduced to borderline normal amplitudes with normal conduction velocities and borderline normal terminal latencies. The CMAP durations are borderline normal to prolonged. Needle EMG shows no signs of active denervation in the muscles examined. In the m. vastus medialis R and lateralis L, only a few motor units are recruitable. The sensory nerve conduction study at the level of the limbs is normal.

Treatment

Initial treatment regime was 400 mg/kg/day intravenous immunoglobulin for five days.

Outcome and follow-up

After five days of IVIg, he was able to stand on his toes again, although a complete recovery of strength had not yet occurred. Bulbar complaints were no longer present. A follow-up two weeks later revealed a regression of all symptoms.

Discussion

AMAN is a rare axonal variant of GBS. It is more prevalent in East Asia, Central and South America, possibly due to increased infection rates with *C. jejuni*. Other pathogens, such as *Haemophilus influenza* and *M. pneumoniae* are reported to be involved in the molecular mimicry mechanism. Despite our efforts no pathogen could be identified. Genetic susceptibility may contribute to AMAN onset and prognosis, although this remains insufficiently understood to date. Most documented cases are reported in Asia and as our patient has Indian roots genetic predisposition is plausible. Large genome-wide association studies (GWAS) on patients with axonal GBS are needed to explore this further. Bulbar palsy is more prevalent in children than in adults (2, 4). Anti-GT1a and anti-GM1b antibodies are associated with bulbar palsy. Failure to determine anti-ganglioside antibodies is a limitation in this case report. A typical finding of GBS is an albumin-cytological dissociation in cerebrospinal fluid. In this patient, the cerebrospinal fluid protein level was normal in the first week of symptoms. Albumin-cytologic dissociation is often not seen until two to three weeks after the acute onset. If found in the first week, the prognosis is often worse. Decreased CMAP amplitudes and RCFs are typical electrophysiological features of axonal GBS (3). The patients EMG confirmed our clinical diagnosis.

Children with AMAN seem to respond better to IVIG than AIDP (8). This suggests the underlying auto-antibody-mediated immune response in AMAN patients is inhibited by IVIg. Five days after the administration of IVIG, the patient could stand on his toes again, and there were no more bulbar symptoms. Two weeks later all symptoms had disappeared.

The present report describes an adolescent with acute motor axonal neuropathy, without evidence of a gastrointestinal infection. It occurred in summer, consistent with earlier reports of summer epidemics. The patient made a full recovery. Clinicians should be aware of this rare axonal variant of GBS in children, characterized by a pure motor involvement (muscle weakness) and co-occurring bulbar palsy.

Take away lessons

1. Axonal GBS is an important variant of classical GBS. AMAN is a pure motor variant without the involvement of the sensory or autonomic nerves.
2. The classic type of GBS is characterized by demyelination, while in AMAN, axonal degeneration occurs, and the myelin sheath remains intact. This is characterized by a reversible conduction block, a reversible conduction failure or decreased compound muscle action potential (CMAP) amplitudes on electrophysiological studies.
3. Further studies are necessary to unravel the etiopathogenesis, define electrophysiological criteria, establish prognostic factors and optimal treatment.

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

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Acquired Torticollis as Presentation of Langerhans Cell Histiocytosis: Two Contrasting Cases

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Keywords
Torticollis ; Langerhans Cell Histiocytosis ; Atlanto-axial subluxation.

Abstract
Langerhans cell histiocytosis (LCH) is a rare disorder that primarily affects young children. Because LCH can affect multiple organs, particularly bone and skin, it presents with a wide range of symptoms. This article reports two different cases with acquired torticollis as the primary complaint. Acquired torticollis is an atypical and less common presentation of LCH. These case reports highlight the importance of identifying a cause for acquired torticollis, which includes LCH in the differential diagnosis. Adequate diagnosis of LCH is important for timely initiation of appropriate treatment to prevent complications and long-term consequences.

Introduction

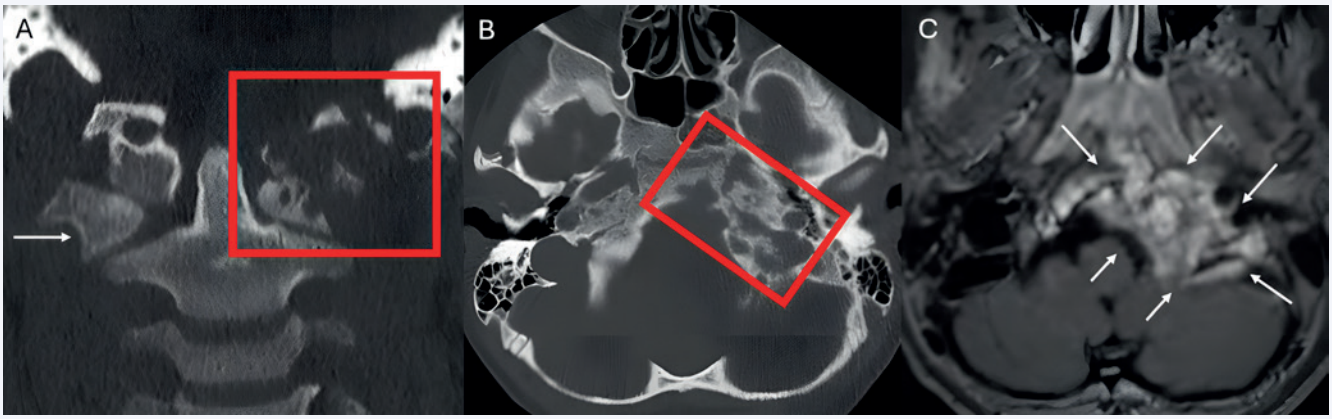
Langerhans cell histiocytosis (LCH) is a rare disorder, mostly affecting children aged one to three years old, but it can occur at any age. It involves pathological single- or multi-organ accumulation of immature myeloid precursor cells resembling Langerhans cells of the skin and mucosa. LCH affects about five children per million annually, but is likely underreported due to its diverse presentation, diagnostic challenges, and self-limiting localized forms (1).

LCH can be localized or multi-organ and most frequently affects the bones, skin and pituitary gland, but can also involve the lungs, lymph nodes, central nervous system (CNS), bone marrow, liver, or spleen (1, 2).

Bone is most commonly affected in children, especially the skull, resulting in pain or swelling (1). Skin lesions include seborrheic-like rashes, eczematous patches, papules, or mucosal ulcers (1, 2). Posterior pituitary involvement often leads to central diabetes insipidus, while anterior pituitary involvement is rare (1). Beyond these common presentations, other symptoms may include gastrointestinal, pulmonary, or lymphatic issues (2).

The presentation of LCH with torticollis as the primary sign is uncommon (3). Acquired torticollis, wich is often indicative of an underlying pathology, may result from trauma, nerve palsy, sternocleidomastoid spasm, infection and rotatory atlanto-axial subluxation (4). LCH is rarely considered in the initial differential diagnoses of torticollis.

FIGURE 1: CT skull base and cervical spine (**A,B**). Coronal reconstructions of the upper cervical spine (**A**) show lytic destruction of the left occipital condyle and the lateral mass of the atlas (red square) and a right sided atlanto-axial and –occipital lateral luxation (white arrow). Axial reconstructions of the skull base (**B**) show aggressive lytic destruction of the left posterior part of the clivus and the petrous apex of the mastoid (red square). On MRI axial T1-weighted images with Gadolinium (**C**) shows avidly enhancing soft tissue in the areas of bony destruction (*white arrows*).



This report describes two children with acquired torticollis who were later diagnosed with craniospinal LCH. Each case involved a unique mechanism of torticollis.

Case 1

The first patient is an eight-year-old boy with no notable clinical or family history. He initially presented with left-sided neck pain occurring after a fall, without torticollis. Two weeks later, he returned with a respiratory infection, accompanied by persistent neck pain. At this time, torticollis with lateral flexion of the neck to the right and painful left-sided lymphadenopathy were observed. No B-symptoms were present. Antibiotics, a cervical collar, and physiotherapy did not alleviate the pain or torticollis. Due to persistent torticollis, an x-ray and magnetic resonance imaging (MRI) of the cervical spine were performed, showing no abnormalities. Ultrasound revealed bilateral lymphadenopathy. Therefore, reactive torticollis caused by a respiratory infection with lymphadenopathy was retained as a working diagnosis.

However, two months later both the torticollis and lymphadenopathy persisted. At this point, our patient showed a lateral flexion of the neck to the right and an apparent rotation of the chin to the left. This position is known as 'cock robin posture', prompting further investigation into an atlanto-axial subluxation as the cause of the torticollis. Subsequently, a dynamic cervical computed tomography (CT)-scan was performed, which confirmed the subluxation and additionally showed significant osteolysis extending into the left occipital condyle, clivus and lateral mass of the atlas. A subsequent MRI demonstrated associated soft-tissue masses in the area of bony destruction, along with two additional comparable lesions in the right parietal bone. These radiologic findings are showed in Figure 1. Based on the location and radiologic characteristics multifocal LCH was suspected, with bone metastases of an unknown primary tumor as the main differential diagnosis. The diagnosis of a single-system multifocal LCH was confirmed by a CT-guided biopsy. Based on the confirmation of the diagnosis, a course of vinblastine and prednisolone was initiated, four months after the initial presentation. Subsequent maintenance therapy was continued for 24 months, resulting in a significant reduction of the lesions. Currently, three years after his initial presentation, the patient remains in clinical remission, with only radiological follow-up required

Case 2

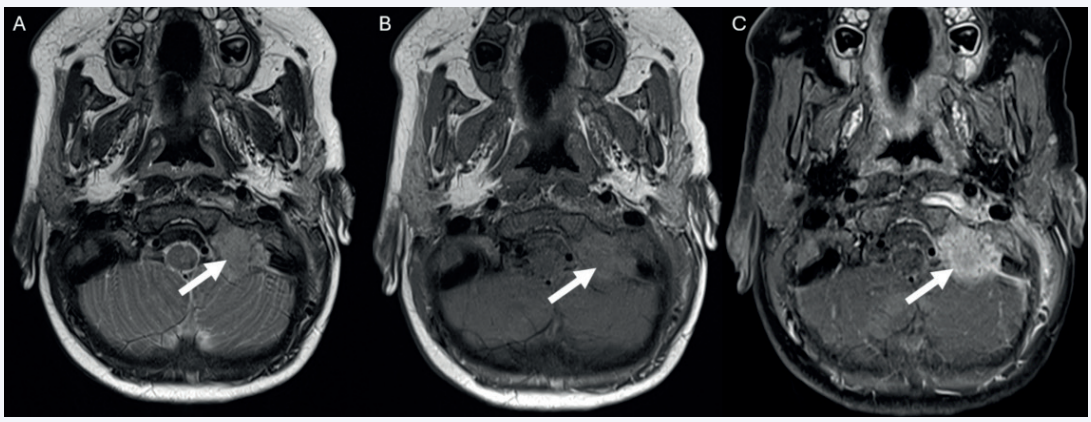
The second patient is a boy without significant medical history, who presented at the age of 19 months with a head tilt to the left. Clinical examination showed torticollis towards the left side, with both lateral flexion and rotation of the chin to the left, and right-sided cervical lymphadenopathy. Initial laboratory investigations showed a slightly elevated C-reactive protein (CRP) value, without any other abnormal findings. A CT-scan and MRI of the skull and neck were performed, showing an area of osteolysis at the level of the left posterior skull base and left occipital condyle with an accompanying soft-tissue component. The MRI-findings in this patient are showed in Figure 2. Additionally, an edematous aspect of the left half of the tongue was seen on MRI, likely correlated with a hypoglossal paresis. The diagnosis of unifocal LCH was ultimately confirmed by CT-guided biopsy. Although the lesion in the second patient was unifocal, systemic treatment with vinblastine and prednisolone was initiated due to the presence of torticollis and hypoglossal nerve compression. Given an adequate decrease in lesion size under this therapy, it was decided to discontinue chemotherapy six months after initiation and continue radiological follow-up. At present, nearly two years after the initial presentation, the patient remains in clinical and radiological remission, with near-complete resolution of the primary lesion and no ongoing treatment.

Discussion

Acquired torticollis is a potential manifestation of many different underlying conditions, and assessment requires simultaneous appreciation of the most common and most threatening differential diagnoses. Among the most common causes are an inflammation of the sternocleidomastoid muscle, neck trauma and acute infections such as upper respiratory tract infections or cervical adenitis. It is crucial to be aware of the life-threatening infections such as a retropharyngeal abscess or Lemierre syndrome, which necessitate prompt diagnosis and intervention. More infrequently, neoplastic diseases, such as CNS or bone tumors, as well as several neurological diseases such as myasthenia gravis can result in torticollis. In addition, torticollis can have ocular causes, such as superior oblique muscle weakness, strabismus and congenital nystagmus, and some miscellaneous causes, specifically gastroesophageal reflux, juvenile rheumatoid arthritis and drug-induced dystonia (4). Therefore, torticollis should not be considered a diagnosis, but rather a sign of an underlying condition.

With a prevalence of five children per million per year, LCH is a very rare disease (1). Bone lesions are the primary manifestation of LCH, with the skull being the most commonly affected region (61%) (3). Based on scattered case reports, only 4.7% of children with LCH involving the head and/or cervical spine present with torticollis (5).

FIGURE 2: MRI brain shows a T2-iso- to slightly hyperintense (**A**), T1-iso-intense (**B**), avidly contrast enhancing, (**C**) mass antero-inferiorly in the squamous part of the occipital bone extending into the left occipital condyle (*white arrows*).



The diagnosis of LCH is often suspected on the basis of imaging studies (typically CT or MRI) that are suggestive of the disease, but histopathological confirmation of the lesions is required for a definitive diagnosis. Due to the wide variety of organ systems involved, radiologic features vary widely. Histopathologic examination reveals uncontrolled proliferation of Langerhans-type cells, typically accompanied by numerous eosinophils, which led to the previous designation eosinophilic granulomas.

Generally, patients with unifocal single-system LCH can be managed with watchful waiting or with local therapies, as these patients usually have a good prognosis. For the multifocal osseous disease, systemic therapy is generally indicated, as these patients have a much higher risk of recurrence and progression. Systemic treatment in the pediatric population generally consists of a combination of prednisolone and vinblastine, as was the case in our two patients (6). Although the lesion in the second patient was unifocal, systemic therapy was chosen in the context of torticollis and hypoglossal canal compression with resulting hypoglossal nerve palsy.

We presented two patients with LCH-related torticollis, with distinct clinical manifestations. Our first patient presented with rotatory atlanto-axial subluxation as the underlying cause of the torticollis, a novel aspect reported only in one previous case report (7). Clinically, he presented with the typical 'cock robin posture' with flexion contralateral to the lesion and rotation of the chin to the side of the injury, due to a spasm of the contralateral sternocleidomastoid muscle (8). The major risk of missing an atlantoaxial dislocation is the progression to acute spinal cord damage (9).

In contrast, our second patient presented with a 'typical' torticollis, with flexion to the side of the lesion, likely due to a compressive effect of the lesion on the sternocleidomastoid muscle. However, the patient we describe is notably younger than most previously reported cases of torticollis associated with LCH.

Despite sharing the etiology of LCH, our patient's clinical differences have distinct implications for diagnosis and management.

Through this case report, we aim to emphasize that both typical and atypical torticollis can be initial symptoms of craniospinal LCH, regardless of age. Swift recognition and treatment are paramount to halt disease progression and prevent subsequent complications such as diabetes insipidus, growth retardation and secondary malignancies (10).

Moreover, in patients presenting with atypical features of torticollis, further investigation is mandatory, as we have demonstrated with the distinctive 'cock robin posture' as a hallmark of a rotatory atlantoaxial subluxation, a specific cause of torticollis that can be seen in bone lesions of LCH (7).

Conclusion

Langerhans cell histiocytosis (LCH) is a rare disease with a broad spectrum of clinical presentations. In this manuscript, we describe two patients who presented with torticollis as the primary sign of LCH, but there were distinct differences in clinical presentation. One patient presented with a 'cock robin posture' indicating a rotatory atlantoaxial subluxation, whereas the other patient presented with a typical torticollis as a result of compression of the sternocleidomastoid muscle. These cases illustrate that both typical and atypical torticollis can be the first symptom of craniospinal LCH. Therefore, LCH must be included in the differential diagnosis of all forms of acquired torticollis to ensure proper diagnosis, treatment and prevention of complications.

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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Blueberry Muffin Syndrome in a Newborn. A Case Report of Transient Extramedullary Hematopoiesis

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Keywords
Blueberry Muffin Syndrome, Extramedullary hematopoiesis, Neonatal leukemia, Newborn.

Abstract
Blueberry Muffin Syndrome (BMS) is a rare condition in newborns characterized by distinctive skin lesions often associated with transient extramedullary hematopoiesis. We present a case of a newborn with BMS focusing on the diagnostic challenges, especially in distinguishing it from acute leukemia. Despite extensive investigations, no specific etiology was found. The skin lesions resolved spontaneously. This case highlights the importance of a multidisciplinary approach in the diagnosis of BMS and underscores the need for a thorough evaluation to exclude severe underlying conditions.

Introduction

Blueberry Muffin Syndrome (BMS) is a rare neonatal condition characterized by red-blue papules, macules, or nodules on the skin. The lesions mostly consist of reactive extramedullary hematopoiesis or neoplastic skin infiltration and are related to underlying conditions, including acute leukemia or metastatic tumors. The term 'blueberry muffin syndrome' (BMS) derives from the purplish maculopapular skin lesions resembling the surface of a blueberry muffin. However, this seemingly innocuous term can mask underlying serious conditions, including malignancies, and therefore requires careful clinical evaluation to identify the cause.

Early and accurate diagnosis is critical due to the broad differential diagnosis (1,2). This report describes a newborn with BMS and transient extramedullary hematopoiesis, emphasizing the diagnostic challenges and the importance of ruling out malignancy.

Clinical Case

A male Caucasian newborn was delivered vaginally at 39 weeks after induction due to decreased fetal movement and altered fetal monitoring. The pregnancy was otherwise uneventful, with no ABO or Rh incompatibility and no family history. Maternal infectious serologies (expanded after delivery) were negative for cytomegalovirus (CMV), toxoplasmosis, hepatitis B, hepatitis C, syphilis, HIV, *Chlamydia trachomatis*, coxsackievirus and human T-lymphotropic virus (HTLV). The mother was immune to rubella and parvovirus and not immune to varicella-zoster virus (VZV).

At birth, the newborn had a low birth weight of 2,345 grams (below the second percentile, consistent with severe hypotrophy) and had experienced perinatal hypoxia-ischemia events with transient acidosis, followed by a good recovery. The Apgar score was 9 at 1, and 7 at 5 minutes of life. At birth, the infant's skin was erythemic and there was no pallor or jaundice. There was no lymphadenopathy on physical examination. A bluish rash on the face, limbs, and back led to the diagnosis of BMS (Figure 1.A).

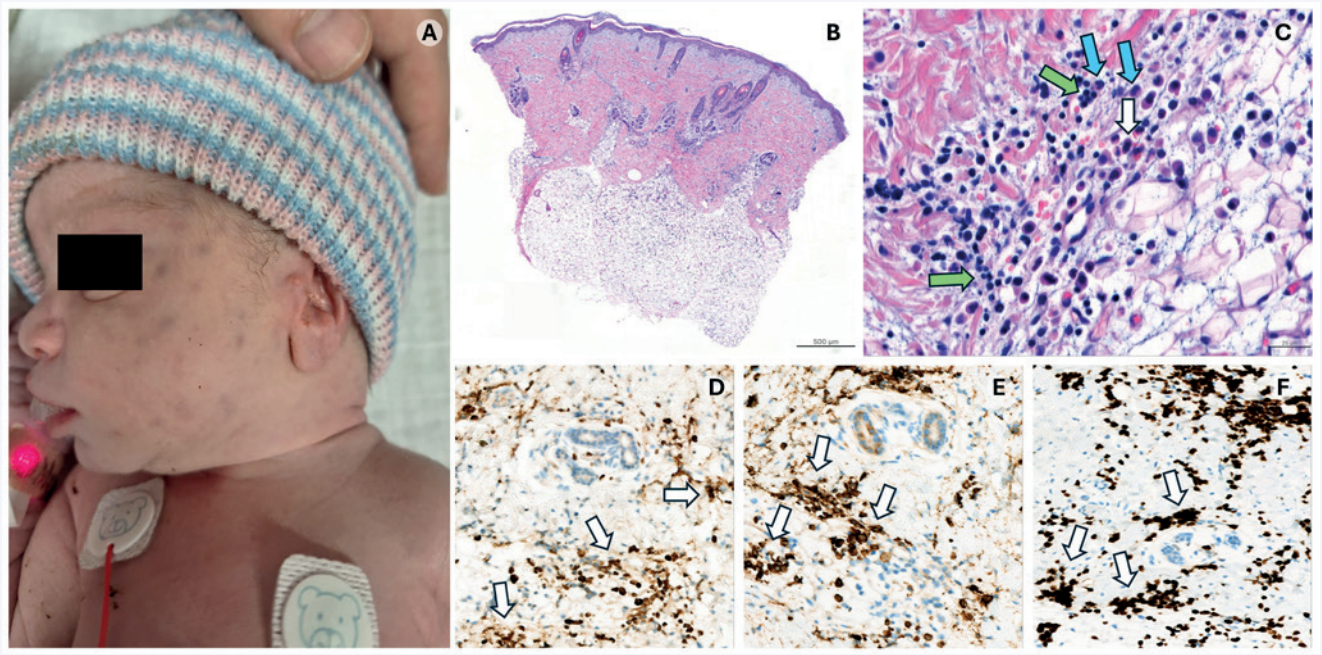
Initial blood tests revealed polycythemia with a hemoglobin level of 22.1 g/dL and a hematocrit of 60.5%, with significant erythroblastosis. The child's direct Coombs test was negative.

Biological analysis revealed mild thrombocytopenia. The white blood cell count showed transient neutropenia and moderate lymphopenia. The absence of hyperleukocytosis in this case indicated a lower probability of leukemia or infection.

The direct bilirubin level was 0.6 mg/dL on the first day of life, and the total bilirubin level was 18.4 mg/dL on the fifth day of life. Other blood parameters, including CRP and creatinine, were normal. Moderate biological disturbances in prothrombin time were observed and returned spontaneously to the expected neonatal range within one week.

Infectious workup, including multiplex PCR for various respiratory viruses, enterovirus PCR on stool, VZV and herpes simplex virus PCR, were negative. Urine CMV PCR was also negative. Imaging

FIGURE 1: A. Infiltrated violaceous macules on the face. B. Skin biopsy (Hematoxylin and Eosin stain, 20x magnification): Dermal-hypodermal infiltration. C. Skin biopsy (Hematoxylin and Eosin stain, 400x magnification): Immature granulocytic population (white arrow) showing granulocytic maturation (blue arrow) associated with an erythroblastic population (green arrow). D-F. Skin biopsy (Immunohistochemistry, 200x magnification): Myeloperoxidase (MPO) staining (D) highlights granulocytic lineage cells (white arrow), and CD71 staining (E) identifies erythroblastic clusters (white arrow). Ki67 staining (F) indicates a high proliferative index (white arrow).



studies, including abdominal ultrasound, chest X-ray, and brain MRI, were performed to investigate potential hepatosplenomegaly or bone abnormalities but did not reveal any significant findings.

Bone marrow aspiration revealed 3.5% blasts without significant morphologic or phenotypic abnormalities. A skin biopsy from the left buttock showed dermal and hypodermal infiltration by immature myeloid cells. The initial differential diagnosis included acute myeloid leukemia (AML) and extramedullary hematopoiesis (Figure 1.B through F). Immunohistochemical analysis revealed CD43, myeloperoxidase, and lysozyme positivity, and a high proliferation index confirmed by anti-Ki67 antibody. The absence of CD34, CD117, and TdT, and the presence of erythroblastic clusters expressing CD71, suggested extramedullary hematopoiesis.

Genetic analysis of mutations was performed to rule out inherited conditions associated with extramedullary hematopoiesis or other hematologic abnormalities. Mutational analysis of *FLT3* and *NPM1* genes in the skin biopsy, and *FLT3*, *NPM1*, *CEBPA*, and *IDH1/2* genes in the bone marrow found no pathogenic variants. These genes are frequently mutated in acute myeloid leukemia (AML), with *CEBPA* in particular being associated with familial AML. The absence of detectable mutations in these genes allowed for the exclusion of approximately 35% of pediatric AML cases. Furthermore, karyotyping of the bone marrow ruled out the presence of the *t(8;16)(p11;p13) (KAT6A-CREBBP)* translocation, which is linked to spontaneously remitting neonatal AML.

The skin lesions resolved spontaneously after eight days of life, and the child was discharged with pediatric follow-up. No specific etiology for the extramedullary hematopoiesis was identified.

TABLE 1: Etiologies of Blueberry Muffin Syndrome.

Non-neoplastic etiologies	Neoplastic etiologies
• **Congenital (TORCH) Infections:** - **T**oxoplasmosis - **O**ther (Syphilis, …) - **R**ubella - **C**ytomegalovirus - **H**erpes simplex virus **Other viral infections**: not classified within the TORCH group : enterovirus (coxsackievirus, …), parechovirus, …	• **Acute Leukemias**: - Acute myeloid leukemia - Acute lymphoblastic leukemia • **Lymphomas** • **Histiocytosis** - **Langerhans cell histiocytosis** - **Juvenile xanthogranuloma** • **Mastocytosis** (cutaneous or systemic) • **Infantile myofibromatosis** • **Metastatic tumors**: - Metastatic neuroblastoma - Metastatic rhabdoid tumor - Metastatic rhabdomyosarcoma - Metastatic tumors acquired via transplacental route • Choriocarcinoma • Melanoma • **Vascular tumors or malformations**: - Hemangioma
• **Hemolytic disease of the newborn**: - ABO and Rh Incompatibility - Hereditary spherocytosis • **Vascular hemodynamic conditions** - Twin-to-Twin transfusion syndrome	

Discussion

BMS can be one of the first manifestations of an underlying systemic pathology, whether reactive or neoplastic, necessitating thorough investigation. The characteristic skin nodules observed in BMS result from reactive extramedullary hematopoiesis or infiltration

TABLE 2: Etiological workup for Blueberry Muffin Syndrome.

Step	Purpose	Tools
Clinical assessment	Identify maternal history, prenatal risk factors, and newborn signs	Physical examination
Laboratory tests	Detect hematological abnormalities: • **Anemia/hemolysis**: Evaluate hemoglobin levels and markers of hemolysis • **Erythroblastosis and leukocytosis**: Assess the number of erythroblasts and leukocytes in the blood • **Evaluation of lymphocyte population**: Determine the dominant lymphocyte subtype (e.g., T-cells, B-cells, NK cells) • **Coagulation disorders**: Assess for abnormalities in clotting factors and platelet function Detect infections (e.g., TORCH,...)	Complete blood count Blood smear Serology PCR
Radiological imaging	Assess visceral involvement: • **Hepatosplenomegaly**: Check for liver and spleen enlargement, which may suggest underlying systemic disease • **Mediastinal mass**: Look for any masses in the mediastinum, possibly indicating lymphoma or other tumors • **Brain or spinal mass**: Identify any intracranial or spinal lesions that may be related to neoplastic processes	**Abdominal ultrasound** **Magnetic resonance imaging (MRI)** **Chest X-ray**
Bone marrow aspiration	Evaluate marrow function and rule out malignancy • **Aberrant marrow population/blasts**: assess for the presence of abnormal cells or blasts, indicating possible leukemia or other marrow pathology • **Genetic abnormalities**: Conduct cytogenetic or molecular tests to detect chromosomal anomalies or specific gene mutations	Morphology Flow cytometry Cytogenetics Molecular analysis
Skin biopsy	Differentiate extramedullary hematopoiesis from malignancies (e.g., leukemia cutis, Langerhans cell histiocytosis, ...)	Histology Immunohistochemistry Molecular analysis

by neoplastic cells depending on the underlying etiology (1,2) (Table 1). Understanding the mechanisms behind these lesions is essential for accurate diagnosis and management.

During fetal development, erythropoiesis begins in the yolk sac between 2 and 10 weeks of gestation, transitions to the liver from 10 to 18 weeks, and shifts primarily to the bone marrow by the third trimester. Extramedullary hematopoiesis occurs when normal bone marrow function is insufficient or disrupted, leading to hematopoietic activity in former hematopoietic sites or new secondary sites such as the skin. This compensatory mechanism can be seen in congenital infections or hematologic disorders, as well as in neoplastic conditions where marrow function is impaired.

Among the most frequent causes of BMS with extramedullary hematopoiesis in the skin are congenital infections and hematologic disorders. Intrauterine infections, including viral agents from the TORCH group (toxoplasmosis, rubella, CMV, herpes), as well as bacterial infections like syphilis, can disrupt normal fetal hematopoiesis. These infections may lead to direct bone marrow suppression, inflammation-driven hematopoietic dysfunction, or immune-mediated hemolysis, all of which may trigger extramedullary hematopoiesis. Similarly, hematologic disorders such as neonatal hemolytic diseases (e.g., ABO or Rh incompatibility, hereditary spherocytosis) and twin-twin transfusion syndrome (TTTS) may result in anemia, stimulating increased erythropoietin (EPO) production, which in turn drives extramedullary hematopoiesis and the development of BMS lesions (3–5). Notably, in TTTS, BMS is typically observed in the donor twin, who experiences chronic anemia.

Neoplastic causes of BMS include both benign and malignant neoplasms. Among hematologic malignancies, acute myeloid leukemia and acute lymphoblastic leukemia are commonly presenting as BMS, either through direct neoplastic infiltration of the skin or due to marrow dysfunction leading to compensatory extramedullary hematopoiesis. Congenital histiocytosis, including juvenile xanthogranuloma (JXG) and Langerhans cell histiocytosis (LCH), can also present with BMS-like lesions, with varying degrees of systemic involvement. In some cases, solid tumors such as neuroblastoma or rhabdomyosarcoma (6,7) may metastasize to the skin, causing a BMS. Transplacental metastases from maternal malignancies, such as melanoma or choriocarcinoma, are rare but should also be considered (7). Other rare neoplastic causes include infantile myofibromatosis and multifocal vascular lesions (8).

Mechanistically, neoplastic processes might impair hematopoiesis through several pathways, including direct marrow infiltration leading to spatial crowding, the release of inhibitory cytokines, and alterations in the bone marrow microenvironment, such as fibrosis. These mechanisms contribute to ineffective hematopoiesis and necessitate compensatory extramedullary hematopoiesis, which manifests clinically as BMS.

The diagnostic approach to BMS relies on differentiating between reactive/secondary extramedullary hematopoiesis, its etiology and neoplastic infiltration (1-2). A structured evaluation begins with a detailed maternal history, including prenatal screening results and infectious exposures, followed by a thorough newborn clinical examination to identify additional warning signs such as hepatosplenomegaly or lymphadenopathy. Laboratory investigations play a key role, with blood tests assessing hematologic parameters and markers of infection, while virological and serological assays help confirm congenital infections. Imaging studies, including ultrasound, X-ray, and MRI, can reveal visceral involvement such as hepatosplenomegaly or the presence of a mediastinal mass (9).

Bone marrow aspiration is crucial to assess the presence of blasts and bone marrow alterations, and to perform cytogenetic and molecular analyses to help distinguish between leukemia and

non-malignant causes of BMS (7). Skin biopsy, as a less invasive and more accessible procedure, plays a key role in distinguishing extramedullary hematopoiesis from neoplastic infiltrations such as histiocytosis, metastatic tumors or leukemic infiltration, which are not necessarily excluded by a negative bone marrow aspiration (9,10). While bone marrow aspiration can often rule out leukemia, cutaneous involvement - termed myeloid sarcoma or leukemia cutis - may arise independently. This dermatologic manifestation can precede, coincide with, or follow the diagnosis of leukemia, highlighting the complementary roles of bone marrow aspiration and skin biopsy in the clinical evaluation. Each of these diagnostic steps, summarized in Table 2, contributes to determine the underlying cause of BMS and guiding appropriate management.

BMS management requires a multidisciplinary approach involving pediatricians, dermatologists, hematologists, and pathologists. While skin manifestations are a key feature, BMS itself is usually asymptomatic. Treatment should target the underlying systemic condition responsible for BMS. In cases of extramedullary hematopoiesis with no definite underlying etiology, regular follow-up is necessary to monitor resolution and detect any evolving pathology (9).

In our case, the skin lesions resolved spontaneously. The favorable progression of the patient's health over an eight-month period argues against the presence of BMS-related complications. Continued clinical monitoring remains essential to detect any potential late-onset manifestations. No specific etiology for the extramedullary hematopoiesis was identified. The hypothesis proposed by clinicians is that potential chronic fetal hypoxemia in late pregnancy, which led to restricted growth, may have promoted extramedullary hematopoiesis. The absence of other symptoms and the normalization of laboratory values supported a favorable clinical course.

Conclusion

BMS, though rare, presents a significant diagnostic challenge due to its broad differential diagnosis. Accurate diagnosis involves a thorough evaluation to differentiate between non-neoplastic and neoplastic causes. This case highlights the importance of a detailed diagnostic approach and multidisciplinary management in ensuring favorable outcomes.

Conflict of interest

The authors and co-authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Patient informed consentient

The authors and co-authors declare that they informed the patient's family of the redaction of this article. The parents consented to the use of the clinical images and clinical information related to this case report.

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A Seven-Month-Old Girl with Hemophagocytic Lymphohistiocytosis Secondary to Systemic Juvenile Idiopathic Arthritis. A Case Report

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Keywords
Hemophagocytic lymphohistiocytosis ; systemic juvenile idiopathic arthritis ; macrophage activation syndrome ; persisting fever ; case report.

Abstract
Hemophagocytic lymphohistiocytosis (HLH) is characterized by an uncontrolled activation of immune cells. HLH can be primary, due to a genetic predisposition, or secondary, due to an underlying disease such as systemic juvenile idiopathic arthritis (sJIA). Primary or secondary HLH and sJIA present similarly. Clinical and biochemical parameters can be used to differentiate between them. In patients with a persistent fever, it is important to consider an underlying immune and/or rheumatologic problem. We present the case of a seven-month-old girl who presented with symptoms of HLH and was later diagnosed with underlying sJIA.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by a dysregulated immune response to antigens, resulting in excessive activation of immune cells and an increase in proinflammatory cytokines. Although the precise pathogenic mechanisms are not well understood, it is established that systemic hyperinflammation may lead to extensive tissue damage, multi-organ failure, and, if untreated, can lead to mortality (1, 2). HLH is subclassified into primary (familial) and secondary forms (1, 3). Primary HLH is a genetic, autosomal recessive disorder typically presenting in early infancy (1). In contrast, secondary HLH is often precipitated by infections, malignancies, or autoimmune and autoinflammatory diseases, and can occur in both immunocompetent and immunocompromised individuals across all age groups (1, 4, 5).

Clinically, HLH manifests with persistent fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, markedly elevated serum ferritin, transaminases, and neurological symptoms caused by hyperproteinaemia and pleocytosis in cerebrospinal fluid (CSF). Lymphadenopathy, skin rashes, jaundice, and edema are less frequently observed. Hemophagocytosis may be seen in the bone marrow, spleen, liver, or lymph nodes; however, its presence is not mandatory for diagnosis. Elevated soluble CD25 (sCD25), a marker of interleukin-2 receptor activation, is often observed in both serum and CSF. Diagnosis is established when five out of eight criteria, as outlined in Table 1, are fulfilled (1, 3).

Immediate therapeutic intervention is paramount in HLH, as untreated primary HLH carries near 100% mortality, while untreated secondary HLH has a mortality rate exceeding 20% (5). With appropriate treatment, mortality rates are reduced to 40% for primary HLH and 8% for secondary HLH (5). Allogeneic hematopoietic stem cell transplantation (HSCT) remains the definitive curative treatment for primary HLH (3). Historically, the HLH-94 and HLH-2004 protocols were used, which incorporated corticosteroids and etoposide prior to HSCT. Currently, the preferred regimen includes targeted immunotherapy (alemtuzumab) combined with corticosteroids and ciclosporin, which have been shown to achieve high survival rates to HSCT (92.3% and 91.6%, respectively) (6). In cases of refractory or relapsing HLH, emerging therapeutic strategies involving immunotherapy and cytokine-targeted therapies are being investigated (2). Furthermore, experimental approaches such as gene therapy and adoptive T cell therapy have shown promise in preclinical studies, particularly in murine models (2).

Secondary HLH, often referred to as macrophage activation syndrome (MAS), is frequently observed in patients with systemic juvenile idiopathic arthritis (sJIA, also known as Still's disease) (3, 7). sJIA is a chronic autoinflammatory disease characterized by persistent arthritis and quotidian fever of at least three days' duration, recurring over a two-week period, generalized lymphadenopathy, a salmon-colored migratory rash, hepatosplenomegaly, and serositis (7). Laboratory findings typically include leukocytosis, neutrophilia, elevated platelet counts, an increased erythrocyte sedimentation rate (ESR),

TABLE 1: Criteria for primary hemophagocytic lymphohistiocytosis and macrophage activation syndrome in a patient with (suspected) sJIA.

	Primary HLH	MAS
Criteria needed	≥ 5/8 optional criteria	Fever Serum ferritin > 684 ng/mL AND ≥ 2 optional criteria
Optional criteria	Fever Splenomegaly Cytopenias affecting at least two lineages in the peripheral blood Hypertriglyceridemia and/or hypofibrinogenemia Hemophagocytosis in bone marrow, spleen or lymph nodes Low or absent natural NK cell activity Hyperferritinemia High levels of sCD25	Low platelets (< 181x10^9/L) Elevated aspartate aminotransferase (> 48 U/L) Elevated triglycerides (> 156 mg/dL) Hypofibrinogenemia (< 360 mg/dL)

elevated C-reactive protein (CRP), and markedly elevated ferritin levels. Therapeutic options for sJIA include methotrexate, anakinra, rilonacept, tocilizumab, glucocorticoids, and ciclosporin (7). MAS may present as the initial manifestation of sJIA, with overt arthritis developing subsequently (3). The diagnosis of MAS in patients with sJIA can be made using the diagnostic criteria outlined in Table 1 (4). Initial management of MAS in sJIA typically involves high-dose intravenous corticosteroids, followed by oral corticosteroids. Additionally, ciclosporin, intravenous immunoglobulins (IVIG), anakinra, and etoposide may be considered (3-5).

Case presentation

A seven-month-old girl with no significant medical history presented with a three-day history of fever. She was initially diagnosed with bilateral otitis media and tonsillitis, for which she was treated with amoxicillin. One week later, she developed a persistent fever and a morbilliform rash that initially appeared on her cheek and subsequently spread to her other body parts, including her palate. Serological testing for Epstein-Barr virus was negative, as were blood and urine cultures. The antibiotic therapy was changed to trimethoprim/sulfamethoxazole and was administered for a total of eight days.

Two weeks later, the patient developed scalded skin on her hands and oral aphthosis. Three weeks after initial presentation, she was hospitalized. Laboratory findings upon admission revealed mild anemia, leukocytosis, neutrophilia, elevated lactate dehydrogenase, elevated C-reactive protein (CRP), and an elevated erythrocyte sedimentation rate (ESR). Relevant laboratory results are presented in Table 2. A nasopharyngeal swab tested positive for bocavirus and respiratory syncytial virus. During her hospitalization, the patient developed a nonpruritic, erythematous, raised rash on her face and feet. She was discharged after three days; however, daily fever spikes persisted, which were hypothesized to be due to a sequence of viral and bacterial infections.`

Four weeks after the initial presentation, the fever persisted. The patient developed hepatomegaly and was readmitted. Infectious etiologies for the persistent daily fever were systematically excluded. Repeated blood cultures were negative, and cerebrospinal fluid (CSF) analysis did not demonstrate signs of intracranial infection or inflammation. Testing for hepatitis E, cytomegalovirus, toxoplasmosis, parvovirus B19, and Leishmania was negative. She was immune to hepatitis B.

Cardiac imaging with echocardiography revealed no evidence of endocarditis, pericarditis, or myocarditis. A chest radiograph was unremarkable. Mantoux tuberculin skin testing and Interferon-gamma release assays (IGRAs) were negative. A bone marrow biopsy and a fluorodeoxyglucose positron emission tomography (FDG-PET scan) revealed no evidence of malignancy. The differential diagnosis also included autoimmune and autoinflammatory diseases. Laboratory results showed elevated complement C3 and normal complement C4 levels. Antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) were positive but non-specific. The patient met four out of eight HLH criteria: fever, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, and elevated sCD25 levels in serum. Flow cytometric analysis of cytotoxic lymphocyte perforin expression and NK-cell degranulation (CD107a expression) were within normal limits. An abdominal ultrasound was negative for splenomegaly. Although the patient exhibited mild anemia, other peripheral blood cell lineages were normal. No evidence of hemophagocytosis was observed in the bone marrow. The HScore for reactive hemophagocytic syndrome, which is used to estimate the likelihood of HLH, was approximately 90%, indicating HLH as the most probable diagnosis (8). After six weeks of fever, the patient was started on high-dose oral corticosteroid therapy. Initially, her fever resolved; however, it recurred after three days due to an intercurrent viral infection.

Three weeks after initiating corticosteroid treatment, the patient developed pain in her right elbow. Ultrasound imaging revealed mild joint effusion, confirming that HLH was secondary to sJIA. Ciclosporin was added to her treatment regimen. Subsequently, the patient developed polyarthritis involving her wrist and metacarpal joints, prompting the initiation of anakinra. To achieve sJIA remission, the patient required also methotrexate and tofacitinib.

TABLE 2: Relevant laboratory parameters for making the diagnosis in this case.

Laboratory parameter (normal values)	Relevant value
Haemoglobin (10.5-13.5 g/dL)	9.8 mg/dL
Leukocyte count (6-17.5 x10^9/L)	31.8 x10^9/L
Neutrophil count (1.9-9.6 x10^9/L)	27.57 x10^9/L
Platelet count (229-494 x10^9/L)	375 10^9/L
Erythrocyte sedimentation rate (< 20 mm/hour)	47 mm/hour
CRP (< 0.5 mg/L)	145.3 mg/L
Ferritin (13-150 µg/L)	17237 µg/L
Fibrinogen (82-383 mg/dL)	78 mg/dL
Triglycerides (< 150 mg/dL)	415 mg/dL
AST (< 89 U/L)	1006 U/L
ALT (< 45 U/L)	643 U/L
sCD25 (458-1997 pg/mL)	16378 pg/mL

TABLE 3: The MH score

Parameter	Value	Points
Age at onset (years)	≤ 1.6 > 1.6	37 0
Neutrophil count (x10^9/L)	≤ 1.4 > 1.4	37 0
Fibrinogen (mg/dL)	≤ 131 > 131	15 0
Splenomegaly	Yes No	12 0
Platelet count (x10^9/L)	≤ 78 > 78	11 0
Haemoglobin (g/dL)	≤ 8.3 > 8.3	11 0

Currently, 23 months after her initial presentation, the patient is in stable condition. She continues to receive frequent follow-up care from both a rheumatologist and an immunologist. Her current medications include anakinra, tofacitinib, and prophylactic azithromycin. Although genetic testing made a primary genetic etiology for HLH unlikely, this cannot be ruled out completely.

Discussion

The clinical manifestations of primary HLH, MAS, and sJIA exhibit substantial overlap. The clinical presentation of primary HLH and MAS is also similar to that of systemic infections, sepsis, endocarditis, and malignancy.

Several laboratory parameters can increase the likelihood of a diagnosis of MAS or sJIA. Soluble CD25 is elevated in MAS and may be normal or elevated in sJIA. The ESR is typically elevated in sJIA, whereas in MAS, the ESR may be normal or show a sudden decline. The fever is typically more persistent in MAS, whereas in sJIA, the fever follows a quotidian pattern. Hemophagocytosis and hypofibrinogenemia can be observed in MAS but not in sJIA (5).

Generalized lymphadenopathy is a common feature of MAS, whereas hepatosplenomegaly is more prevalent in primary HLH. Additionally, pancytopenia and hypofibrinogenemia are generally more pronounced in primary HLH than in MAS (9).

The MAS/HLH (MH) score can be used to estimate the probability that signs and symptoms are caused by primary HLH or sJIA-associated MAS can be estimated (Table 3, (9)). A lower score indicates a higher likelihood of MAS. In our patient, a score of 52 points resulted in an approximately 36% probability of primary HLH over MAS. The optimal cutoff for the MH score is 60 or higher, providing

Providing a sensitivity of 91% and a specificity of 93% for distinguishing primary HLH from MAS (9).

Genetic testing can definitively confirm a primary HLH diagnosis. However, some patients with sJIA who develop MAS may have heterozygous mutations in certain familial HLH genes. Moreover, the genetic testing results may not be available immediately (10). NK cell function assays are typically faster to obtain. Reduced or absent NK cell activity is a key diagnostic criterion for primary HLH, though it can also be observed in MAS (1, 3, 4).

Conclusion

In patients with persistent fever, making an accurate diagnosis can be challenging. It is essential to consider underlying immunodeficiencies, immune dysregulation, or autoimmune and autoinflammatory diseases, as well as infectious diseases and malignancies. If HLH is suspected, it is critical to assess ferritin, fibrinogen, and triglycerides as part of the diagnostic work-up, evaluate NK cell function, and perform a bone marrow biopsy. The HScore for reactive hemophagocytic syndrome can be used to estimate the likelihood of HLH. Additionally, the MH score may aid in determining the probability that the signs and symptoms are attributable to either primary HLH or MAS. Both primary HLH and MAS require immediate care. These patients should be managed in specialized centers with expertise in immunology and rheumatology, as prompt diagnosis and treatment are crucial for a favorable prognosis.

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ESSENTIELE GEGEVENS – NAAM VAN HET GENEESMIDDEL Enterol 250 mg poeder voor orale suspensie - Enterol 250 mg harde capsules. *Saccharomyces boulardii* CNCM I-745 – KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Enterol 250 mg poeder voor orale suspensie: Elk zakje poeder voor orale suspensie bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x 109 levensvatbare cellen op het ogenblik van de fabricage en 1 x 109 gelyofiliseerde levensvatbare cellen op de vervaldatum). Enterol 250 mg harde capsules: Elke harde capsule bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x 109 levensvatbare cellen op het ogenblik van de fabricage en 1 x 109 gelyofiliseerde levensvatbare cellen op de vervaldatum). Hulpstof(fen) met bekend effect (zie rubriek 4.4 van de SKP): Enterol 250 mg poeder voor orale suspensie: fructose, lactosemonohydraat, sorbitol. Enterol 250 mg harde capsules: lactosemonohydraat. Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de SKP. FARMACEUTISCHE VORM Enterol 250 mg poeder voor orale suspensie: Poeder voor orale suspensie. Enterol 250 mg harde capsules: Harde capsule. KLINISCHE GEGEVENS **Therapeutische indicaties** • Preventie van diarree bij behandeling met breedspectrumantibiotica van patiënten voorbeschikt tot het ontwikkelen van diarree door Clostridium difficile of hervallen in een diarree veroorzaakt door Clostridium difficile. • Adjuverende behandeling naast orale rehydratie van acute diarree bij kinderen tot 12 jaar. **Dosering en wijze van toediening** Dosering: Volwassenen: 2 tot 4 harde capsules of 2 tot 4 zakjes per dag, in 2 innames. Pediatrische patiënten Kinderen: 2 harde capsules of 2 zakjes per dag, in 2 innames. Wijze van toediening: • Harde capsules: de harde capsules met wat water inslikken. • Zakjes: het poeder mengen in een glas water. Te nemen voorzorgen voorafgaand aan gebruik of toediening van het geneesmiddel Vanwege een risico op besmetting via de lucht, mogen zakjes of capsules nooit worden opengemaakt in patiëntenkamers. Beroepsbeoefenaren in de gezondheidszorg moeten tijdens het hanteren en het toedienen van probiotica handschoenen dragen, waarna de handschoenen onmiddellijk moeten worden weggegooid en de handen moeten worden gewassen (zie rubriek 4.4 van de SKP). Duur van de behandeling: Preventie van een nieuwe episode of recidief van diarree door Clostridium difficile: 4 weken. Behandeling van diarree als aanvulling op orale rehydratie bij het kind: 1 week. Contra-indicaties: • Overgevoeligheid voor de werkzame stof of voor één van de in rubriek 6.1 van de SKP. •Patiënten met een centrale veneuze katheter, patiënten in kritieke toestand of immuungecompromitteerde patiënten, vanwege een risico op fungemie (zie rubriek 4.4 van de SKP).• Allergie voor gisten, vooral *Saccharomyces boulardii* CNCM I-745. Bijwerkingen: De bijwerkingen worden hieronder geklasseerd per orgaansysteem en volgens de frequentie. Die laatste wordt als volgt gedefinieerd: zeer vaak (≥ 1/10), vaak (≥ 1/100, < 1/10), soms (≥1/1.000, < 1/100), zelden (≥ 1/10.000, < 1/1.000), zeer zelden (< 1/10.000), niet bekend (kan met de beschikbare gegevens niet worden bepaald). Systeemorgaanklasse Frequentie Infecties en parasitaire aandoeningen Zeer zelden : fungemie in patiënten met een centraal veneuze katheter en in patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP), mycose door *Saccharomyces boulardii* CNCM I-745 Frequentie niet bekend : sepsis bij patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP) Immuunsysteemaandoeningen Zeer zelden : anafylactische shock Bloedvataandoeningen Zeer zelden : anafylactische shock Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen Zeer zelden : dyspneu Maagdarmstelselaandoeningen Zeer zelden : verstopping, epigastralgie, abdominaal meteorisme (epigastralgie en abdominaal meteorisme werden waargenomen in klinische studies) Huid- en onderhuidaandoeningen Zeer zelden : jeuk, exantheem, Quincke-oedeem Algemene aandoeningen en toedieningsplaatsstoornissen Zeer zelden : dorst Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijk bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem. België - Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie - Galileelaan 5/03 - B-1210 Brussel - Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN BIOCODEX Benelux NV/SA - Humaniteitslaan 292, 1190 Brussel - België Tel : 0032(0)23704790 NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Enterol 250 mg poeder voor orale suspensie: BE 269026 Enterol 250 mg harde capsules in glazen flesje: BE 269035 Enterol 250 mg harde capsules in blisterverpakking: BE 397896 AFLEVERINGSWIJZE Vrije aflevering DATUM VAN HERZIENING VAN DE TEKST Herziening: 04/2023 - Goedkeuring: 09/2023

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BIOCODEX Benelux

Vaccination as a Tool to Prevent Antimicrobial Resistance: Challenges and Opportunities in Belgium

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Vaccination ; antimicrobial resistance ; health policy.

Executive Summary

Vaccination is one of the most effective preventive healthcare measures, offering significant potential to reduce antimicrobial resistance (AMR). Despite this, Belgium faces systemic challenges in fully integrating vaccination into its healthcare ecosystem. These challenges include fragmented data infrastructure, inequitable access to vaccines, and a lack of coordination among stakeholders.

The present white paper highlights the issues raised during an expert roundtable discussion conducted at the European Plotkin Institute for Vaccinology, ULB, on November 18th, 2024, and outlines actionable recommendations to address these challenges. By improving governance, fostering collaboration, and leveraging data, Belgium can strengthen its vaccination strategy and take a leadership role in combating AMR.

Introduction

Antimicrobial resistance (AMR) is a significant global public health threat, with the World Health Organization (WHO) estimating that bacterial AMR was directly responsible for 1.27 million deaths worldwide and contributed to 4.95 million deaths in 2019. The economic impact of AMR is also substantial, with the World Bank estimating that it could result in additional healthcare costs of up to US$ 1 trillion per year by 2050 (1).

AMR occurs when microorganisms such as bacteria, viruses, fungi, and parasites evolve and develop the ability to resist the effects of antimicrobial drugs that were once effective in treating infections they cause. This resistance makes standard treatments ineffective, leading to persistent infections and increased risk of disease spread, severe illness, and death (1, 2). The primary drivers of AMR are the misuse and overuse of antimicrobials in both humans and animals.

Vaccines have a key role to play against the excessive and/or inappropriate use of antimicrobials. The WHO recently estimated that a better use of vaccines could reduce the number of antibiotics globally needed by 22% or 2.5 billion defined daily doses every year, supporting worldwide efforts to address AMR. To this end, the WHO has specifically developed a strategy for "Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance", as an action plan annexed to the Immunization Agenda 2030 (3).

To mark the 2024 WHO world AMR awareness week, the EPIV-ULB organized, on November 18th, a round table aiming at fostering collective and national commitments in potentiating the role of vaccines in the fight against AMR. As the new AMR National Action Plan (NAP) 2025-2029 is expected early this year, the specific objectives were to delineate the actions that are both first line priorities and reasonably achievable during this next NAP time span, focusing on three critical areas in which Belgium faces systemic challenges meeting the WHO recommendations:

1. How to improve monitoring and data sharing for epidemiological information?
2. How to integrate vaccination more effectively into the primary care ecosystem?
3. How to foster research and development of (future/new) vaccines with AMR impact?

Towards efficient public health databases

In its action framework, the WHO emphasizes the key role of collecting and analyzing relevant data to assess the impact of vaccines on antimicrobial resistance, including linking vaccination data with antimicrobial use and resistance data, with the highest possible level of geographic and demographic accuracy; further insisting on the fact that these data should be included in AMR national action plans.

Fragmented infrastructure & vaccination data

Belgium's healthcare data landscape is fragmented. Regarding vaccination registration alone, the COVID-19 pandemic demonstrated the advantages of a centralized national registry, but this integration was mainly driven by the emergency nature of the situation, and has not been sustained post-pandemic: Flanders, Brussels, and Wallonia each use separate vaccination registration systems (Vaccinet, Vaccicard, eVax, etc.), which are, despite some efforts, not yet fully interoperable. Healthcare professionals must log in to multiple platforms to access a patient's vaccination history, creating unnecessary administrative burden that not only hinders global access to vaccines (without a unified system, both tracking vaccination coverage and ensuring consistent delivery across regions remain challenging), but also leads to an overall loss of medically relevant information. There is a pressing need to extend existing tools/registries and creating efficient & compatible solutions.

As the goal would be to build a data system that facilitates data sharing for healthcare providers but also public health and research, connecting vaccination coverage data with epidemiological, drug consumption, and more economical data such as days of work lost to incapacity would provide valuable insights, especially when focusing on socio-economic impact of vaccines as well as their impact on AMR. Lastly, the problem of the delay in the availability of data themselves was evoked, raising the possible usefulness of collecting and analyzing data on reimbursement, which are more readily accessible and can help to shed a different light on the links between AMR and vaccination.

It is by linking this information that researchers and public health officials can analyze the effectiveness of vaccines in a multidimensional optic (i.e. reduction of AMR, infections, and hospitalizations), helping understanding the broader impact of vaccination programs on public health outcomes, and inform health authorities. For instance, the effectiveness of combinations of vaccines could be assessed as a secondary endpoint for their health impact and potential to reduce AMR. This data can then be used to guide research, vaccination strategies and public health policies.

Efforts oriented towards creating interoperable registries are underway. But this should happen much faster than what is happening today. While collaboration agreements between regions and federal authorities to share data are necessary, the efficiency of discussions is impaired by the multiplicity of regional authorities involved (AVIQ, Vivalis, ONE, Zorg en Gezondheid…) and approval needed by each competent entity. These barriers should be removed in the near future if we want to have an efficient and structured access to these data for healthcare professionals, researchers & public health authorities.

Data protection regulation

Additionally, legal and GDPR constraints currently hinder the mobilization of such data in many ways. Currently, while vaccination data can be used for research, linking it to disease data is restricted by law, which only allows highly aggregated data to be shared, leading to a loss of valuable information.

While investing in vaccination, evaluating and communicating its public health impact requires data demonstrating its efficacy, data sharing remains a sensitive topic, with fears about personal data being disclosed. A constructive public and professional debate on these sensitive questions appears necessary in Belgium.

The newly created health data agency (HDA)'s aim is to make health data more easily, securely and transparently available under Findability, Accessibility, Interoperability, and Reuse (FAIR) Guiding Principles. This new organization should be allowed to grow in its role and find a way to overcome the hurdles discussed above that are currently keeping it to provide the concrete solutions that are awaited for good quality data access. It should be noted that this issue is not unique to Belgium; many countries face similar challenges.

One Health approach

Finally, when it comes to epidemiological monitoring, the collection scale exceeds the national and human health levels and there is a need of both a European approach and a One Health Approach. The National Action plan has typically integrated these two approaches.

For this reason, vaccination surveillance (in both humans and animals) should be a part of the next National Action plan on AMR along with antibiotic resistance and consumption data.

Proposed priority action

1. Prioritize interoperability between vaccination registries across regions or the extension of existing solution to the national level to facilitate data analyses.
2. Establish processes accelerating access to vaccination data, for instance through connection of registration and reimbursement data.
3. Give the HDA the resources and a framework so that they can focus on their core priorities & accelerate speed in having FAIR data for the different stakeholders active in Healthcare.
4. Make vaccination surveillance in both humans and animals part of the next National Action Plan AMR.

Expanding the reach and providing equity in access to vaccines

The WHO action framework also highlights the need to expand the reach of existing vaccines with a known impact on AMR in order to achieve greater coverage, by increasing funding, capacity, functionality and accessibility of supply systems, and by updating the recommendations to include the role of vaccines in combating AMR.

Disincentive for networking in primary care ecosystem

The integration of vaccination into the primary care ecosystem is crucial towards this goal. While General Practitioners (GPs) and pharmacists could and should work together towards improved access to vaccines, current policies foster competition rather than collaboration, including at the financial level. This dynamic is against the extension of accessibility of vaccination point for

the population, especially for those not having a dedicated GP, creating inequity in access. The recent implementation of RSV immunization to prevent infant bronchiolitis in Belgium highlighted this lack of coordination in this integration process. The absence of a unified plan and clear leadership led to significant administrative burden and confusion among stakeholders.

Additionally, and as discussed above, the lack of interoperability of registries is, in itself, an obstacle to penetration and therefore optimal coverage of existing vaccines. Furthermore, the resulting lack of sound data finally lead to inequity in access to vaccines. Indeed, some vaccines, like meningitis type B or RSV vaccines, are not reimbursed (except for pregnant women) because they are deemed not cost-effective which is influenced by the fact that this cost-effectiveness assessment is solely based on the direct effects of vaccination on public health. In turn, the lag between reimbursement and recommendations from National Immunization Technical Advisory Groups put healthcare professionals in uncomfortable position regarding recommending vaccines that are not reimbursed, further limiting their reach and jeopardizing equity in access. The picture might considerably change if indirect (global societal impact) effect of these vaccinations could be considered in such cost-effectiveness assessment.

Limited lifelong vaccination plans

While Belgium has robust childhood vaccination programs, the system falls short for adult vaccination. Currently, there are no clear, lifelong vaccination schedules. Adults aged 18–65, elderly individuals, individuals at risk and pregnant women often do not know which vaccines they should receive and when. Belgian immunization programs should be strengthened to provide proactive support to vaccination throughout the life course.

Vaccine hesitancy, education and awareness gaps

Finally, barriers to vaccine uptake need to be addressed, with a focus on understanding patient reasoning. The proliferation of information sources, including the internet and social media, has shifted the landscape, emphasizing individual freedom over collective good, complicating the communications between healthcare providers and patients regarding vaccination. The COVID-19 pandemic has highlighted the need for healthcare professionals to understand both the importance of vaccination and vaccine hesitancy, and the influence of misinformation and perceived disease severity in the decision process. Additionally, public awareness of adult vaccination remains low, with many individuals unaware of the health and economic benefits of prevention. Even within hospitals (e.g. nurses), vaccination rates have declined post-COVID, underscoring the fact that healthcare professionals (HCP) often lack sufficient training on the importance of vaccination in general, but also more particularly in combating AMR. The importance of prevention is often underemphasized in curricula, despite its proven value.

Proposed priority actions

5. Improve governance between competent authorities to ensure effective vaccination and prevention strategies.
6. Enhance the development of a vaccination schedule for adults, especially targeting pregnant women, the elderly and at risk individuals. Make this schedule part of a health population management approach with defined coverage target.
7. Promote collaboration between GPs and pharmacists to streamline vaccination delivery.
8. Consider including indirect vaccine benefits in the cost-effectiveness analysis.
9. Consider the inclusion of recommended but non-reimbursed vaccines in official vaccination schedules to raise awareness amongst HCP & the population.
10. Increase education in healthcare providers studies curricula about the importance of vaccination and prevention.

Fostering research and development

There is a need to focus on developing vaccines that address the most pressing public health needs, with an emphasis on efficacy. Fostering research and development (R&D) for vaccines to combat antimicrobial resistance (AMR) is a multifaceted challenge in which aligning the perspectives of private companies and public entities is essential.

The challenging new European Clinical Trial Information System (CTIS)

The implementation of the Clinical Trials Information System (CTIS) aims to improve the evaluation of clinical trials by providing a standardized method for assessing data across multinational studies. Belgium, with its center of excellence, has taken a leading role in evaluating vaccine trials.

Scientific advice for clinical trials is available at the national level before filing, and companies need to seek early advice to adapt their research to comply with regulations.

But, while big pharmaceutical companies have the experience to navigate the system, and despite the fact that multiple support mechanisms are being offered, smaller companies often seek advice too late, after they have already begun their clinical trials, which can lead to significant challenges.

Professionalization of ethical committee

The networking of ethical committees is also a challenge, particularly regarding complex products, such as vaccines. In Belgium, ethical committees are often "general" ones, linked to organizational entities (such as hospitals) that might lack the necessary expertise to analyze adequately vaccines trials, leading to inconsistent decisions. To circumvent this, the Netherlands, for instance, have created ethical committees that are dedicated to specific drug groups.

The Belgian ecosystem in a global world

The strengthening of EU regulations versus others (US, China, etc.) is becoming a barrier to European and Belgian biotech entrepreneurship. The Medical Device Regulation has led to a 30% decrease in startups in Belgium, as companies move from EU to the US to avoid regulatory hurdles. However, recent vaccine trials, particularly during the COVID-19 pandemic, have shown that countries like Belgium can have a significant impact by conducting small, specific, targeted clinical trials that can complement larger multicentric, competitive international studies.

Proposed priority actions

11. Develop a centralized public support to CTIS complexities for vaccine trials.
12. Develop a framework for specialized ethical committees on vaccines both in terms of content to be given & timing to provide an answer.
13. Develop a framework where pharmaceutical companies, government and research institutions work together and align on priorities like AMR.
14. Strengthen dialogue between funding agencies and Belgian regulatory authorities to sustainably facilitate (pre-)clinical research in the field of AMR.

Conclusion

We here propose 14 priority actions that are reasonably achievable during the next Belgian AMR National Action Plan timespan.

PRIORITY ACTIONS

1	Prioritize interoperability between vaccination registries across regions or the extension of existing solution to the national level to facilitate data analyses.
2	Establish processes accelerating access to vaccination data, for instance through connection of registration and reimbursement data.
3	Give the HDA the resources and a framework so that they can focus on their core priorities & accelerate speed in having FAIR data for the different stakeholders active in Healthcare.
4	Make vaccination surveillance in both humans and animals part of the next National Action Plan AMR.
5	Improve governance between competent authorities to ensure effective vaccination and prevention strategies.
6	Enhance the development of a vaccination schedule for adults, especially targeting pregnant women, the elderly and at risk individuals. Make this schedule part of a health population management approach with defined coverage target.
7	Promote collaboration between GPs and pharmacists to streamline vaccination delivery.
8	Consider including indirect vaccine benefits in the cost-effectiveness analysis.
9	Consider the inclusion of recommended but non-reimbursed vaccines in official vaccination schedules to raise awareness amongst HCP & the population.
10	Increase education in healthcare providers studies curricula about the importance of vaccination and prevention.
11	Develop a centralized public support to CTIS complexities for vaccine trials.
12	Develop a framework for specialized ethical committees on vaccines both in terms of content to be given & timing to provide an answer.
13	Develop a framework where pharmaceutical companies, government and research institutions work together and align on priorities like AMR.
14	Strengthen dialogue between funding agencies and Belgian regulatory authorities to sustainably facilitate (pre-)clinical research in the field of AMR.

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Si vous ne recommandez pas la vaccination contre le MenB à vos patients,

qui le fera ?

81% des parents considèrent leur médecin comme la source principale d'information concernant la vaccination de leurs enfants (n=800)[2]

BEXSERO
Vaccin méningococcique groupe B
(ADNr, composant, adsorbé)

BEXSERO est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B.[1]

RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT : Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT :** Bexsero suspension injectable en seringue préremplie. Vaccin méningococcique groupe B (ADNr, composant, adsorbé) ; EU/1/12/812/001 ; EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004. Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine recombinante NadA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine de fusion recombinante fHbp de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Vésicules de membrane externe (OMV) de Neisseria meningitidis groupe B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4[2] : 25 microgrammes • [1] produite dans des cellules d'E. coli par la technique de l'ADN recombinant - [2] adsorbée sur hydroxyde d'aluminium (0,5 mg Al^{3+}) - [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H). Pour la liste complète des excipients, voir rubrique 6.1 du RCP complet. **FORME PHARMACEUTIQUE :** Suspension injectable. Suspension liquide blanche opalescente. **DONNÉES CLINIQUES : Indications thérapeutiques :** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par Neisseria meningitidis de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration :** Posologie : **Tableau 1. Résumé de la posologie : Age lors de la première dose :** Nourrissons de 2 à 5 mois[a]. **Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c] - Primovaccination : Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c]. **Age lors de la première dose :** Nourrissons de 6 à 11 mois. **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose au cours de la deuxième année de vie avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose :** Enfants de 12 à 23 mois. **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 2 à 10 ans. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • **Age lors de la première dose : Adolescents (à partir de 11 ans) et adultes*. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • [a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. - [b] En cas de retard, la dose de rappel ne devrait pas être administrée audelà de l'âge de 24 mois. - [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'autres doses de rappel n'ont pas encore été déterminés. - [d] Voir rubrique 5.1 du RCP complet. - * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration : Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, souscutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **Effets indésirables :** Résumé du profil de sécurité : La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69 % à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et Haemophilus influenzae de type b), contre 44 % à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables : Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) - Fréquent : (≥ 1/100 à < 1/10) - Peu fréquent : (≥ 1/1 000 à < 1/100) - Rare : (≥ 1/10 000 à < 1/1 000) - Très rare : (< 1/10 000). Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles). Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans) :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Troubles du métabolisme et de la nutrition : Très fréquent : troubles alimentaires. Affections du système nerveux : Très fréquent : somnolence, pleurs inhabituels, céphalée. Peu fréquent : convulsions (y compris convulsions fébriles). Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections vasculaires : Peu fréquent : pâleur (rare après le rappel). Rare : syndrome de Kawasaki. Affections gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel). Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans). Peu fréquent : eczéma. Rare : urticaire. Affections musculosquelettiques et systémiques : Très fréquent : arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité. Peu fréquent : fièvre (≥ 40 °C). Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois). **Adolescents (à partir de 11 ans) et adultes :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques et systémiques : Très fréquent : myalgies, arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise. Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois). Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique :** Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance - Boîte Postale 97 - 1000 Bruxelles - Madou - Site internet: www.notifieruneffetindesirable.be - e-mail: adr@afmps.be. **Luxembourg :** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ :** GSK Vaccines S.r.l.,Via Fiorentina 1, 53100 Sienne, Italie. **DATE D'APPROBATION DU TEXTE :** 26/04/2023 (v15). **MODE DE DELIVRANCE :** Sur prescription médicale.

Références : 1. SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

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Beschermt de baby **tijdens het volledige RSV-seizoen**.[1]

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▼Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden. Zie rubriek 4.8 voor het rapporteren van bijwerkingen. NAAM VAN HET GENEESMIDDEL Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit. Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit. Elke voorgevulde spuit bevat 50 mg nirsevimab in 0,5 ml (100 mg/ml). Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit. Elke voorgevulde spuit bevat 100 mg nirsevimab in 1 ml (100 mg/ml). Nirsevimab is een gehumaniseerd immunoglobuline G1 kappa (IgG1κ) monoklonaal antilichaam dat geproduceerd wordt uit ovariumcellen van de Chinese hamster (Chinese hamster ovary, CHO) met behulp van recombinant-DNA-technologie. Hulpstoffen met bekend effect: Dit middel bevat 0,1 mg polysorbaat 80 (E433) in elke doseringseenheid van 50 mg (0,5 ml) en 0,2 mg in elke doseringseenheid van 100 mg (1 ml). FARMACEUTISCHE VORM Oplossing voor injectie (injectie). Heldere tot opalescente, kleurloze tot gele oplossing met een pH-waarde van 6,0. THERAPEUTISCHE INDICATIES Beyfortus is geïndiceerd voor de preventie van lagere-luchtwegaandoeningen veroorzaakt door het respiratoir syncytieel virus (RSV) bij: - Pasgeborenen en zuigelingen tijdens hun eerste RSV-seizoen. - Kinderen tot 24 maanden oud die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen (zie rubriek 5.1). Beyfortus dient te worden gebruikt in overeenstemming met officiële aanbevelingen. DOSERING EN WIJZE VAN TOEDIENING Dosering Zuigelingen tijdens hun eerste RSV-seizoen De aanbevolen dosering is een enkelvoudige dosis van 50 mg intramusculair toegediend voor zuigelingen met een lichaamsgewicht < 5 kg en een enkelvoudige dosis van 100 mg intramusculair toegediend voor zuigelingen met een lichaamsgewicht ≥ 5 kg. Beyfortus moet worden toegediend vanaf de geboorte voor zuigelingen die tijdens het RSV seizoen zijn geboren. Voor diegenen die buiten het seizoen geboren zijn, dient Beyfortus idealiter te worden toegediend voorafgaand aan het RSV-seizoen. De dosering bij zuigelingen met een lichaamsgewicht van 1,0 kg tot < 1,6 kg is gebaseerd op extrapolatie. Hiervoor zijn geen klinische gegevens beschikbaar. Naar verwachting zal blootstelling bij zuigelingen van < 1 kg hogere blootstellingen opleveren dan bij zuigelingen die meer wegen. De voordelen en risico's van het gebruik van nirsevimab bij zuigelingen van < 29 weken) jonger dan 8 weken. Er zijn geen klinische gegevens beschikbaar over zuigelingen met een postmenstruele leeftijd (zwangerschapsduur bij geboorte plus chronologische leeftijd) van minder dan 32 weken (zie rubriek 5.1). Kinderen die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen De aanbevolen dosis is een enkelvoudige dosis van 200 mg intramusculair toegediend als twee injecties (2 x 100 mg). Beyfortus dient idealiter te worden toegediend voorafgaand aan aanvang van het tweede RSV-seizoen. Voor personen die een hartoperatie ondergaan met cardiopulmonale bypass, kan zodra de persoon stabiel is na de operatie een extra dosis toegediend worden om adequate nirsevimab-serumspiegels te garanderen. Als dit binnen 90 dagen na ontvangst van de eerste dosis Beyfortus plaatsvindt, dient de aanvullende dosis tijdens het eerste RSV-seizoen 50 mg of 100 mg te zijn, afhankelijk van het lichaamsgewicht, of 200 mg tijdens het tweede RSV-seizoen. Als er meer dan 90 dagen zijn verstreken sinds de eerste dosis, kan de aanvullende dosis een enkelvoudige dosis van 50 mg zijn, ongeacht het lichaamsgewicht, tijdens het Eerste RSV-seizoen of 100 mg tijdens het tweede RSV-seizoen om de rest van het RSV seizoen te dekken. De veiligheid en werkzaamheid van nirsevimab bij kinderen in de leeftijd van 2 tot 18 jaar zijn niet vastgesteld. Er zijn geen gegevens beschikbaar. Wijze van toediening Beyfortus is alleen voor intramusculaire injectie. Het wordt intramusculair toegediend, bij voorkeur in de anterolaterale zijde van de dij. De gluteale spieren mogen niet routinematig als injectieplaats worden gebruikt vanwege het risico op beschadiging van de ischiaszenuw. Zijn er twee injecties nodig, gebruik dan twee verschillende injectieplaatsen. Zie rubriek 6.6 voor instructies inzake speciale hanteringsvereisten. CONTRA-INDICATIES Overgevoeligheid voor de werkzame stof of voor een van de in rubriek 6.1 vermelde hulpstoffen. BIJWERKINGEN Samenvatting van het veiligheidsprofiel De meest voorkomende bijwerking was rash (0,7%) die binnen 14 dagen na toediening optrad. Het merendeel van deze bijwerking was licht tot matig van intensiteit. Aanvullend werden pyrexie en injectieplaatsreacties binnen 7 dagen na toediening gemeld met een prevalentie van respectievelijk 0,5% en 0,3%. Injectieplaatsreacties waren niet ernstig. Lijst van bijwerkingen Hieronder staan de bijwerkingen die zijn gemeld bij 2.966 voldragen en premature zuigelingen (zwangerschapsduur, Gestational Age (GA) ≥ 29 weken) die nirsevimab kregen in klinische onderzoeken en tijdens het toezicht na het in de handel brengen. De bijwerkingen die zijn gemeld in gecontroleerde klinische onderzoeken zijn ingedeeld volgens systeem/orgaanklasse (SOC) van MedDRA. Binnen elke SOC zijn voorkeurstermen gerangschikt op afnemende frequentie en vervolgens op afnemende ernst. De frequenties van optreden van bijwerkingen wordt gedefinieerd als: zeer vaak (≥ 1/10); vaak (≥ 1/100 tot < 1/10); soms (≥ 1/1.000 tot < 1/100); zelden (≥ 1/10.000 tot < 1/1.000); zeer zelden (< 1/10.000) en niet bekend (kan met de beschikbare gegevens niet worden bepaald). Immunsysteemaandoeningen · Niet bekend - Overgevoeligheid A Bijwerkingen uit spontane melding Huid- en onderhuidaandoeningen · Soms – Rash B Rash is gedefinieerd door de volgende gegroepeerde voorkeurstermen: rash, maculo-papulaire rash, vlekkerige rash Algemene aandoeningen en toedieningsplaatsstoornissen · Soms – Injectieplaatsreactie C; Pyrexie C Injectieplaatsreactie is gedefinieerd door de volgende gegroepeerde voorkeurstermen: injectieplaatsreactie, injectieplaatspijn, injectieplaatsverharding, injectieplaatsoedeem, zwelling van injectieplaats Zuigelingen met een verhoogd risico op ernstige RSV-ziekte in hun eerste seizoen De veiligheid is onderzocht in MEDLEY bij 918 zuigelingen met een verhoogd risico op ernstige RSV ziekte, onder wie 196 extreem premature zuigelingen (GA < 29 weken) en 306 zuigelingen met chronische longziekte van prematuriteit of hemodynamisch significante aangeboren hartziekte die hun eerste RSV seizoen ingingen, die nirsevimab (n=614) of palivizumab (n=304) kregen. Het veiligheidsprofiel van nirsevimab bij zuigelingen die nirsevimab ontvingen in hun eerste RSV-seizoen was vergelijkbaar met het vergelijkende geneesmiddel palivizumab en consistent met het veiligheidsprofiel van nirsevimab bij voldragen en premature zuigelingen GA ≥ 29 weken (D5290C00003 en MELODY). Zuigelingen die kwetsbaar blijven voor ernstige RSV-ziekte in hun tweede seizoen De veiligheid werd beoordeeld in MEDLEY bij 220 kinderen met chronische longziekte van prematuriteit of hemodynamisch significante congenitale hartziekte die nirsevimab of palivizumab kregen in hun eerste RSV-seizoen en vervolgens nirsevimab kregen in hun tweede RSV-seizoen (180 proefpersonen kregen nirsevimab in zowel seizoen 1 als 2, 40 kregen palivizumab in seizoen 1 en nirsevimab in seizoen 2). Het veiligheidsprofiel van nirsevimab bij kinderen die nirsevimab kregen in hun tweede RSV-seizoen was consistent met het veiligheidsprofiel van nirsevimab bij voldragen en premature zuigelingen GA ≥29 weken (D5290C00003 en MELODY). De veiligheid werd ook onderzocht in MUSIC, een open-label onderzoek zonder controlegroep met enkelvoudige dosis bij 100 immuungecompromitteerde zuigelingen en kinderen ≤24 maanden die nirsevimab ontvingen in hun eerste of tweede RSV-seizoen. Dit omvatte deelnemers met ten minste een van de volgende aandoeningen: immunodeficiëntie (gecombineerd, antilichaam of andere etiologie) (n=33); systemische behandeling met hoge doses corticosteroïden (n=29); orgaan- of beenmergtransplantatie (n=16); gebruik van immunosuppressieve chemotherapie (n=20); andere immunosuppressieve behandeling (n=15) en HIV-infectie (n=8). Het veiligheidsprofiel van nirsevimab was consistent met wat werd verwacht voor een populatie van immuungecompromitteerde kinderen en met het veiligheidsprofiel van nirsevimab bij voldragen en premature zuigelingen GA ≥29 weken (D5290C00003 en MELODY). Het veiligheidsprofiel van nirsevimab bij kinderen tijdens hun tweede RSV-seizoen was consistent met het veiligheidsprofiel van nirsevimab dat werd waargenomen tijdens hun eerste RSV-seizoen. Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via: België: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten: www.fagg.be – Afdeling Vigilantie: Website: www.eenbijwerkingmelden.be – e-mail: adr@fagg-afmps.be HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly, Frankrijk NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN EU/1/22/1689/001 - 50 mg, 1 voorgevulde spuit voor eenmalig gebruik EU/1/22/1689/002 - 50 mg, 1 voorgevulde spuit voor eenmalig gebruik met naalden EU/1/22/1689/003 - 50 mg, 5 voorgevulde spuiten voor eenmalig gebruik EU/1/22/1689/004 - 100 mg, 1 voorgevulde spuit voor eenmalig gebruik EU/1/22/1689/005 - 100 mg, 1 voorgevulde spuit voor eenmalig gebruik met naalden EU/1/22/1689/006 - 100 mg, 5 voorgevulde spuiten voor eenmalig gebruik DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING Datum van eerste verlening van de vergunning: 31 oktober 2022 DATUM VAN HERZIENING VAN DE TEKST Goedkeuringsdatum: 01/2025. Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau http://www.ema.europa.eu

* tijdens hun eerste RSV-seizoen.

Referentie:
1. Beyfortus SKP, jan 2025.

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