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Newborn Screening

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Paediatric Pharmacotherapy for Common Obesity: Position Statement of a Tertiary Multidisciplinary Paediatric Rehabilitation Centre for Chronic Diseases

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1. Harb et al, Systematic review and meta-analysis confirm effectiveness of L reuteri for infantile colic. J Pediatr Gastroenterol Nutr 2016. **2.** Coccorullo et al,L reuteri DSM 17938 in infants with chronic constipation: a double-blind, randomized, placebo controlled study. J pediatr 2010 ; 157: 598-602. **3.** Indrio et al, L reuteri accelerates gastric emptying and improves regurgitation in infants, Eur J Clin Invest 2010. **4.** Vivatvakin et al,Effect of a whey-predominant starter formula containing LCPUFAs and oligosaccharides (FOS/GOS) o GI comfort in infants. Asia Poe J Clin Nutr 2010 ; 19(4): 473-80. **5.** Infante et al, Modi cation of stool's water content in constipated infants: management with an adapted infant formula. Nutr J 2011; 10:55-8. **6.** Chevalier B et al. Arch Pediatr 2009; 16(4):343-352 . **7.** Flittner et al. Feeding commercial soy formula or partially hydrolysate, low lactose formula resolves symptoms in fussy infants. Pediatric ressearch 2007 ; 62(4) : 520.

* Nutrients 2021: 13;3336, Vandenplas et al. An observational Real-life study with a new Infant formula in infants with Functional gastro-intestinal disorders.

Ce document est exclusivement réservé à l'information des professionnels de la santé.

Avis important pour tous les (para) médicaux: L'Organisation Mondiale de la Santé (OMS) recommande d'informer les femmes enceintes et les mamans de nourrissons sur les avantages et la supériorité de l'allaitement maternel, et plus particulièrement sur le fait qu'il fournit la meilleure alimentation et la meilleure protection contre les maladies infantiles. Les mères devraient recevoir des conseils sur la préparation, et le maintien de la lactation, avec un accent particulier sur l'importance d'une alimentation équilibrée pendant la grossesse et après l'accouchement. L'introduction inutile du biberon, d'autres aliments et boissons, doit être découragée car cela aura un effet négatif sur l'allaitement au sein. De même, les mères doivent être averties de la difficulté de revenir sur la décision de ne pas allaiter. Avant de conseiller une mère d'utiliser un lait infantile, elle doit être informée sur les conséquences sociales et financières de sa décision: par exemple, un bébé qui est exclusivement nourri au biberon nécessite environ 450g de poudre par semaine. Dès lors, les circonstances et le coût pour la famille doivent être pris en considération. Les mamans doivent savoir que l'allaitement au sein n'est pas seulement le meilleur aliment pour leur bébé mais aussi le plus économique. Si la décision d'utiliser une préparation pour nourrissons est prise, il est important de donner aux parents des instructions correctes sur les méthodes de préparation, en soulignant que l'eau non bouillie, des bouteilles non stérilisées ou une dilution incorrecte peuvent rendre le bébé malade. **Avec les compliments de Nestlé.** ER: K. Desmedt, Nestlé Belgilux SA/NV, Rue de Birminghamstraat 221 - 1070 Bruxelles/Brussel, BCE/KBO 0402.231.383. PID4066 – Septembre 2026.

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Referenties: 1. Data on file, Danone, 2025. **2.** Oude Nijhuis M, et al. Growth, safety and tolerance of an new hydrolysed rice formula in infants with CMA poster presentation p52 EAACI PAAM. V.U.: N.V. Danone Belux, Werkhuizenkaai 160, 1000 Brussel

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The silent troublemakers… disruptors!

Since the 1960s, the environments in which children grow up have undergone profound changes, with plastics, food packaging, cosmetics, treated textiles, toys and building materials becoming commonplace. Among the tens of thousands of chemicals that surround us, it is estimated that between 800 and 1,400 possess endocrine-disrupting properties. These endocrine disruptors (EDs) are exogenous substances capable of interfering with the synthesis, secretion, transport or action of hormones. The paradox of their toxicity is that it does not follow the classic dose-response pattern: a low dose can be more harmful than a high one, effects can occur long after exposure and above all, the window of exposure rather than the dose often determines the type of damage. This is precisely why children, and even more so foetuses, are the most vulnerable. The first 1000 days, from conception to around the age of two, constitute a critical period of hormonal development, including sexual differentiation, brain maturation, and the establishment of the thyroid and metabolic axes. In utero, the placenta is not an impermeable barrier to these substances. In infants, diet and feeding containers, teether and toys brought to the mouth and the greater skin contact relative to body mass are additional factors of exposure. The effects of transgenerational exposure via parental gametes are also under discussion. Biomonitoring studies carried out in Belgium such as the Vlaams Humane-Biomonitoring Programme (VHBP) in Flanders and the biomonitoring campaign by the Public Service Scientific Institute (ISSEP) in Wallonia have confirmed the observation done in many countries: the entire population is impregnated with many substances such as bisphenols, phthalates, parabens, perfluorinated compounds (PFAS), flame retardants and glycol ethers and the higher impregnation levels are found in children (1, 2).

The paediatric data is gradually accumulating. Associations are described as plausible and, for certain substances, probable with cryptorchidism or hypospadias, precocious puberty (particularly in girls), neurodevelopmental disorders (ADHD, autism spectrum disorders, reduced IQ), obesity and metabolic disorders, thyroid diseases, and even certain types of leukaemia and childhood cancers (3, 4). None of these associations amounts to perfect experimental causality, but all call for caution, responsibility and greater awareness. This issue of the Belgian Journal of Paediatrics aims to address this concern. Our "Made In Belgium" section summarises the thesis of Christophe Barrea on the "Impacts of antenatal exposure to a mixture of endocrine disruptors on cognitive and neuromotor functions in preschool children". His work supports negative associations between prenatal exposure to EDs and specific cognitive functions in children. As often reported in the literature, his findings illustrate a sex-specific effect and highlight the value of analyses that more closely reflect real-world health scenarios by assessing the effects of mixtures rather than the effect of an isolated substance. The journal also wants to highlight the awareness campaign recently launched by the Federal Public Service for Public Health, Food Chain Safety and the Environment on protecting children from endocrine disruptors (5).

Due to the complexity of this subject, it is essential that first-line practitioners and the entire paediatric community are involved. Three potential pitfalls must be avoided. The first is denial: using the lack of absolute proof as an excuse to say nothing, when, as toxicologists remind us, the absence of evidence of harm must not be confused with evidence of the absence of harm. The second is alarmism: turning every consultation into a catalogue of dietary restrictions, making parents feel guilty for not having chosen the chemical composition of their environment. The third, undoubtedly the most insidious, is delegation: treating this as an issue for toxicologists and regulators alone and failing to pass the message on to our patients and their families. Paediatricians have an irreplaceable

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role that neither the epidemiologist nor the legislator can fulfil. They know the history of the child and the family, they watch the windows of vulnerability pass one by one — conception, pregnancy, breastfeeding, complementary feeding, starting school — and they remain a trusted source of health information for parents. Counselling on environmental health should gradually achieve the same status as advice on nutrition, sleep, or screen time. Concrete levers exist and only need to be relayed: prefer glass and stainless steel to plastics, in particular when heating food; limit young children's contact with non-essential cosmetics; ventilate and dust interiors, where EDs accumulate in household dust; favour fresh, minimally processed foods, less exposed to food-contact materials. These simple, realistic messages must be accompanied by an essential reminder: the benefits of breastfeeding far outweigh the risks associated with the low levels of contamination in breast milk.

This approach by local stakeholders does not absolve health authorities and regulators of their responsibility. For a long time, the European Union has been a pioneer in introducing regulations based on a reversal of the burden of proof, requiring the industry to demonstrate the safety of a substance before it is placed on the market. Today, the European Commission has launched a series of legislative simplification "Omnibus packages". Some amendments have been introduced or are under discussion to relax labelling requirements, facilitate temporary derogations for previously banned substances and weaken the precautionary principle on which European plant health regulations were founded (6,7).

EDs call for a paradigm shift: at a time when we are gaining ever better control of the infectious and nutritional diseases in children, it is their chemical environment that is silently becoming one of the major determinants of their future health. Paediatrics still has a role to play in raising awareness of this issue and ensuring it is heard at every consultation and at all levels of our societies. With this editorial introduction, we hope you enjoy reading our autumn issue and find it informative.

Christophe Chantrain and Marc Raes

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RESEARCH ARTICLE

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Quality Assessment of the Collaboration and Experiences of General Practitioners and Allied Healthcare Providers Supported by a Liaison Team in Pediatric Palliative Care: A Single-centre Survey

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Keywords

Paediatric palliative care; Primary care; Home-based care: Liaison team

Abstract

Background
Paediatric palliative care is a holistic approach to the care for children with life-limiting or life-threatening conditions and involves collaboration among general practitioners, home care nurses, and physiotherapists. However, many of these healthcare providers lack experience in paediatric palliative care. In our centre, this care is coordinated by the liaison team KITES.

Aim
To evaluate the quality of collaboration between primary healthcare providers and KITES, and to identify perceived needs and opportunities for improvement.

Design
A cross-sectional survey study using a validated questionnaire.

Setting/participants
General practitioners, home care nurses, and physiotherapists who provided palliative care to a child (< 18 years) in collaboration with the palliative liaison team KITES in the past three years.

Results
Response rate was 38%. Overall, only 3% had received training in paediatric palliative care. Almost all health care providers considered symptom control and emotional support very important. Bereavement care was more important for general practitioners than for allied health care providers. Support provided by KITES was mainly focused on symptom management and organization and coordination of care. Psychological support provided was more constrained. Collaboration and communication between general practitioners, nurses and KITES was well-established, while contact with the treating paediatrician was limited.

Conclusions
Health care providers lack training in paediatric palliative care. Support by the liaison team focused mainly on symptoms and organization of care. The psychological support provided by the liaison team and the involvement of the treating paediatrician could be improved.

Introduction

Palliative care is a well-known concept in adult medicine, defined by the World Health Organisation (WHO) as 'an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual' (1). Although children are considered in the definition, paediatric palliative care (PPC) presents additional challenges, such as the wide range of cognitive abilities and emotional maturity in the paediatric population (2). Therefore, this WHO definition has been adopted by the International Meeting for Palliative Care in Children, Trento (IMPaCCT), defining palliative care in children as 'the active total care of the child's body, mind and spirit'. PPC should start at the time of diagnosis and should continue throughout the course of the disease, which may lead to long trajectories, coinciding with treatment directed at the disease (3). PPC should also involve giving support to the family, including siblings. Moreover, as parents are central to the child's well-being, they should be involved in all aspects. In 2022, the IMPaCCT standards were revised through the Global Overview – Paediatric Palliative Care Standards (GO-PPaCS), taking into account different settings and resources (4). Complex chronic conditions – grouped by Chris Feudtner

TABLE 1: Degree of importance of certain care aspects scored by GPs and allied HCPs.

Degree of importance	Irrelevant (n)		No importance (n)		Very low importance (n)		Low importance (n)		Moderate importance (n)		High importance (n)		Paramount importance (n)	
	GP	HCP	GP	HCP	GP	HCP	GP	HCP	GP	HCP	GP	HCP	GP	HCP
Pain - and symptom control	0	0	0	0	0	1	0	1	1	1	14	3	11	20
Other comfort care	0	1	0	0	0	0	0	1	3	1	14	4	9	20
Emotional support of the child	1	1	0	0	0	1	1	0	3	0	13	6	8	19
Emotional support of the parents	0	0	0	0	0	0	0	1	2	0	11	7	13	19
Emotional support of the siblings	0	3	0	0	0	0	3	0	5	4	11	9	7	11
Bereavement care after the child has died *	0	5	0	0	0	1	0	4	3	5	14	7	9	5
Domestic help	2	7	3	4	6	1	5	4	5	7	5	2	0	2
Assistance with administration	0	9	1	2	3	3	2	3	12	6	8	4	0	0
Organization and start-up of care	0	4	0	0	0	2	1	2	11	3	7	7	7	9
Coordination of care	0	4	0	0	0	1	3	2	8	3	12	8	3	9
Providing medical equipment**	0	5	0	1	1	0	4	2	10	3	8	9	3	7
Providing other equipment	0	3	1	0	2	0	8	0	9	0	4	0	4	1

GP: general practitioner; HCP: health care professional; n: number of GPs or number of allied HCPs;
*Comparison high or paramount importance versus others between GPs and HCPs: p-value 0.011; **p-value 0.045

according to the affected organ system (neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, haematologic or immunologic, metabolic, congenital or genetic, malignant, premature/neonatal, or other conditions), were further classified into 3 categories: i.e. life-threatening conditions (with high probability of premature death), life-limiting conditions (with no reasonable hope of cure and expected premature death), and terminal illness (when death is inevitable for a life-threatening or life-limiting disease) (5). Although PPC may seem rare, its importance becomes evident when considering that children aged 1–18 represent over 30% of the world's population, and life-threatening illnesses such as cancer cause roughly 2.5 million deaths among children each year (6, 7). Curative treatment is not always the most beneficial for a child's well-being; sometimes pain relief and supportive care become more important to enhance quality of life (8–9). Early integration of PPC for children diagnosed with a progressive and/or life-limiting condition, rather than waiting until curative options are exhausted, is therefore recommended (3, 10). Home-based PPC is particularly important since it is associated with improved quality of life, and with a reduced symptom burden (11). In Belgium, home-based PPC is coordinated through eight liaison organizations that connect hospital services with home care: KITES (UZ Leuven), KOESTER (UZ Ghent), Oever (UZ Antwerpen), ComfortKIDZ (UZ Brussel), Globul'home (UZ Brussel), Equipe Interface pédiatrique (UCL Saint-Luc), Equipe Luciole (CHC MontLégia), and the paediatric liaison team (CHR-CHU Citadelle, Liège) (12). These liaison teams comprise specialized nurses, doctors, and sometimes psychologists and social workers, all trained to guide families and healthcare providers (HCPs) in PPC. Although most HCPs including home care nurses and general practitioners (GPs) lack specialized training in PPC and have only limited experience in the field, their frequent contact with children and families in PPC places them in a unique position in this unique and difficult care (13, 14). Therefore, liaison teams aim to support them with knowledge, practical training, and ongoing guidance (12). Between 2010 and 2014, a total of 3,607 children and adolescents were cared for by the Belgian liaison teams. Fifty percent of these patients had an oncological condition, while 27% were diagnosed with a neurological or metabolic disorder. During this period, 428 of the patients passed away, 51% of whom died at home (15). In recent years, the proportion of children with neurological disorders has increased to 38% in 2023, while the relative proportion of oncological patients has decreased (25% in 2023) (16). Research on HCP experiences with PPC is limited, often involving small study groups, few prospective data. Additionally, studies mainly focus on GPs while underrepresenting other HCPs such as home care nurses (17-19). Using a retrospective survey, we evaluated both the experience of GPs and allied HCPs with PPC, and the quality of collaboration between them and KITES, the liaison

TABLE 2: Prevalence of symptoms during palliative and terminal phases, and which symptoms were difficult to control according to GPs and allied HCPs.

Symptom	Palliative phase (n)		Terminal phase (n)		Difficult to control (n)	
	GP	HCP	GP	HCP	GP	HCP
Pain	15	18	9	10	4	6
Decreased general condition caused by disease progression	15	17	10	11	6	8
Dyspnoea	13	10	11	11	7	8
Anorexia	12	12	5	5	0	0
Nausea	7	10	4	6	2	2
Constipation	4	7	4	3	0	0
Fear	7	12	3	8	5	7
Asthenia	9	18	5	12	4	6
Skill loss	7	11	5	12	7	7
Dysphagia	4	7	2	7	1	2
Rattling breath*	4	7	3	12	0	5
Sadness	4	9	2	7	1	4
Mental decline	2	2	3	3	2	2
Anger	2	6	1	3	2	2

GP: general practitioner; HCP: health care professional; n: number of GPs or number of allied HCPs;
*Comparison between GPs and HCPs in terminal phase: p-value 0.0411

team our hospital partners with, aiming at identifying areas for improvement.

Methods

A retrospective cross-sectional survey was performed using the questionnaire developed and published by van der Geest et al. (19). The study was approved by the Onderzoek Begeleidings Commissie of KU Leuven (MP010652 for GPs in 2019 and MP19227 for allied HCPs in 2022). HCPs were invited to participate if they had provided palliative care to a child under the age of 18 years, with assistance from KITES in the 3 years before the survey. The questionnaire was sent to the HCPs by KITES via email and regular post, and was distributed in two stages: August–November 2019 for GPs and March 2023–November 2024 for allied HCPs. Paper questionnaires were returned anonymously to KITES, online questionnaires were collected via Google Form (GPs) and Qualtrics (allied HCPs). After one month, both groups received a reminder to complete the survey. Analysis was performed by the first authors (KD and MT). The questionnaire inquired about a) general information and training in PPC; b) HCPs' role in PPC including responsibilities and challenges; c) collaboration with other HCPs and communication with families; d) support from KITES and 5) personal reflection on the palliative care process. We used descriptive statistics for all variables and to present the answers provided. Median age of HCPs and patients were compared using a Mann-Whitney U test. Percentages were calculated based on the number of HCPs who answered to the specific question. To evaluate differences between GPs and allied HCPs, we compared the proportion of professionals who rated items as being of "high" or "paramount" importance to those rating them as of "very low or "low" importance. For categorical data (Yes/No or present/absent), we compared the proportion of "yes" or "present" responses relative to the total number of responses. Ratios were compared by the Fisher's exact test. A p-value < 0.05 was considered statistically significant.

Results

1. Population

In total, 74 GPs met the inclusion criteria and were contacted. Twenty-six (12 men, 14 women) responded, resulting in a 38% response rate. Their ages ranged from 30 to 68 years, with a median of 24.5 years of professional experience. Sixteen GPs (62%) had completed training in palliative care, though none had received training specifically focused on PPC. They had collectively cared for 30 children in the past three years, with a median of one and a maximum of three patients per physician, which was at least 10 times less than adult patients. The underlying pathology was cancer in 53% of the patients. Their median age at death was 11 years (ranged from 5 days to 18 years). In the second part of the survey 85 allied HCPs were contacted. Thirty-four (30 women, 4 men) completed the questionnaire (response rate 40%): 23 nurses, 9 physiotherapists, and 1 social worker; one did not specify his profession. The median age was 44 years, with a median of 20 years of experience. Twelve allied HCPs (35.3%) had training in palliative care, of whom 2 specifically in PPC. They had treated 43 patients in the preceding three years, which

TABLE 3: Collaboration with different professionals and its importance according to GPs and allied HCPs.

	Collaborated with this professional (n)		Considered as one of the most important partners (n)		Collaboration wanted but did not take place (n)	
	GP	HCP	GP	HCP	GP	HCP
KITES	24	20	21	21	1	2
Home nurse	19	6	19	8	0	2
Treating specialist	17	6	11	9	6	8
(Other) general practitioner	11	15	7	14	1	3
Physiotherapist	6	7	3	4	1	1
Paediatrician	5	4	3	2	1	2
Pharmacy	4	5	3	3	0	0
General practitioner in training	1	0	0	0	0	0
Social worker	1	0	1	0	0	0
Occupational therapist	1	0	0	0	0	0
School	0	0	0	0	1	0
Educator	1	1	1	0	0	0

GP: general practitioner; HCP: health care professional; n: number of GPs or number of allied HCPs

was for most allied HCPs at least 10 to 20 times less than adult palliative patients they had cared for. Although this survey included another group of patients, the underlying diagnosis was again cancer in 52% of the patients. The median age at death was 7.5 years (ranged from 3 months to 25 years). Five allied HCPs were present at the time of death. Five patients were still alive at the time of this questionnaire. GPs were mostly contacted by the family (38%), KITES (38%) or the treating specialist (35%). Similarly, allied HCPs were almost equally contacted by the family (56%) or by KITES (59%) but less frequently by the treating specialist (21%).

2. Symptoms, symptom control and other aspects of care

All HCPs expressed a strong sense of responsibility throughout the child's palliative trajectory. Both, GPs and allied HCPs considered pain and symptom control extremely important, as well as emotional support of the child, the parents and in most cases also the siblings (table 1). They felt quite confident providing this support. Bereavement care after the child's death was valued more by GPs ($p = 0.0111$). On the other hand, there was less agreement between HCPs on the importance of logistic help (such as organization of care, domestic help, etc.). The most frequently reported symptoms in the palliative phase were pain, decreased general condition, dyspnoea, and anorexia. Allied HCPs also reported fear, skill loss, and sadness (table 2). In the terminal phase, these symptoms persisted. Additionally, rattling breath was reported significantly more often by allied HCPs than by GPs in this phase ($p = 0.04$). Skill loss was most frequently identified as a difficult to manage symptom (by all GPs who reported skill loss as an important symptom, and 60% of allied HCPs). Decreased general condition, dyspnoea and fear were also reported as difficult to control by more than half of the professionals. In contrast, only 30% of them considered pain as difficult to control (table 2).

3. Collaboration and communication

Most participants identified KITES, the GP and home nurses as highly important partners. This collaboration was perceived as well-established (table 3) and of good or excellent quality. On the other hand, collaboration with treating specialists was also considered important but was sometimes lacking (table 3). Collaboration with physiotherapists, occupational therapists and social workers seem much less important to non-existing. Support provided by KITES focused mainly on symptom management and organization/coordination of care, while the psychological support was rated as limited. Additionally, allied HCPs were supported more for technical skills and were assisted more directly in giving care ($p=0.0014$ and $p=0.0468$ respectively). Of note, these results should be interpreted with caution, since the response rate by allied HCPs for this section was extremely low (32%).

4. Experienced feelings

The most prominent feeling of HCPs was powerlessness, both during the palliative and terminal phase (table 4). Allied HCPs reported sadness during the terminal phase more often and acceptance after death less frequently than GPs. With time evolving, the feeling of acceptance grew in both groups and had become the most frequently reported feeling at the time of completing the questionnaire.

TABLE 4: Experienced feelings during different phases of care by GPs and allied HCPs.

Experienced feelings	Palliative phase (n)		Terminal phase (n)		After death (n)		At the moment of the questionnaire (n)	
	GP	HCP	GP	HCP	GP	HCP	GP	HCP
Fear	2	4	4	2	0	0	0	0
Sadness	5	7	8	13	12	12	1	5
Powerlessness	15	16	14	14	3	7	4	3
Anger	1	2	0	0	1	2	0	1
Combativeness	1	3	0	1	0	0	0	1
Acceptance	7	4	6	4	15	9	18	11
Fatigue	2	3	2	1	3	2	0	0
Other: Frustration	1	-	1	-	0	-	0	-
Other: Insecurity	1	1	0	0	0	0	0	0
Other: Supportive	1	-	0	-	0	-	0	-
Other: "Feeling of wanting to do it very well"	1	-	0	-	0	-	0	-
Other: Relief	0	-	0	-	1	1	0	-
Other: Gratitude	0	1	0	-	0	1	1	-
Other: Doubt	-	0	-	0	-	0	-	1
Other: Resignation	-	0	-	0	-	0	-	1

GP: general practitioner; HCP: health care professional; n: number of GPs or number of allied HCPs

Discussion

Main findings

This study assessed how primary care providers experienced support from the liaison team KITES when delivering PPC at home. Consistent with previous reports documenting limited education, both GPs and allied HCPs reported very limited exposure and training (18, 20-21). None of the physicians and only 3% of allied HCPs had received PPC-specific training. However, lack of training may contribute to challenges in symptom management and comprehensive care, emphasizing the importance of support by a liaison team. The value of multidisciplinary collaboration between GPs, specialized nurses, physical therapists, psychologists, and social workers to ensure high-quality PPC is well known but GPs often struggle to align with specialized teams and hospitals (12, 19, 22-24). However, previous research indicated that poor communication could lead to misunderstandings and fragmented care, while clear information exchange reduces uncertainty and anxiety among parents and caregivers and is essential for high-quality PPC (17, 24-26). Nonetheless, guidelines and standardized protocols to improve communication are lacking (18). Telehealth and eHealth can improve accessibility and coordination in PPC, while video consultations and mobile applications may reduce hospital visits and facilitate communication among HCPs and families (23, 27-29). Yet, the implementation of these tools faces challenges such as limited training, resistance among some HCPs, and unequal access (27, 28). Our survey showed that collaboration between KITES, families, and care providers generally worked well, but confirmed that communication with treating specialists was more difficult, even though a specialized liaison team was involved. Pain and symptom management, comfort care, and emotional support were identified as central components of PPC. Although some HCPs reported uncertainty, most felt comfortable providing care. Support from KITES centred on symptom management, organizational aspects, and assisting allied HCPs with technical skills and giving care. This aligns with literature indicating that GPs typically coordinate care, while nurses provide daily care and physical therapists promote physical well-being through mobility promotion and pain management (12, 21, 23, 30, 31). On the other hand, psychological support by KITES for HCPs - although crucial - was often perceived as insufficient. This disparity may reflect limited resources related to psychological care, contributing to challenges in addressing the emotional needs of patients and their families. Emotional stress among HCPs is also widely documented and was evident in our survey too (11, 12, 15, 17–19, 20, 21, 32). After the child's death, emotions often shifted from sadness towards acceptance, but allied HCPs, particularly nurses, reported more intense grief. This may be explained by several factors: the death of a child is inherently experienced as highly unnatural, and nurses are frequently more closely involved in the child's direct care, sometimes even with the child at the time of death. Psychological care for patients, families, and HCPs should therefore be strengthened within KITES, and would be according to the IMPaCCT standards. This

could consist of continued care by the psychologist known to the patients and families and specialized in the child's underlying condition, as well as involving a psychologist as member of the KITES team.

What this study adds

This study validates and extends the existing literature on PPC. Multidisciplinary collaboration is well valued but our survey adds new insights into how primary care providers feel supported by a liaison team, demonstrating that such a team mitigates knowledge gaps, strengthen symptom management, and enhance coordination. The liaison team KITES was perceived as a key intermediary, coordinating care and facilitating communication between GPs, allied HCPs, and the child's family. Psychological care, however, remains an unmet need for both families and caregivers (17, 22, 33). Integrating psychologists into liaison teams could address this critical gap in emotional and psychological care.

Strengths and limitations

A key strength of our study is the relatively large study population within the field of PPC, an area in which research data are often limited. Furthermore, a multidisciplinary perspective on the provision of care was achieved by including two essential professional groups, GPs and allied HCPs. This approach enhanced the analysis by integrating insights from both medical and supportive care disciplines. Interestingly, the opinions of GPs and allied HCPs did not differ much on the various topics. Several limitations must be acknowledged. The extensive questionnaire led to incomplete responses and potential loss of data. Besides, the monocentric retrospective design limits generalizability but previous publications from other centres and countries support our observations. Moreover, parents' perspectives – central figures in PPC – were not included, resulting in a missing dimension of the experience. Additionally, although the sample size is relatively large for PPC research, it remains small compared to broader primary care or other paediatric studies. Furthermore, despite an acceptable response rate, the use of a voluntary questionnaire may have introduced non-response bias and self-selection bias, as professionals with a particular interest in or strong opinions about paediatric palliative care may have been more likely to participate. This could have influenced our results and have led to existing gaps being underestimated or overlooked. Recall bias cannot be excluded either, given the retrospective nature of the survey and the reliance on participants' memory of previous experiences. However, as the death of a child after a long disease is very impactful, these events are likely well remembered by health professionals. Interpretation bias may also have occurred, as respondents might have understood certain concepts or questions differently despite efforts to ensure clarity. Finally, some topics could have been explored more, to better understand the need of GPs and allied HCPs, e.g. what kind of training they would like, whether or not the identified gaps were similar to those in adult palliative care,.... This could be a topic for future research.

Conclusion

Primary HCPs involved in PPC receive limited formal training, which contributes to ongoing insecurity regarding pain and symptom management, and providing psychosocial support. Introducing the fundamental concepts of PPC into palliative care training or general HCP training is needed. While liaison teams such as KITES offer valuable practical support and serve as a key collaborator alongside GPs and allied HCPs, optimizing communication tools and expanding psychological expertise in the liaison teams may help address an important gap. Strengthening these areas is essential to better equip HCPs and ultimately improve the quality of PPC.

Statements

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Vermindering symptomen na 3 dagen

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* Nutrients 2021: 13;3336, Vandenplas et al. An observational Real-life study with a new Infant formula in infants with Functional gastro-intestinal disorders.

Dit document is voorbehouden voor gezondheidsspecialisten.

Belangrijke informatie voor (para)medici: de Wereldgezondheidsorganisatie (WHO) heeft aanbevolen om zwangere vrouwen en moeders van zuigelingen te informeren over de voordelen en de superioriteit van borstvoeding. In het bijzonder dat borstvoeding de beste voeding is en de beste bescherming tegen ziektes biedt. Moeders moeten ook begeleid worden met de voorbereiding op en de verderzetting van borstvoeding, met de nadruk op het belang van de kwaliteit van hun eigen voeding tijdens de zwangerschap en na de geboorte. Onnodige introductie van gedeeltelijke flesvoeding of andere voedingsmiddelen of dranken zou ontmoedigd moeten worden omdat het een negatieve invloed op borstvoeding kan hebben. Bovendien moeten moeders gewaarschuwd worden dat zij niet terug kunnen komen op hun beslissing om geen borstvoeding meer te geven. Voordat een moeder besluit om flesvoeding te geven, zou ze geadviseerd moeten worden over de sociale en financiële gevolgen van haar beslissing, bijvoorbeeld als een baby exclusief flesvoeding krijgt, dan is meer dan 450 gram per week nodig, dus de familiale omstandigheden en de kosten moeten in overweging worden genomen. Moeders moeten eraan herinnerd worden dat borstvoeding niet alleen de beste voeding, maar ook de meest economische voeding is. Wanneer toch wordt besloten om flesvoeding te geven is het belangrijk om de juiste instructies mee te geven omtrent het gebruik van deze voeding en erop te wijzen dat ongekookt water, niet gesteriliseerde zuigflessen of een onjuiste bereiding de baby ziek kan maken. **Met vriendelijke groeten, Nestlé Babyvoeding.** VU: K. Desmedt, Nestlé Belgilux SA/NV, Rue de Birminghamstraat 221 - 1070 Bruxelles/Brussel, BCE/KBO 0402.231.383. PID4067 – September 2026.

RESEARCH ARTICLE

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Bridging the Gap: A Survey of Emergency Staff Perspectives on Paediatric Pain Management in an Academic Hospital

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Keywords

Pain Management; Pain Scales; Paediatric Analgesia; Painful Procedures

Abstract

Background
Paediatric pain is a common reason for emergency department (ED) presentation, yet pain assessment and management remain inconsistent despite the availability of evidence-based interventions. Limited data exist on clinicians' perspectives regarding barriers to optimal paediatric pain care.

Methods
We conducted a monocentric cross-sectional survey among physicians and nurses working in a tertiary-care ED. The questionnaire assessed paediatric pain assessment practices, pharmacological and non-pharmacological management, procedural analgesia, clinician confidence, and perceived barriers. Quantitative data were analysed descriptively and by subgroup comparison.

Results
Of 225 eligible staff members, 108 responded (48% response rate), and 87 completed questionnaires were included (38.7% inclusion rate). While 91% of respondents reported routinely assessing pain at presentation, only 18% consistently reassessed pain after interventions or procedures. Familiarity with paediatric-specific pain scales was limited, with only 10% and 7% reporting use of the Wong–Baker FACES and FLACC scales, respectively. Only 16% of participants reported high confidence in paediatric analgesic administration, whereas lack of formal training was identified as the most important barrier (47%). Procedural pain management showed substantial variability; 52% of respondents reported no analgesia or anxiolysis during bladder catheterization, and 46% reported none during cast application. Non-pharmacological interventions, particularly distraction techniques, were widely used and perceived as effective. Most participants emphasized the need for improved training and standardized protocols.

Conclusion
Significant gaps persist in paediatric pain reassessment, clinician confidence, and procedural pain management in the ED. Standardized protocols, targeted education, and multimodal approaches may improve guideline-concordant and child-centred paediatric pain care.

Introduction

Pain is one of the leading reasons for presentation to the emergency department (ED), particularly in paediatric populations, where children account for a substantial proportion of visits (1,2). Painful conditions and procedures are common in the paediatric ED and may contribute to significant distress, anxiety, and negative long-term healthcare experiences if inadequately managed (3-5). Despite growing awareness and the availability of evidence-based interventions, paediatric pain management in the ED remains suboptimal. Studies consistently report inadequate pain assessment and undertreatment, with children frequently receiving less analgesia than adults with comparable conditions (6,7). Increasing ED crowding, time pressure, and workflow demands further complicate timely and effective pain care (8). Although multimodal approaches combining pharmacological and non-pharmacological strategies have shown beneficial effects on procedural pain and anxiety, implementation in routine emergency care remains inconsistent (9,10). Current literature has primarily focused on patient outcomes and intervention efficacy, while less attention has been paid to the experiences and perspectives of ED healthcare professionals responsible for paediatric pain management. Greater insight into clinicians' practices, perceived barriers, and challenges is needed to support guideline-concordant and child-centred pain care in the emergency setting. This survey therefore aims to explore how ED physicians and nurses assess and manage paediatric pain and to identify factors influencing optimal pain care in daily clinical practice.

TABLE 1: Demographic Characteristics of Participants.

		Count (N)	Count (%)
Profession	Emergency Nurse	39	44.8%
	Emergency Physician	21	24.1%
	Paediatric Nurse	1	1.1%
	Paediatrician	21	24.1%
	Surgeon	3	3.4%
	Other	2	2.3%
Years of Clinical Experience	0-5	43	49.4%
	6-10	14	16.1%
	11-15	7	8.0%
	16-20	6	6.9%
	>20	17	19.5%
Paediatric Patient Volume	0	1	1.1%
	1-5	42	48.3%
	6-15	21	24.1%
	16-30	8	9.2%
	>30	15	17.2%
Formal Training	No	75	86.2%
	Not Sure	3	3.4%
	Yes	9	10.3%

Materials and Methods

Study Design and Setting

A monocentric, cross-sectional survey was conducted at UZ Leuven, a tertiary care emergency department. The study aimed to explore healthcare professionals' (doctors and nurses) experiences and perceptions regarding paediatric pain management, including barriers, facilitators, and current practices.

Participants

Eligible participants included all physicians and nurses actively working in the emergency department during the study period. Participation was voluntary, and responses were anonymized to ensure confidentiality.

Survey Instrument

A structured questionnaire was developed based on existing literature and previous surveys on paediatric pain management (1,2,10). The survey included sections on demographics, professional background, assessment and management of paediatric pain, use of procedural sedation and analgesia, non-pharmacologic interventions, perceived barriers (to analgesia administration and to overall pain and anxiety management), and suggestions for improvement. The survey addressed general pain management practices across all types of paediatric pain presentations (including procedural pain), rather than analysing subcategories separately. Questions comprised multiple-choice items, Likert-scale ratings, and open-ended responses to capture qualitative insights. The questionnaire was developed based on prior research and guidelines in paediatric pain management; an interdisciplinary panel of ED clinicians reviewed items for face validity and clarity, and minor revisions were made based on feedback to ensure content validity.

Data Collection

The survey was administered online using LimeSurvey. Invitations were sent via institutional email to all eligible staff. To maximize response rates, three reminder emails were issued at one-week intervals following the initial invitation. Data collection was open from March to mid-April 2026. We excluded surveys that were largely incomplete from the final analysis. Some respondents did not answer every question; these missing responses were not imputed, and denominators for percentages reflect the number of respondents for each specific item.

Statistical Analysis

Quantitative responses were analysed using descriptive statistics (frequencies, percentages, means, and standard deviations). Group comparisons (e.g. between physicians and nurses) were performed using appropriate statistical tests (chi-square tests for

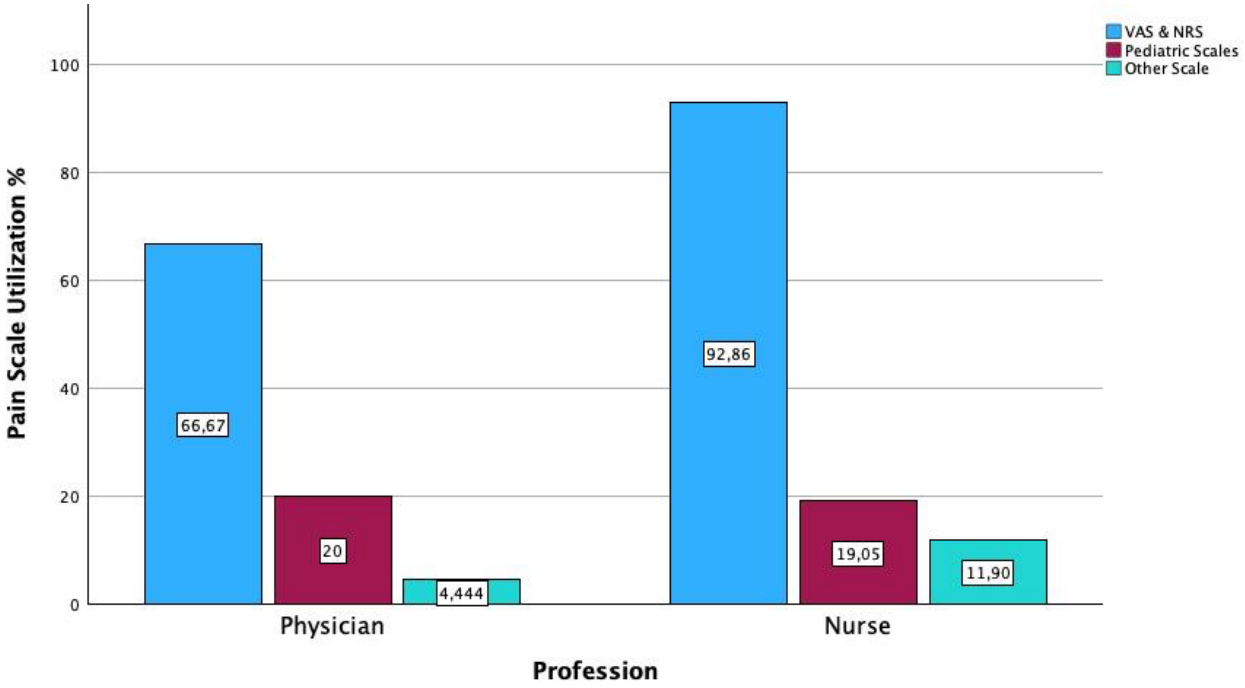


FIGURE 1: Frequency of Pain Scale Utilization By Professional Category.

categorical variables and t-tests for continuous variables). SPSS version 30.0 was used for the statistical analysis. Qualitative responses from open-ended questions were collected to capture additional insights but were included in the final manuscript. All analyses were conducted in accordance with institutional guidelines for research ethics. The study was approved by the Institutional OBC (MP031293) and completion of the survey was considered to constitute informed consent.

Results

Participant characteristics

Of 225 eligible staff, 108 initiated the survey (48% response rate), and 87 completed questionnaires were included in the analysis (38.7% of eligible staff). Nurses accounted for 46% of respondents and physicians for 52% (Table 1). Among physicians, specialties included Paediatrics (n = 21), Emergency Medicine (n = 21), and Surgery (n = 3). Fifty percent of participants had fewer than 5 years of clinical experience, and 20% had more than 20 years of experience. Approximately 70% of respondents reported seeing fewer than 15 paediatric patients per week. Among general ED providers, 76% of emergency physicians and 58% of emergency nurses reported treating fewer than five paediatric patients weekly. Specific training in paediatric pain management was reported by 10.3% of respondents (n = 9), including 7 paediatric specialists.

Pain Assessment Practices

Pain assessment at initial presentation was reported as "always" by 45% of participants and as "often" by 46%. Consistent reassessment of pain after painful procedures or therapeutic interventions was reported by 18% (95% CI: 11.6%–27.8%) of participants The 10-point Visual Analogue Scale (VAS) or similar numeric rating scales were familiar to nearly all respondents, indicating that most staff rely on general pain scales even for children. In contrast, familiarity with paediatric-specific pain scales was limited -only 10% and 7% of participants reported using the Wong–Baker FACES and FLACC scales, respectively, for young children. Use of paediatric-specific pain scales did not differ significantly between physicians and non-physicians (20% vs 19%; $\chi^2(3, 87) = 1.95$, $p = 0.58$) or by paediatric experience (22.7% vs 18.5%; $\chi^2(3,87) = 1.67$ $p = 0.66$) (Figure 1). Reported barriers to paediatric pain assessment included difficulty assessing pain in non-verbal or young children (62.5%; 95% CI [52.3%, 72.7%]) parental presence complicating assessment (51%), lack of patient cooperation (40%), insufficient formal training in paediatric pain assessment (35.6%), and time pressure in the ED environment (35%).

Pain management practices

Pharmacological

Only 16% (95% CI [8.3%, 23.7%]) of respondents reported being "very confident" or completely comfortable with paediatric analgesic administration. Moderate confidence was reported by 35% of participants, while 12.5% reported uncertainty or discomfort with paediatric analgesic use. No significant association was identified between years of clinical experience and self-rated confidence in paediatric analgesia ($\chi^2(16, 87) = 13.0$, $p = 0.66$) (Figure 2). Within the trauma team subgroup two of the three participants reported uncertainty regarding paediatric pain medication use.

TABLE 2: Frequency and Distribution of Analgesic Choices Across Mild, Moderate, and Severe Pain Intensity Levels.

	None	Paracetamol	NSAIDs	Tramadol	Fentanyl	Morphine	Ketamine	Other
Mild Pain (n=87)	9 (10.3%)	81 (93.1%)	21 (24.1%)	0	0	0	0	0
Moderate Pain (n=87)	1 (1.1%)	76 (87.4%)	54 (62.1%)	11 (12.6%)	0	0	0	0
Severe Pain (n=86)	1 (1.1%)	46 (53.5%)	36 (41.9%)	24 (27.9%)	46 (53.5%)	12 (14%)	11 (12.6%)	2 (2.3%)
Percentages exceed 100% as respondents could select multiple options								

The frequency and distribution of analgesic choices across mild, moderate, and severe pain intensity levels is shown in Table 2. For mild pain, 93% of participants selected acetaminophen (paracetamol) as first-line treatment, and 24% reported use of non-steroidal anti-inflammatory drugs (NSAIDs). For moderate pain, paracetamol was used by 87% of participants, and 62% reported its use in combination with NSAIDs. Opioid use for moderate pain included tramadol in 12.6% (11/87) of respondents. No respondents reported use of morphine, fentanyl, or ketamine for moderate pain. For severe pain, 53.5% of participants reported use of intravenous fentanyl. Morphine was reported by 14% and ketamine by 13%. Tramadol was reported by 28%. NSAID use was reported by 42%. It is important to note that not all respondents answered every question, and analyses for each item use the number of responses to that item as the denominator (n=86 for severe pain). Emergency physicians reported higher use of fentanyl and ketamine compared with paediatricians ($p < 0.01$). The most frequently reported barrier specific to analgesic administration was lack of formal education or training in paediatric pain pharmacotherapy (47%,Table 3), 29.9% of participants reported no barriers to giving analgesics. No significant difference was observed between respondents with and without paediatric experience ($p = 0.098$). A significant difference was observed between nurses and physicians ($p = 0.008$). Reported barriers also included uncertainty about dosing or guidelines (31%) and fear of adverse effects in children (30%). Parental reluctance and limited drug availability were reported less frequently.

Non-Pharmacological

The use of non-pharmacological strategies to alleviate paediatric pain and anxiety was widespread (Table 4). Distraction techniques (such as toys, games, or storytelling) were the most commonly employed non-drug intervention, reported by the vast majority of participants (mentioned by 83 respondents, ~95%). Other frequently used non-pharmacological measures included offering pacifiers or oral sucrose for infants (64% of respondents), encouraging breastfeeding or oral feeding for comfort (54%), and using comfort positioning (holding or swaddling children in secure, comforting positions; 52%). In contrast, specialized support from paediatric psychologists or play therapists was rarely available, with only 3 participants reporting access to such services during paediatric procedures. In terms of perceived efficacy, nearly half of participants (45%) believed these non-pharmacological methods definitely reduce children's anxiety during painful procedures, while an additional 49% observed at least some partial anxiety reduction when using them.

Pain Management by Procedure

The survey assessed analgesic use across common emergency department (ED) procedures (Table 5). For venipuncture/IV cannulation, 76% of respondents reported use of topical local anaesthetics, while 28% reported no analgesic or anxiolytic measures. 56% of respondents reported use of systemic analgesia (most commonly opioids), and 67% reported use of

TABLE 3: Identified barriers to the administration of pain medication across professional disciplines.

	None	Lack Of Training	Fear of Side Effects	Parental Resistance	Drug Shortage	Insecurity About Guidelines	Other
Total	26 (29.9`%)	41 (47.1%)	26 (29.9%)	10 (11.5%)	3 (3.4%)	27 (31%)	4 (4.6%)
Paediatrician	6 (28.6%)	11 (52.4%)	8 (38.1%)	2 (9.5%)	1 (4.8%)	3 (14.3%)	0 (0%)
Emergency Physician	7 (33.3%)	7 (33.3%)	7 (33.3%)	2 (9.5%)	0 (0%)	7 (33.3%)	2 (9.5%)
Surgeon*	0 (0%)	3 (100%)	1 (33.3%)	0 (0%)	0 (0%)	2 (66.7%)	0 (0%)
Emergency Nurse	11 (28.2%)	19 (48.7%)	10 (25.6%)	5 (12.8%)	2 (5.1%)	15 (38.5%)	2 (5.1%)
*Surgeon group only consists of three participants. Percentages exceed 100% as respondents could select multiple options.							

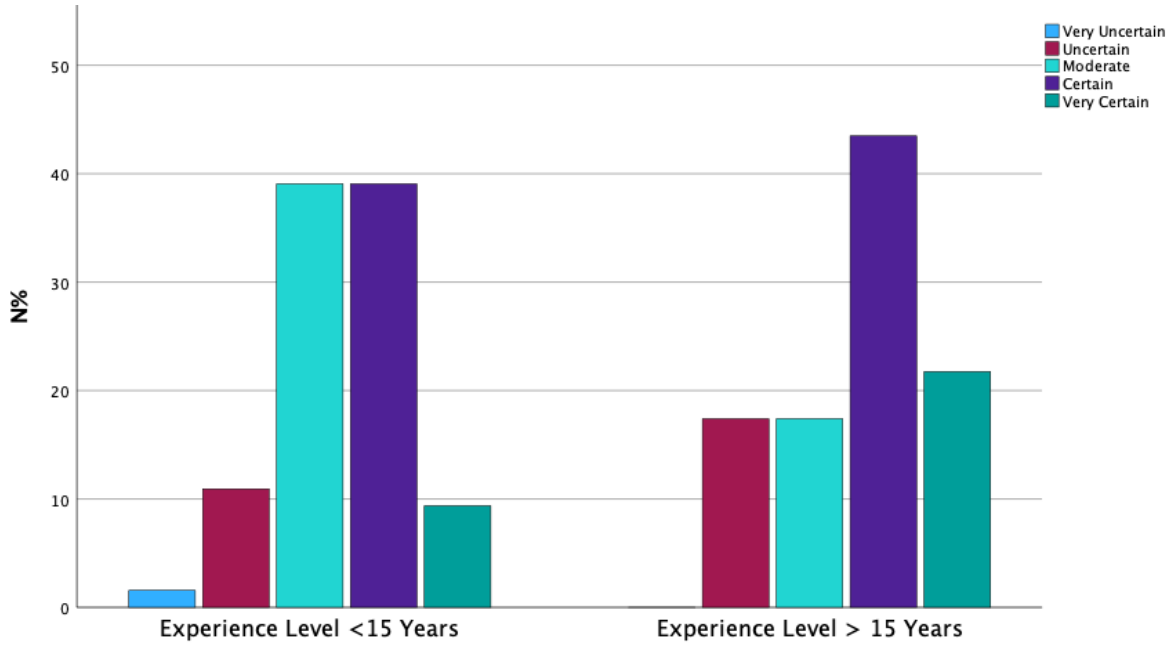


FIGURE 2: Association Between Professional Experience and Self-Rated Certainty in Paediatric Pain Management.

procedural sedation for fracture reduction. For bladder catheterization, 52% of respondents reported no analgesic or anxiolytic use. And 46% reported no analgesic or anxiolytic use for orthopaedic cast application. For lumbar puncture, 52% of respondents reported using a topical aesthetic, while 23% reported performing the procedure without any analgesic or anxiolytic measures. When asked to identify the most significant barriers to providing effective overall paediatric pain and anxiety management in the ED (including non-pharmacological aspect), participants reported a multifaceted set of challenges (Table 6). The most frequently cited barrier was insufficient specialized training in paediatric pain management, endorsed by approximately 21% of respondents. Time constraints in a busy ED were the second most common barrier (17.5%). and the absence of standardized protocols was the next major obstacle (~15%) reported. Notable barriers included inadequate staffing (14.8%) and the inherent difficulty of assessing pain in young children (12.7%). Very few respondents (~3%) felt that lack of medication availability was a significant barrier.

Importance of Pain management and Improvement

There was unanimous agreement among participants on the importance of effective pain management for children: 35% rated it "important" and 65% "very important," with 100% of respondents affirming that paediatric pain control is a priority in emergency care. Looking forward, the survey asked participants to identify key requirements for improving paediatric pain management in their ED. The top priorities were overwhelmingly enhanced training and education (selected by 75.9% of respondents) and the development or updating of standardized paediatric pain management protocols (71.3%). Many also emphasized the need for a more child-friendly environment in the ED (47%) to reduce anxiety and pain, as well as improved age-appropriate pain assessment tools (28.7%). In contrast, relatively few saw "better access to pharmacological agents" as a pressing need (only ~14% selected this), implying that the drug formulary was generally considered adequate.

Discussion

Despite substantial advances in paediatric pain management, inadequate analgesia remains a persistent challenge in emergency care. This study demonstrates that although emergency department clinicians consistently recognize pain management as a clinical priority, this awareness does not reliably translate into a standardized protocol-driven practice. As a result, children continue to experience preventable and undertreated pain during emergency encounters (11).

A central finding of this study is the discontinuity between initial pain recognition, intervention, and structured reassessment. While pain is frequently identified at presentation, systematic follow-up after analgesic administration is inconsistently performed, reflecting an "evaluation gap" described in prior literature (12). Similar deficiencies have been reported across paediatric emergency and trauma settings, where clinical pathways fail to ensure completion of the assessment–treatment–reassessment cycle (13). A key contributor to this gap appears to be the inconsistent integration of validated paediatric pain assessment tools into routine practice. The study by Ali et al is a good example of a structured way to implement post-analgesia pain assessment in a clinical trial which is transferable to standard clinical practice

TABLE 4: Table 4: Distribution and Frequency of Reported Non-Pharmacological Interventions for Pain Management By Profession.

Intervention	Response	Emergency Nurse		Emergency Physician		Paediatric Nurse		Paediatrician		Trauma Surgeon	
		N	N%	N	N%	N	N%	N	N%	N	N%
Distraction	No	3	7.7%	0	0.0%	0	0.0%	0	0.0%	1	33.3%
	Yes	36	92.3%	21	100.0%	1	100.0%	21	100.0%	2	66.7%
Swaddling	No	26	66.7%	14	66.7%	0	0.0%	2	9.5%	2	66.7%
	Yes	13	33.3%	7	33.3%	1	100.0%	19	90.5%	1	33.3%
Breastfeeding	No	21	53.8%	15	71.4%	0	0.0%	0	0.0%	3	100.0%
	Yes	18	46.2%	6	28.6%	1	100.0%	21	100.0%	0	0.0%
Pacifier	No	15	38.5%	11	52.4%	0	0.0%	1	4.8%	3	100.0%
	Yes	24	61.5%	10	47.6%	1	100.0%	20	95.2%	0	0.0%
Heat/Cold Therapy	No	31	79.5%	18	85.7%	0	0.0%	16	76.2%	3	100.0%
	Yes	8	20.5%	3	14.3%	1	100.0%	5	23.8%	0	0.0%
Comfort Positioning	No	20	51.3%	14	66.7%	1	100.0%	6	28.6%	1	33.3%
	Yes	19	48.7%	7	33.3%	0	0.0%	15	71.4%	2	66.7%
Paediatric psychologists or play therapists	No	38	97.4%	21	100.0%	0	0.0%	20	95.2%	3	100.0%
	Yes	1	2.6%	0	0.0%	1	100.0%	1	4.8%	0	0.0%
None	No	38	97.4%	21	100.0%	1	100.0%	21	100.0%	2	66.7%
	Yes	1	2.6%	0	0.0%	0	0.0%	0	0.0%	1	33.3%
Other	No	32	82.1%	21	100.0%	1	100.0%	19	90.5%	3	100.0%
	Yes	7	17.9%	0	0.0%	0	0.0%	2	9.5%	0	0.0%

Percentages exceed 100% as respondents could select multiple options.

(14). Although international guidelines, including those from the European Society for Emergency Medicine, emphasize the use of age-appropriate, validated instruments, their inconsistent application likely reduces both the accuracy of pain evaluation and the reliability of reassessment over time (15). However, the evaluation gap is not only an individual caregiver problem, it reflects broader system-level constraints. In high-acuity emergency environments, competing clinical priorities, overcrowding, and workflow pressures often result in reassessment being deprioritized relative to diagnostic or life-saving interventions (11,16). Evidence from resource-limited settings similarly demonstrates that structural bottlenecks and the absence of standardized pain pathways impede consistent monitoring of analgesic response (17). Collectively, these findings suggest that the principal barrier is not recognition of pain, but the failure to embed reassessment into routine emergency workflows as a mandatory clinical step.

Beyond structural constraints, clinician-related factors also contribute to variability in reassessment practices. Prior work has shown that paediatric pain assessment is sometimes influenced by subjective judgment and uncertainty regarding the reliability of children's pain expression (11). Such variability may lead to inconsistent thresholds for reassessment and analgesic escalation. The findings of this study support the need for institutionalised, protocol-driven pain management systems to reduce variability in care. Current practice patterns suggest reliance on individual clinician decision-making rather than embedded clinical pathways (11). Evidence from implementation studies demonstrates that structured protocols significantly improve both process and outcome measures. Nurse-initiated analgesia pathways, for example, have been associated with faster time to treatment and improved pain reassessment rates (18). Similarly, structured nurse-driven protocols have been shown to improve caregiver satisfaction and analgesic consistency (19). Current guidelines advocate algorithm-based approaches that integrate early analgesic initiation and mandatory reassessment (15). In this context, intranasal fentanyl is increasingly recommended as a first-line option for moderate-to-severe pain due to its rapid onset and favourable safety profile (20,21). Limited use of tramadol aligns with ongoing safety concerns. Importantly, effective protocols extend beyond pharmacological escalation and include multimodal strategies combining pharmacological and non-pharmacological interventions.

A concerning finding was the inconsistent management of procedural pain, particularly during routine interventions such as bladder catheterisation, where analgesia or anxiolysis was frequently absent. This aligns with prior evidence demonstrating systematic

TABLE 5: Reported Frequency of Pharmacological and Non-Pharmacological Interventions Across Different Clinical Procedures.

Procedure	None	Non- Pharmacological	Pharmacological / Systemic	Topical	Sedation	Other
IV Access	24 (27.6%)	50 (57.5%)	6 (6.9%)	66 (75.9%)	10 (11.5%)	1 (1.1%)
Bladder catheterization	45 (51.7%)	38 (43.7%)	7 (8%)	8 (9.2%)	2 (2.3%)	3 (3.4%)
Lumbar puncture	20 (23%)	34 (39.1%)	19 (21.8%)	45 (51.7%)	21 (24.1%)	3 (3.4%)
Fracture reduction	1 (1.1%)	13 (14.9%)	49 (56.3%)	3 (3.4%)	58 (66.7%)	5 (5.7%)
Suturing	2 (2.3%)	29 (33.3%)	29 (33.3%)	58 (56.7%)	15 (17.2%)	3 (3.4%)
Wound care	27 (31%)	40 (46%)	34 (39.1%)	15 (17.2%)	11 (12.6%)	3 (3.4%)
Casting (plaster)	40 (46%)	25 (28.7%)	27 (31%)	2 (2.3%)	9 (10.3%)	5 (5.7%)
Percentages exceed 100% as respondents could select multiple options.						

under-treatment of so-called "minor" procedures, despite clear evidence of significant distress and potential long-term psychological impact (12). Such findings reflect the continued normalisation of procedural pain in emergency settings, particularly when procedures are perceived as routine or low-risk (11). However, current international guidelines strongly oppose this practice, recommending routine prevention of procedural pain through multimodal strategies, including topical, inhalational, and dissociative approaches (15). Evidence further supports the use of nitrous oxide-based regimens as effective, workflow-compatible interventions that reduce procedural pain and anxiety while maintaining operational efficiency (22).

The observed analgesic prescribing pattern demonstrates a partial deviation from the WHO Paediatric Pain Ladder framework, particularly in moderate-to-severe pain management (23). A marked preference for fentanyl over morphine was identified, consistent with current evidence supporting fentanyl as a first-line opioid in acute paediatric care due to its rapid onset and reduced adverse effect profile (21,24). Conversely, limited use of tramadol aligns with ongoing safety concerns regarding unpredictable metabolism in paediatric populations. These findings suggest partial adaptation of contemporary pharmacological evidence; however, inconsistency remains in structured escalation pathways and procedural analgesia application. Interestingly, nearly one-third of participants reported no significant barriers to administering analgesics to children. This subgroup may represent a particularly experienced or well-supported portion of staff, suggesting that adequate training and resources can enable clinicians to overcome common barriers.

TABLE 6: Proportional Distribution of Reported Barriers to Adequate Pain and Anxiety Management in Emergency Departments.

	Count (N)	(Count %)
No Limitations	9	3.9%
Time Pressure	40	17.5%
Difficult Pain Score Assessment	29	12.7%
Medication Shortage	7	3.1%
Staffing Shortage	34	14.8%
Clinical Culture	26	11.4%
Lack Of Training	48	21.0%
Lack Of Protocol	34	14.8%
Other	2	0.9%
Percentages exceed 100% as respondents could select multiple options.		

Non-pharmacological interventions were widely integrated into routine care, reflecting increasing alignment with multimodal pain management principles. Distraction techniques were frequently used and associated with perceived reductions in anxiety, consistent with evidence supporting behavioural interventions in procedural pain management (24). Emerging evidence suggests that digital distraction technologies, including virtual reality, may offer superior analgesic and anxiolytic effects compared with traditional distraction methods (25,26). Additionally, established infant comfort measures such as sucrose, breastfeeding, and pacifier use were consistently applied, consistent with international recommendations (23). Comfort positioning was also frequently used and is supported by evidence demonstrating reduced physiological stress responses compared with restraint-based approaches (27). However, access to specialised psychosocial support was limited. This is notable given evidence linking such services to reduced procedural distress, decreased sedation requirements, and improved caregiver satisfaction (28). Their limited availability suggests reliance on frontline staff to deliver behavioural support, potentially contributing to variability in non-pharmacological care.

A key strength of this study is its multidisciplinary design, incorporating perspectives from both nursing and medical staff across multiple specialties, thereby providing a comprehensive view of paediatric pain management practices in the emergency department. The study also identifies actionable gaps across the assessment–intervention–reassessment cycle, offering

clinically relevant targets for quality improvement. However, several limitations should be acknowledged. First, the sample included a high proportion of early-career clinicians, particularly among nursing staff, which may have influenced reported confidence and protocol familiarity. Second, the single-centre design at a tertiary academic hospital limits generalisability, particularly given the unique workflow in which paediatric emergency care is managed separately from general emergency medicine. Third, the extremely small sample for certain subgroups (e.g. surgeons, n=3) limits statistical power and the reliability of any comparisons involving those groups. Fourth, reliance on self-reported data introduces the possibility of social desirability bias. Finally, the cross-sectional design prevents assessment of temporal changes in practice or the impact of future interventions.

Conclusion

This study demonstrates a clear and clinically significant disparity between the recognition of paediatric pain and the consistent execution of a complete assessment–treatment–reassessment cycle in the emergency department. Although initial pain screening appears to be well embedded in practice, a substantial evaluation gap, reflected in the low rate of post-intervention reassessment (18.4%), represents a critical breakdown in the continuity of care. This gap indicates that pain management is frequently initiated but not systematically evaluated for effectiveness, limiting the ability to ensure adequate analgesic response. The underlying barriers appear to be predominantly structural and educational rather than purely logistical. These include ongoing uncertainty regarding pharmacological choices, concerns about potential adverse effects, and limited familiarity with validated paediatric pain assessment tools such as the FLACC and Wong-Baker FACES scales. Together, these factors contribute to inconsistent application of standardized pain assessment and monitoring practices, undermining evidence-based care delivery. In addition, the perception of parental involvement as a limiting factor by more than half of respondents (51%) highlights a persistent tension in clinical practice and underscores the need to strengthen the implementation of family-centred care principles. Rather than being viewed as an obstacle, caregiver involvement should be systematically integrated as a supportive component of paediatric pain assessment and reassurance, particularly in younger or non-verbal children. Addressing these challenges requires a shift away from ad hoc clinical decision-making toward a standardized, protocol-driven, and nurse-empowered model of care. Evidence from structured initiatives such as the PROSA program and the Kids Pain Collaborative demonstrates that implementation of standardized triage algorithms and nurse-initiated analgesia pathways can significantly improve timeliness of treatment and ensure mandatory reassessment, thereby closing critical gaps in the care continuum. Ultimately, closing the evaluation gap is essential not only for improving acute pain relief but also for mitigating the long-term psychological consequences associated with poorly managed early healthcare experiences, including heightened procedural anxiety and needle phobia. Sustained improvement will depend on targeted education of clinical staff, reinforcement of validated assessment tool usage, and the formal integration of multimodal, age-appropriate pain management strategies into routine emergency department workflows.

Statement

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

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RESEARCH ARTICLE

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Evolution of Cerebral Palsy Diagnosis in a High-Risk Neonatal Population: A Cohort Study over Two Decades

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Keywords

Cerebral Palsy; Early Diagnosis;
Neonatal Follow-Up; Prematurity; Neurodevelopment

Abstract

Background
Early diagnosis of cerebral palsy (CP) enables timely intervention and improved outcomes. International guidelines recommend standardized tools such as magnetic resonance imaging (MRI), the Hammersmith Infant Neurological Examination (HINE), and the Prechtl General Movements Assessment (GMs). In Belgium, a structured and reimbursed neonatal follow-up program for preterm infants (prematurity convention) was introduced in 2012. This study evaluated how the diagnostic process of CP has evolved in this context.

Methods
We conducted a retrospective cohort study including children with CP admitted to the Neonatal Intensive Care Unit of University Hospitals Leuven. Two birth cohorts were compared: pre-implementation (2006-2010) and post-implementation (2016-2020). Clinical and neurodevelopmental data were extracted from medical records. Primary outcomes were age at diagnosis and use of standardized tools. Secondary outcomes included timing of parental communication, referral to specialized care, and initiation of early interventions.

Results
Seventy-eight children were included (38 in 2006-2010; 40 in 2016-2020). Median age at diagnosis did not differ significantly between cohorts (12.0 vs. 10.5 months; p=0.564). Children with higher Gross Motor Function Classification System (GMFCS) levels were diagnosed earlier (p=0.003). The more recent cohort showed earlier communication of motor concerns, earlier referral, and earlier initiation of interventions such as constraint-induced movement therapy and home guidance.

Conclusions
Despite the introduction of structured follow-up, age at diagnosis did not decrease. However, diagnostic age was comparable to international programs with full guideline implementation. Improvements in communication, referral, and intervention timing were observed over time. Further integration of standardized tools may enhance early detection and outcomes.

Introduction

Cerebral palsy (CP) is the most frequently diagnosed physical disability in childhood (1). It occurs worldwide, with a higher prevalence reported in low- and middle-income countries (2). The Surveillance of Cerebral Palsy in Europe (SCPE) defines CP as a group of permanent disorders of movement and posture that cause activity limitation and are attributed to non-progressive disturbances occurring in the developing foetal or infant brain (3). CP is classified into three main motor types - spastic, dyskinetic, and ataxic - which can be further categorised as unilateral (affecting one side of the body) or bilateral (affecting both sides) (3). Although it is primarily a motor disorder, comorbidities are common and may include chronic pain, intellectual disability, epilepsy, hip displacement, behavioural disorder and hearing or visual impairments (4).

Historically, perinatal asphyxia was considered the primary cause of CP. However, over the years multiple antenatal, perinatal, and postnatal risk factors have been identified, including intrauterine growth restriction, congenital anomalies, prematurity, neonatal seizures, hypoglycaemia, and infections (5). Advances in neonatal intensive care have significantly improved survival rates among preterm and critically ill newborns (6). While these infants remain at high risk for long-term neurodevelopmental impairments, including CP, overall prevalence of CP in high-income countries has remained stable or declined over recent

TABLE 1: Neonatal characteristics.

Neonatal characteristics	Children born 2006-2010 (%) N = 38 (100)	Children born 2016-2020 (%) N = 40 (100)	P-Value
Male	24 (63.2)	24 (60.0)	0.774
Gestational age in weeks (%)			0.034
Extremely preterm: <28 weeks	3 (7.9)	14 (35.0)	
Very preterm: 28-31 weeks	14 (36.8)	9 (22.5)	
Preterm: 32-36 weeks	11 (28.9)	8 (20.0)	
Term: 37-41 weeks	10 (26.3)	9 (22.5)	
Birth weight in grams, mean (SD)	2106 (942)	1661 (972)	0.784
Multiple pregnancy (%)	10 (26.3)	13 (32.5)	0.549
Antenatal steroids (%)			0.889
No	11 (40.7)	13 (35.1)	
Complete	13 (48.1)	19 (51.4)	
Incomplete	3 (11.1)	5 (13.5)	
Invasive respiratory support (%)			0.857
None	15 (39.5)	14 (35.0)	
<4h	2 (5.3)	1 (2.5)	
4h – 24h	5 (13.2)	7 (17.5)	
2 days – 180 days	16 (42.1)	18 (45.0)	
≥ 180 days	0 (0.0)	0 (0.0)	
Bronchopulmonary Dysplasia (%)	4 (10.5)	11 (27.5)	0.057
Retinopathy of Prematurity (%)			0.008
No	25 (78.1)	21 (53.8)	
Yes, not treated	0 (0.0)	1 (2.6)	
Yes, treated	0 (0.0)	11 (28.2)	
Not performed	7 (21.9)	6 (15.4)	
Necrotizing Enterocolitis (%)	4 (10.5)	5 (12.5)	0.785
Sepsis			0.602
Clinically suspected	6 (15.8)	10 (25.0)	
Culture proven	13 (34.2)	12 (30.0)	
White matter disease on ultrasound (%)			0.079
No white matter disease	17 (44.7)	11 (27.5)	
Transient periventricular flaring	3 (7.9)	2 (5.0)	
Persistent hyperechogenicity	9 (23.7)	21 (52.5)	
Localized cysts	3 (7.9)	4 (10)	
Cystic periventricular leukomalacia	6 (15.8)	2 (5.0)	
Intracerebral haemorrhage (%)			0.946
No intracerebral haemorrhage	18 (47.4)	16 (40.0)	
IVH grade 1	8 (21.1)	10 (25.0)	
IVH grade 2	4 (13.2)	6 (15.0)	
IVH grade 3	4 (10.5)	3 (7.5)	
Periventricular haemorrhagic infarction	2 (5.3)	4 (10.0)	
Other haemorrhages	1 (2.6)	1 (2.5)	
Neurological examination at discharge (%)			0.709
Normal	24 (64.9)	29 (72.5)	
Suspected	6 (16.2)	6 (15.0)	
Abnormal	7 (18.9)	5 (12.5)	
Time of oral autonomy in weeks, mean (SD)	37.32 (2.14) (n=19)	39.77 (2.76) (n=31)	0.198

decades (2). Given the neuroplasticity of the developing brain, early diagnosis is essential to ensure that interventions are timely and effective. As a result, significant research has been conducted in recent years to enhance diagnosis and treatment strategies (7, 8). In 2017, international guidelines for early and accurate diagnosis of CP were published. Before the corrected age of 5 months, magnetic resonance imaging (MRI), together with clinical signs found in the Prechtl Qualitative Assessment of General Movements (GMs), and the Hammersmith Infant Neurological Examination (HINE) are recommended (9, 10). After 5 months, MRI and HINE remain the most predictive tools (8). For diagnosing unilateral CP specifically, the Hand Assessment for Infants (HAI is valuable due to its focus on asymmetries in hand function (11 – 13).

Recent studies have demonstrated that implementing international guidelines for early detection of CP can significantly lower the age of diagnosis. In the United States, Maitre et al. (2020) showed that applying a standardised pathway using the recommended tools across a follow-up network led to a decrease in diagnostic age, with 76% of children diagnosed before 12 months (14). Similarly, in Australia, Te Velde et al. (2021) reported that structured implementation of the standardised tools both reduced the age at CP diagnosis and improved guideline adherence to international guidelines (15). For infants at risk of unilateral CP, Ryll et al. (2021) found that the Hand Assessment for Infants (HAI) could accurately predict CP from as early as 3.5 months, with sensitivity up to 93% (16). These findings highlight the clinical value of structured, guideline-based assessment in improving early diagnosis.

Early intervention plays a pivotal role in optimizing motor, cognitive, and communication skills, while also preventing and managing associated comorbidities. Beyond improving outcomes for the child, timely intervention also supports the mental well-being of parents and caregivers. Delayed diagnosis has been linked to higher levels of parental stress, anxiety, and depression (8, 17). Therefore, intervention should also integrate parental education and psychological support alongside child-focused therapy.

University Hospitals Leuven (UHL) has a 36-bed level 4 NICU and is a CP reference centre, one of five nationally recognised centres in Belgium that collaborate in CP-related data collection. Since a substantial proportion of infants later diagnosed with CP have identifiable perinatal risk factors, this setting provides a unique opportunity to investigate the timing of diagnosis, referral, and outcomes in a high-risk cohort.

The objective of this study was to evaluate how the diagnostic process of children with cerebral palsy (CP) has evolved over time at UHL, by comparing two birth cohorts (2006-2010 and 2016-2020) with regard to the timing of CP diagnosis and the diagnostic tools used. We hypothesized that, following the implementation of structured and reimbursed neonatal follow-up within the Belgian prematurity convention in 2012, children in the more recent cohort would be diagnosed at a younger age and would have earlier access to specialised care and interventions.

Materials and Methods

Data collection

We conducted a retrospective cohort study to identify children with a diagnosis of CP after discharge from the NICU in UHL by querying the database of the UHL CP reference centre.

Since 2012, a structured and reimbursed neonatal follow-up program for preterm infants (prematurity convention) has been implemented in Belgium. Within this program, follow-up assessments are scheduled at fixed time frames after discharge and often alternate with visits to the local paediatrician. Infants born before 31 weeks of gestation and/or with a birth weight below 1500 g are eligible for four multidisciplinary assessments, scheduled at approximately 4, 9, and 24 months corrected age and around 60 months chronological age. Infants born at 31 weeks of gestation with a birth weight of at least 1500 g are eligible for two reimbursed assessments, including one assessment during infancy or early childhood and one between 4.5 and 5.5 years. The assessments are reimbursed through the Belgian healthcare system, although parents pay a small co-payment. To evaluate the potential impact of this structured follow-up programme, two birth cohorts were defined: a pre-implementation cohort (2006-2010) and a post-implementation cohort (2016-2020). The study periods were selected pragmatically as two five-year cohorts, and all eligible children born during these periods were included. Given the retrospective and exploratory nature of the study and the use of the available patient population, no formal a priori sample size calculation was performed, and no minimally clinically relevant difference in age at CP diagnosis was predefined. Inclusion criteria were a documented history of NICU admission at UHL at birth between 2006-2010 or 2016-2020, and a confirmed diagnosis of CP documented in the medical file, based on the Surveillance of Cerebral Palsy in Europe (SCPE) definition (3).

Exclusion criteria were transfers from an external hospital for surgery or second opinions, neurodevelopmental disorders not consistent with CP (e.g. genetic syndromes), degenerative or progressive neurological disorders (e.g. leukodystrophies, hereditary spastic paraplegia), neoplasms, and non-perinatal acquired brain injuries (e.g. shaken baby syndrome, post-NICU meningitis).

Potentially eligible patients were identified through the hospital's administrative and clinical databases, in

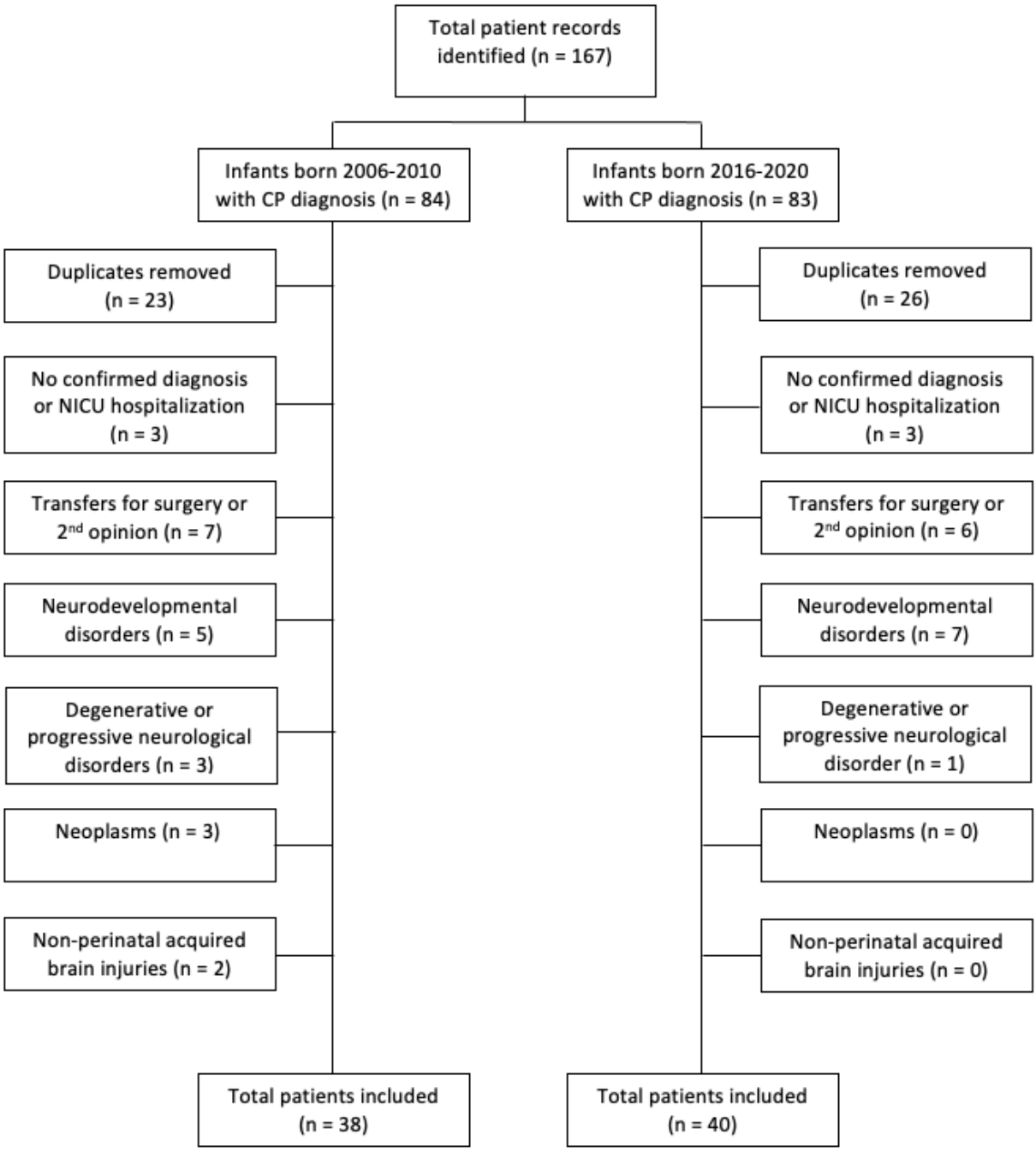


FIGURE 1: Flowchart of patient selection.

collaboration with the CP reference centre. To ensure comprehensive case identification, both diagnostic coding data and records of CP-related clinical consultations were used. All records were subsequently reviewed manually to confirm eligibility. Inclusion and exclusion criteria were applied based on detailed chart review to define the final study population.

One researcher (RD) performed manual chart review and extracted relevant clinical data using a standardised data collection form.

Data definitions and outcome parameters
All definitions were established a priori. Variables were grouped into three categories: neonatal variables, follow-up and intervention variables, and diagnostic and clinical outcomes.

Neonatal variables were sex, gestational age in weeks, birth weight, multiple birth, exposure to antenatal corticosteroids, duration of invasive respiratory support in days. Bronchopulmonary dysplasia (BPD) was defined as supplemental oxygen use for more than 28 days and at 36 weeks postmenstrual age. Retinopathy of prematurity (ROP) was categorised as absent, present without treatment, present requiring treatment, or not assessed. Necrotizing enterocolitis was defined according to Bell's criteria (18). Sepsis was defined as

clinically suspected if antibiotic treatment was given for more than 72 hours, or as proven if blood culture was positive. White matter disease on cranial ultrasound was categorised based on De Vries et al. (19). Persistent hyperechogenicity was defined as periventricular echodensities that were iso- or hyperechogenic relative to the choroid plexus, persisting for more than 2 weeks, but without cystic involution. Intraventricular haemorrhage (IVH) was graded according to Papile et al., with the highest grade documented (20). Time to oral autonomy was recorded in weeks postmenstrual age. Neurological examination at discharge referred to the routine clinical assessment documented in the medical record. Examinations were performed by either a neonatologist or a paediatric resident and were not based on a standardised neurological assessment tool. The level of detail varied between medical records.

Follow-up and intervention variables included corrected age in months at the first follow-up visit after discharge and corrected age in months at the first documented communication to parents of concerns regarding motor development before CP diagnosis. Age at first follow-up after discharge was defined as the age at the earliest documented clinical follow-up after NICU discharge. This was based either on a scheduled appointment recorded in the discharge letter or on the first subsequent consultation identified in the electronic medical record system. Initiation of physiotherapy, home guidance, and constrained-induced movement therapy (CIMT) was noted, together with the corrected age in months at which each intervention was started.

Diagnostic and clinical outcomes included corrected age in months at CP diagnosis and at referral to the CP reference centre. Motor type, laterality classified as unilateral or bilateral, and the first documented Gross Motor Function Classification System (GMFCS) level were recorded. Brain MRI findings were categorised according to the SCPE as maldevelopments, predominant white matter injury, predominant grey matter injury, miscellaneous findings, or normal (21). Use of standardised neurological and motor assessment tools, including HINE, GMs, and HAI, was also documented.

Statistical analysis

Data were analysed using IBM SPSS Statistics (version 29.0). Descriptive statistics were used to summarize patient characteristics and outcomes. Categorical variables are presented as counts and percentages, while continuous variables are described using means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on distribution. Normality was assessed using the Shapiro-Wilk test. For group comparisons, independent samples t-tests were applied for normally distributed continuous variables and Mann-Whitney U tests when the assumption of normality was violated. Categorical variables were compared using chi-square tests. For some comparisons, statistical testing could not be performed due to insufficient valid data in one of the groups. In these cases, results are reported descriptively without accompanying p-values. Visualizations were created in R using the ggplot 2 package (22, 23).

Ethical approval

Ethical approval for this study was obtained from the Ethics Committee of University Hospital Leuven in accordance with institutional and national guidelines (S69315). Due to the use of existing medical records, the requirement for additional informed consent was waived by the ethics committee.

Results

Neonatal characteristics

We screened a total of 167 patient records. After excluding cases without a confirmed CP diagnosis, without NICU hospitalization, or meeting other exclusion criteria as described above, 78 patients were included in the final cohort for analysis, of whom 38 were born between 2006-2010 and 40 between 2016-2020 (see Figure 1). These cohorts correspond to the pre-implementation and post-implementation phases of the structured neonatal follow-up program, respectively. During these periods, a total of 3326 and 3417 infants were admitted to the NICU at UHL, respectively, providing the background population for this study.

Neonatal characteristics are summarized in table 1. The proportion of males was comparable between cohorts (63.2% in 2006-2010 vs. 60.0% in 2016-2020; p=0.774). Children in the recent cohort were significantly more often born extremely preterm (7.9% in 2006-2010 vs. 35.0% in 2016-2020; p=0.034). Birth weight did not differ between groups.

Retinopathy of prematurity was more frequently observed in the 2016–2020 cohort (21.1% in 2006-2010 vs. 53.8% in 2016-2020; p=0.008). Other neonatal complications, including BPD, sepsis, NEC and IVH did not differ significantly. Cystic periventricular leukomalacia was present in 15.8% in the 2006-2010 cohort versus 5% in the 2016-2020 cohort. At discharge, the routine clinical neurological examination was documented as normal in 64.9% of children in the 2006-2010 cohort and 72.5% in the 2016-2020 cohort (p=0.709).

Follow-up and interventions

The follow-up and intervention variables are summarized in table 2. In both cohorts, the corrected age at first follow-up was comparable (median 2 months corrected age in 2006-2010 vs. 1 month corrected age in 2016-2020; p=0.165), with the majority of children initially seen by the neonatology team (76.3% in 2006-2010 vs. 77.5% in 2016-2020). Among children with available documentation, the first recorded

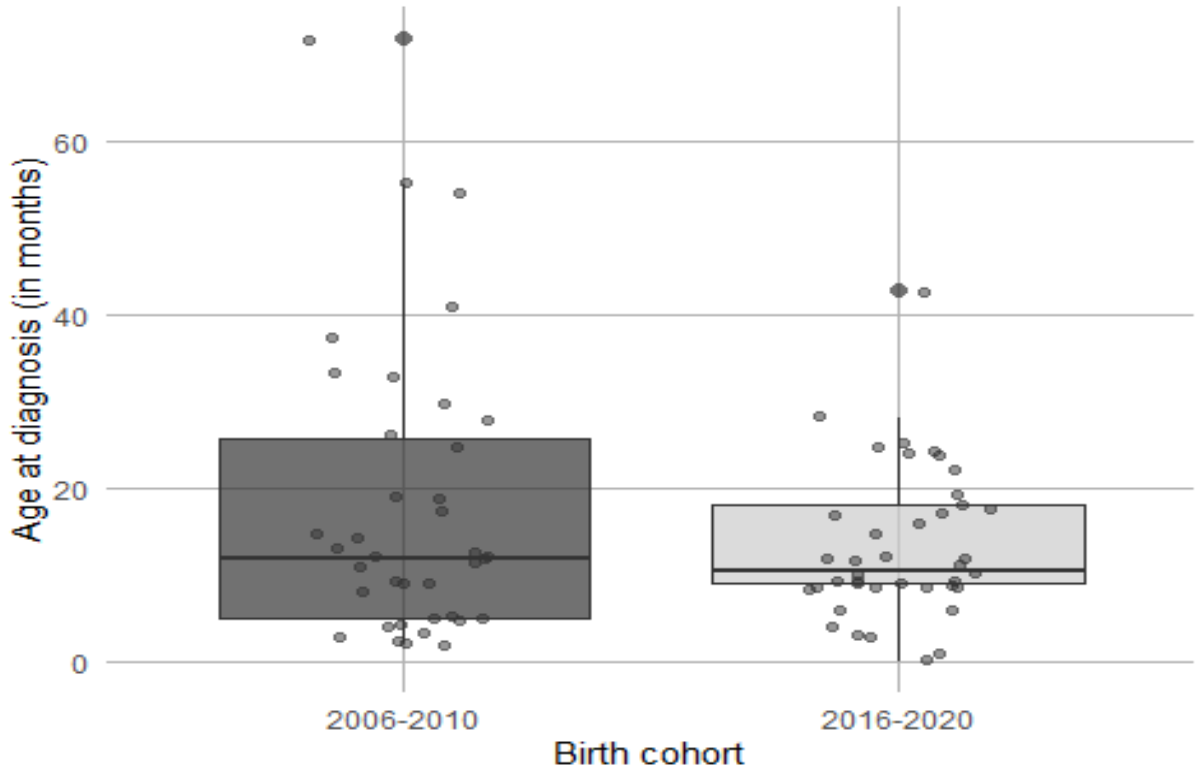


FIGURE 2: Age at cerebral palsy diagnosis by birth cohort. Boxplots showing the distribution of age (corrected age in months) at cerebral palsy (CP) diagnosis for the 2006-2010 and 2016-2020 birth cohorts. Each dot represents an individual child, the bold horizontal line indicates the median, the upper and lower lines represent the interquartile range (IQR).

communication of motor developmental concerns to parents occurred at a significantly younger corrected age in the 2016–2020 cohort (median 6 months corrected age in 2006-2010 vs. 0 months corrected age in 2016-2020; p<0.001). Documentation of parental communication was markedly more frequent in the post-implementation cohort (13% in 2006-2010 vs. 70% in 2016-2020).

The initiation of physiotherapy did not differ significantly (100% in 2006-2010 vs. 97.5% in 2016-2020; p=0.327). However, constrained induced movement therapy (CIMT) was both started more frequently (13.2% in 2006-2010 vs. 42.5% in 2016-2020; p=0.004) and at a significantly earlier age in the 2016-2020 cohort (mean 125.3 months corrected age in 2006-2010 vs. 14.7 months corrected age in 2016-2020; p=0.016). Similarly, home guidance was initiated at a younger age in the recent cohort (median 11 months corrected age in 2006-2010 vs. 2.5 months corrected age in 2016-2020; p=0.024).

Diagnostic and clinical outcomes

There was no significant difference in the time to diagnosis between the two cohorts (median 12 corrected age in 2006-2010 vs. 10.5 months corrected age in 2016-2020; p=0.564) (figure 2). The range was wider in the earlier cohort (2-72 months corrected age in 2006-2010 vs. 0-43 months corrected age in 2016-2020), and a clear peak in diagnosis was observed at 9 months in the recent cohort. The median age of diagnosis decreased with increasing GMFCS scale and this was equal in the two cohorts (p=0.016) (figure 3). Referral to the CP reference centre occurred significantly earlier in the more recent cohort (median 33 months corrected age in 2006-2010 vs. 25 months corrected age in 2016-2020; p<0.001). In addition, the interval between diagnosis and referral was shorter (median 14.5 months corrected age in 2006-2010 vs. 6.0 months corrected age in 2016-2020; p<0.001) (figure 4).

On brain MRI, predominant white matter injury was the most common finding in both cohorts (84.2% in 2006-2010 vs. 84.6% in 2016-2020; p=0.961). No significant differences were observed between groups in the distribution of maldevelopment, white matter injury, or grey matter injury, although miscellaneous abnormalities were more frequently reported in the 2016–2020 cohort (21.1% in 2006-2010 vs 46.2% in 2016-2020; p=0.020).

The HINE was not used in the earlier cohort but was applied in 10 children in the 2016-2020 cohort. The GMs was not performed in either cohort. The HAI was performed once in the recent cohort.

TABLE 2: Follow-up and intervention variables. If data were missing, the number of included cases was indicated in parentheses.

Follow-up and intervention variables	Children born 2006-2010 (%) N = 38 (100)	Children born 2016-2020 (%) N = 40 (100)	P-Value
First follow-up, corrected age in months (IQR)	2 (2) (n=36)	1 (2) (n=39)	0.165
Mention to parents, corrected age in months, median (IQR)	6 (29) (n=5)	0 (0) (n=28)	<0.001
Physiotherapy			
Started	38 (100.0)	39 (97.5)	0.327
Corrected age in months, median (IQR)	3 (7)	4 (9)	0.811
Constrained-Induced Movement Therapy			
Started	5 (13.2)	17 (42.5)	0.004
Corrected age in months, mean (SD)	125.25 (65.53)	14.67 (15.31)	0.016
Home guidance			
Started	24 (63.2)	22 (55.0)	0.515
Corrected age in months, median (IQR)	11 (19)	2.5 (16)	0.024

TABLE 3: Diagnostic and clinical outcomes. If data were missing, the number of included cases was indicated in parentheses.

Diagnostic and clinical outcomes	Children born 2006-2010 (%) N = 38 (100)	Children born 2016-2020 (%) N = 40 (100)	P-Value
Time of diagnosis, corrected age in months, median (IQR)	12 (22)	10.5 (9)	0.564
Referral to CP reference centre, corrected age in months, median (IQR)	33 (18) (n=38)	25 (17) (n=39)	<0.001
Motor type (%)			0.045
Spastic	36 (94.7)	32 (88.9)	
Dyskinetic	2 (5.3)	0 (0.0)	
Ataxic	0 (0.0)	0 (0.0)	
Mixed	0 (0.0)	4 (11.1)	
Unilateral – bilateral (%)			0.890
Unilateral	15 (39.5)	16 (41.0)	
Bilateral	23 (60.5)	23 (59.0)	
First GMFCS documented (%)			0.299
GMFCS I	19 (50)	20 (51.3)	
GMFCS II	8 (21.1)	9 (23.1)	
GMFCS III	7 (18.4)	4 (10.3)	
GMFCS IV	2 (5.3)	6 (15.4)	
GMFCS V	2 (5.3)	0 (0.0)	
MRI			
Maldevelopment (%)	6 (15.8)	5 (12.8)	0.710
Predominant white matter injury (%)	32 (84.2)	33 (84.6)	0.961
Predominant grey matter injury (%)	8 (21.1)	5 (12.8)	0.335
Miscellaneous (%)	8 (21.1)	18 (46.2)	0.020
Normal (%)	1 (2.6)	0 (0.0)	0.367

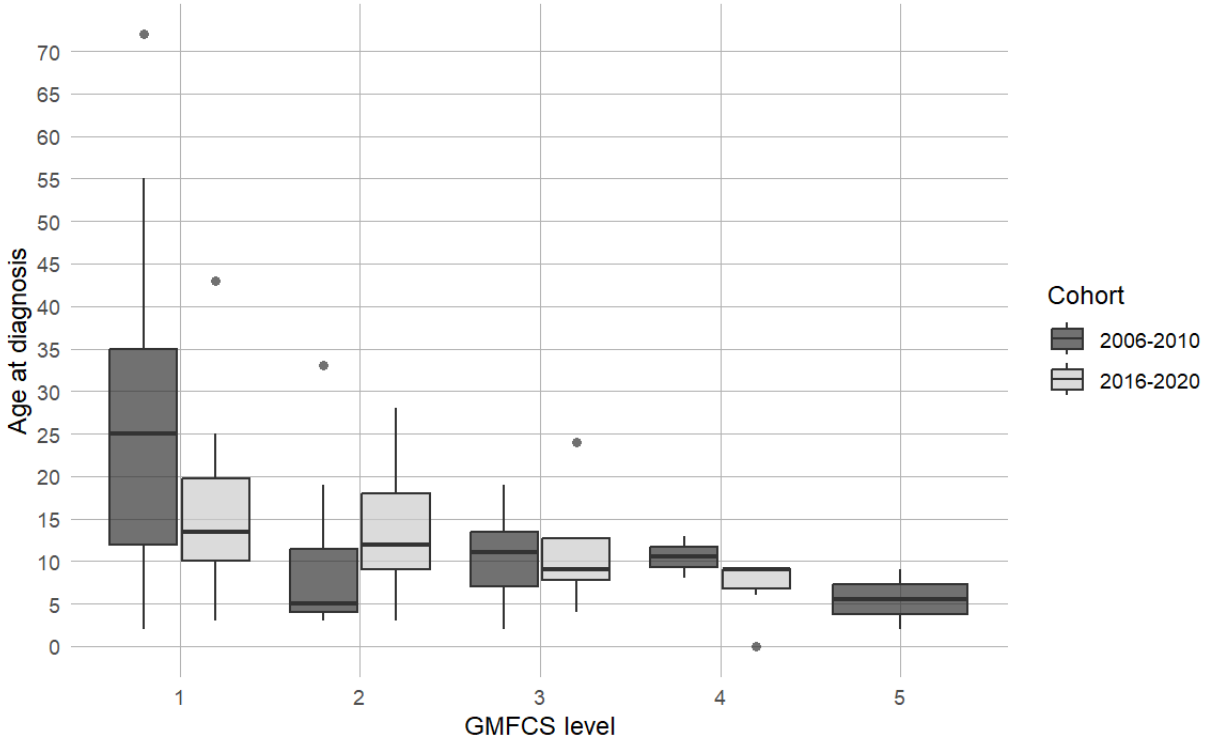


FIGURE 3: Age at cerebral palsy diagnosis by GMFCS level and birth cohort. Boxplots showing the age (corrected age in months) at cerebral palsy (CP) diagnosis by Gross Motor Function Classification System (GMFCS) level for the 2006-2010 (dark) and 2016-2020 (light) birth cohorts. The bold horizontal line indicates the median, the upper and lower lines represent the interquartile range (IQR). For GMFCS level 5, no cases were present in the 2016-2020 cohort.

Discussion

In this study, we investigated changes in the timing and approach to CP diagnosis in two high-risk neonatal birth cohorts a decade apart. We hypothesized that the implementation of structured and reimbursed neonatal follow-up within the Belgian prematurity convention in 2012 would result in earlier diagnosis of CP, as well as earlier referral and initiation of intervention.

The results show that the median age at diagnosis did not differ significantly between the two birth cohorts, with a median of 10.5 months corrected age in the most recent cohort. Contrary to our hypothesis, the introduction of structured follow-up was not associated with a statistically significant reduction in age at diagnosis. Nevertheless, the observed diagnostic age is close to that reported in international studies following full implementation of early detection guidelines. Maitre et al. reported a reduction in median diagnostic age from 19.5 months (95% CI 16.2-22.8) to 9.5 months (95% CI 4.5-14.6) following introduction of a standardised early detection pathway (14). Ryder et al. observed a decrease from 18.5 to 7.5 months after implementing a quality improvement initiative (24). Notably, the diagnostic age observed in our recent cohort approached these international findings despite the limited routine use of standardised assessments such as the GMs, HINE, and HAI at UHL during the study period. More systematic integration of these tools may therefore offer further opportunities to advance early detection. International initiatives across different clinical settings emphasize that their successful implementation requires coordinated multidisciplinary pathways (25).

Several factors may explain why no significant reduction in diagnostic age was observed. First, elements of structured follow-up and heightened clinical awareness may already have been present at our centre prior to the formal implementation of the prematurity convention in 2012, thereby attenuating measurable differences between cohorts. Second, the study population consisted exclusively of high-risk infants admitted to a tertiary NICU, who are likely to have benefited from closer surveillance and earlier recognition of motor abnormalities even before standardisation. Together, these factors suggest that the incremental effect of formal reimbursement and structuring of follow-up may be more difficult to detect in such a setting.

The higher proportion of extremely preterm children in the 2016-2020 cohort may partly explain the higher frequency of ROP, as lower gestational age is an important risk factor for ROP. However, because the study included only children with CP rather than all infants admitted to the NICU, these findings should not be interpreted as temporal trends in the overall NICU population. As extremely preterm infants are eligible for structured neonatal follow-up and closer surveillance, the difference in gestational age distribution may have influenced the timing of CP recognition. The independent contribution of gestational age and ROP to diagnostic age could not be determined in this relatively small cohort. As expected, children with more



FIGURE 4: Time between diagnosis and referral by birth cohort. Boxplots showing the interval (in months) between cerebral palsy (CP) diagnosis and referral to the CP reference center for the 2006-2010 and 2016-2020 birth cohorts. Each dot represents an individual child, the bold horizontal line indicates the median, the upper and lower lines represent the interquartile range (IQR).

severe motor impairment (higher GMFCS levels) were diagnosed earlier, likely because clinical signs are more apparent and developmental deviations more pronounced in infancy. This association between functional severity and earlier diagnosis has been consistently reported in literature, including by McIntosh (26). This finding underscores the ongoing challenge of timely identification of children with milder motor impairments, who may present with subtler signs and are therefore at higher risk of delayed diagnosis. The relatively high proportion of examinations documented as normal at discharge should also be interpreted cautiously, as these were routine, non-standardised clinical assessments performed by a neonatologist or paediatric resident. Subtle neurological abnormalities may therefore not have been detected or documented at that time.

The distinct diagnostic peak at 9 months corrected age may partly reflect the timing of scheduled assessments within the national prematurity follow-up program, which provides standardised assessments for infants born before 31 weeks of gestation and/or below 1500 g. Consistent follow-up at predefined intervals facilitates early recognition of motor difficulties. However, the clustering of diagnoses around the nine-month assessment also suggests that scheduled visits may influence the timing of diagnosis. Earlier risk-based assessments using recommended standardised tools could allow selected high-risk infants to be identified before nine months, although our study was not designed to determine the optimal timing or frequency of follow-up assessments. Supporting the value of systematic follow-up, Hubermann et al. found that children with a history of NICU admission received a CP diagnosis at a younger age compared to those without NICU hospitalization, highlighting the added value of systematic follow-up after intensive care (27).

In the available medical records, communication of motor developmental concerns to parents was documented at a significantly earlier age among children with available data in the 2016-2020 cohort. This communication was also documented for a substantially higher proportion of children in the more recent cohort, suggesting more consistent recording in the medical files. However, the comparison of timing should be interpreted cautiously, as this information was missing for most children in the 2006-2010 cohort. It therefore remains unclear whether the observed difference reflects earlier communication itself, changes in documentation practices, or both. Early communication of developmental concerns, when it occurs, may facilitate timely referral and intervention, while also providing parents with earlier psychosocial support and reducing uncertainty. Furthermore, referral to the CP reference centre occurred significantly earlier, and the interval between diagnosis and referral was shorter, suggesting improved coordination and accessibility to specialised care.

Despite earlier documented communication of motor developmental concerns in the more recent cohort, physiotherapy was not initiated earlier. However,

physiotherapy was nearly universal and was already initiated at a young, corrected age in both cohorts, leaving limited room for further reduction in age at initiation. Moreover, because information on the timing of communication was unavailable for many children, the temporal relationship between communication and initiation of physiotherapy could not be reliably assessed. In contrast, CIMT was initiated both more frequently and at an earlier age. Only 5 infants in the 2006-2010 cohort received CIMT, whereas its more frequent use in the later cohort may reflect the growing body of evidence supporting its effectiveness in improving hand function and bimanual activities, as well as its inclusion in international guidelines (7, 28, 29). In our cohort, CIMT was used in children with unilateral CP and in selected children later classified as having bilateral CP with marked asymmetry of upper-limb involvement.

Taken together, several components of the diagnostic and care pathway differed favourably in the more recent cohort. However, these changes cannot be attributed to structured neonatal follow-up alone. During the study interval, awareness of early CP detection increased, international diagnostic and early-intervention guidelines were disseminated, rehabilitation practices evolved, and local documentation and referral pathways may have changed. The observed differences may therefore reflect the combined influence of structured follow-up and broader developments in early CP care.

A major strength of this study is the comparison of two birth cohorts a decade apart, enabling evaluation of temporal changes in diagnostic timing and follow-up practices. Despite recommendations, standardised tools such as HINE, GMs, and HAI were infrequently used in both cohorts, indicating room for improvement in local practice. This finding aligns with the conclusions of Hidalgo-Robles et al., who identified major implementation barriers, including limited training, staffing constraints, and lack of coordinated pathways, despite widespread agreement on the clinical value of these tools (30). Our findings therefore provide an important benchmark for evaluating the impact of future implementation of early detection guidelines. One example is that, since 2021, standardized HAI assessments have been implemented in the clinical follow-up program at UHL for children at risk for developing unilateral CP, and CIMT has been initiated as early as 4 months of age. As implementation continues, further improvements in early diagnosis, intervention, and outcomes may be expected. The findings are directly relevant for clinicians involved in high-risk infant follow-up programs and support the alignment of local care pathways with international early detection guidelines. Limitations include the retrospective design and reliance on the completeness of medical records. Missing data affected several variables and were more pronounced for some outcomes in the earlier cohort, potentially introducing information and documentation bias and limiting the reliability of comparisons between cohorts. Assessments, interventions, or communications occurring outside the available medical records may have been missed, and the absence of documentation cannot be interpreted as evidence that these did not occur. Additional limitations include the potential underrepresentation of children diagnosed outside our reference centre and the single-centre setting. The relatively small sample size, combined with the considerable variability in age at diagnosis, particularly in the earlier cohort, may have limited the ability to detect a modest but potentially clinically relevant difference between cohorts. Larger, preferably multicentre studies are therefore needed to evaluate changes in diagnostic timing with greater statistical precision. Because cohort allocation was based on calendar period, the potential contribution of structured neonatal follow-up could not be separated from other concurrent changes in clinical practice and documentation. Nevertheless, these results provide a realistic reflection of diagnostic practice in a tertiary NICU setting and highlight key opportunities for advancing early CP detection.

Conclusion

This study provides insight into how the diagnostic process of cerebral palsy (CP) in a high-risk neonatal population has evolved over time. In contrast to our initial hypothesis, no significant reduction in age at diagnosis was observed between the two birth cohorts. Nevertheless, the median age at diagnosis in the most recent cohort was comparable to that reported in international programs with full implementation of early detection guidelines.

The more recent cohort was characterized by more frequent documentation of communication about motor concerns, earlier referral to specialised care, and more timely initiation of interventions such as CIMT and home guidance. Among children with available data, communication was also documented at an earlier age, although this finding should be interpreted cautiously because of substantial missing data in the earlier cohort. While causal relationships cannot be established, these findings suggest improvements in clinical practice and care organisation over time.

Together, these results indicate favourable changes over time in several components of the early recognition and management of CP. Further integration of evidence-based assessment tools such as GMs, HINE, and HAI, alongside continued optimization of follow-up pathways, may help to further enhance early detection and improve outcomes.

Conflict of interest statement

The authors declare that they have no conflicts of interest relevant to this study.

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Lung Pediatry

BELGIAN RESPIRATORY SOCIETY

NIEUW



De Belgian Respiratory Society (BeRS) organiseert de **"1st Belgian Paediatric Lung Day"** gewijd aan de respiratoire gezondheid van kinderen

EEN NIEUWE ONTMOETINGSPLEK VOOR DE PEDIATRISCHE PNEUMOLOGIE

Dit nieuwe Engelstalige programma, georganiseerd door de Paediatric Lung Working Group van de Belgian Respiratory Society (BeRS), vindt plaats op 11 december 2026 in het BMCC in Brugge en wil van deze eerste editie het startpunt maken van een jaarlijkse afspraak voor professionals die betrokken zijn bij de respiratoire zorg voor kinderen.

- Van astma en complexe luchtwegaandoeningen tot de zorg voor kinderen met neurologische of neuromusculaire aandoeningen: pediatrische pneumologie vereist specifieke expertise en een multidisciplinaire aanpak.
- Deze eerste editie richt zich tot kinderpneumologen, kinderartsen, pneumologen, huisartsen, kinesitherapeuten, verpleegkundigen en andere zorgprofessionals die betrokken zijn bij de respiratoire zorg voor kinderen. De deelnemers krijgen de kans om van gedachten te wisselen over de nieuwste wetenschappelijke inzichten, complexe klinische casussen en de belangrijkste uitdagingen waarmee jonge patiënten en hun families worden geconfronteerd.
- Het programma besteedt ook aandacht aan de impact van de omgeving op de respiratoire gezondheid van kinderen, waaronder roken, vapen en het bevorderen van een rookvrije zwangerschap.

EEN SESSIE GEWIJD AAN COMPLEXE CASUSSEN



Deze interactieve sessie is gewijd aan de bespreking van complexe casussen van pediatrisch astma, met bijzondere aandacht voor diagnose, behandeling, opvolging en psychosociale aspecten.

- Wilt u een casus indienen?
- Stuur uw abstract uiterlijk op 9 november 2026 naar ***karin.decaestecker@azdelta.be*** en maak kans om uw casus te presenteren en te bespreken met experts en deelnemers.

JONG WETENSCHAPPELIJK TALENT IN DE KIJKER



Heeft u een interessante klinische casus om te delen of wetenschappelijke resultaten om te presenteren?

- Grijp deze eerste editie aan om uw werk in de kijker te zetten en actief bij te dragen aan het wetenschappelijke programma.
- Dien uw abstract in binnen één van de twee categorieën: Clinical Case of Scientific Abstract.
- De geselecteerde abstracts worden mondeling gepresenteerd tijdens het congres en de beste abstract in elke categorie wordt bekroond met een prijs van € 500.
- Abstracts moeten in het Engels worden opgesteld, beperkt zijn tot 350 woorden en uiterlijk op 9 november 2026 worden verzonden naar ***ckempeneers@chuliege.be***.



« Met deze eerste editie willen we een ontmoetingsplek creëren waar Belgische professionals die betrokken zijn bij de zorg voor kinderen met respiratoire aandoeningen hun kennis kunnen delen, van elkaar kunnen leren en samen kunnen nadenken over de uitdagingen van morgen. »
Prof. Céline Kempeneers, Chair BeRS Working Group Lung Pediatry

PRAKTISCHE INFORMATIE

- **Inschrijvingen en informatie over het indienen van abstracts vindt u op www.bers.be.**
- **Plaats en datum: BMCC – Brugge – Vrijdag 11 december 2026**
- **De deelnemers aan dit evenement krijgen eveneens toegang tot het programma van de Belgian Pneumology Days 2026, die op vrijdag 11 december gelijktijdig plaatsvinden in het BMCC.**

RESEARCH ARTICLE

Belg J Paediatr. 2026;28(3):239-250

Heated Cot Use during the First Postnatal Days in Term Neonates: A Multicentre Retrospective Observational Study

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Keywords

Thermoregulation; Term Neonates;
Heated Cot; Warmth Mattress: Neonatal Care

Abstract

Purpose

Maintaining normothermia is a key component of optimal neonatal care, as both hypothermia and hyperthermia are associated with increased morbidity and mortality across gestational ages. This study evaluated the relationship between the use of heated cot and thermal outcome during the first postnatal days.

Methods

This multicentre retrospective comparative study included healthy neonates (N= 1371) born at ≥36 weeks gestation and weighing >2.2 kg in two maternity units using different thermoregulatory protocols: heated cot care versus standard cot care. The primary outcome was normothermia; secondary outcomes included hypothermia and hyperthermia.

Results

Heated cot use was associated with significantly more normothermia (OR 1.48, 95% CI 1.28–1.72) and less hypothermia (OR 0.51, 95% CI 0.42–0.63), but significantly more hyperthermia (OR 1.72, 95% CI 1.28–2.31). These associations were time-dependent, as demonstrated by a significant interaction between heated cot use and postnatal age for normothermia and hypothermia. In neonates small for gestational age, heated cot use was associated with both higher odds of normothermia (OR 2.0, 95% CI 1.35–2.95) and lower odds of hypothermia (OR 0.42, 95% CI 0.26–0.67). Similar non-significant trends were observed with lower birthweight and gestational age.

Conclusions

Heated cot use was associated with more normothermia and less hypothermia, but also more hyperthermia. Routine use in all healthy neonates may not be warranted, although selected high-risk neonates may benefit.

Introduction

Maintaining normothermia is essential for optimal neonatal care, as both hypo- and hyperthermia are linked to increased morbidity and mortality across all gestational ages (1–4). All newborns are at risk of thermoregulatory instability due to a high surface-to-weight ratio, high metabolic rate, limited glycogen stores, and immature thermoregulation (2–6), with preterm infants being at highest risk due to additional anatomical and physiological immaturity. Risk of thermoregulatory instability is further increased by low birth weight, asphyxia, congenital anomalies, low environmental temperature, and socio-economic and knowledge-related factors (3,5,7). Hypothermia in newborns leads to increased metabolism to normalize temperature. Consequently, this increases oxygen and glucose consumption, putting the newborn at risk for respiratory and metabolic problems, such as acidosis and hypoglycaemia (6). Either hypoglycaemia leads to hypothermia due to limited glycogen storage, or hypothermia leads to hypoglycaemia due to energy consumption to maintain body temperature (8). Prolonged cold stress may result in delayed transition from foetal to neonatal circulation and is associated with poor weight gain, neurological complications, coagulation defects, impaired cardiac function, jaundice, haemorrhage and even death (3,6,9). Notably, hyperthermia has also been associated with morbidity, including irritability, apnoea, poor feeding, dehydration, and tachycardia (4).

Heat loss occurs through evaporation of fluid from the skin immediately after birth, radiation to the cooler environment, conduction when the infant is placed on cold surfaces, and convection caused by air movement (9). Based on these principles, recommendations include providing a warm delivery room at

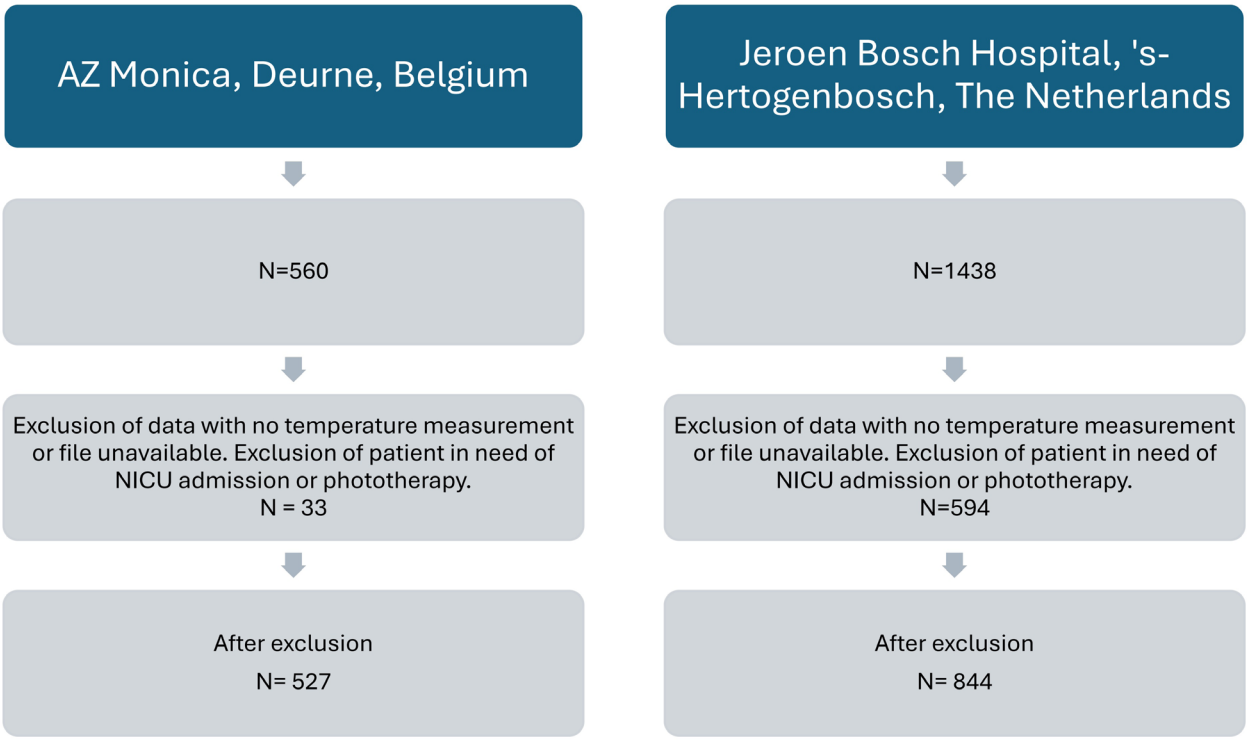


FIGURE 1: Patient screening and inclusion within the prespecified study window at Jeroen Bosch Ziekenhuis ('s-Hertogenbosch) and AZ Monica (Deurne). Exclusion criteria and numbers are shown per centre.

25°C, immediately drying the infant and removing wet blankets, covering the neonate with a clean blanket, and keeping the baby skin to skin to the mother, since kangaroo mother care improves thermoregulation. The use of preheated blankets and surfaces and radiant warmers is an additional support of thermoregulation (2–4,6,9–14). External heat is of importance, especially in lower environmental temperatures such as the operating theatre for term and preterm infants (15).

For vulnerable populations, such as premature infants, heat loss preventing strategies such as incubator care, radiant warmers, heated cots, and continuous temperature monitoring have been extensively studied and are widely implemented in neonatal care units (4,16). Although the importance of thermoregulation in the immediate postnatal period is well established and reflected in the WHO guidelines, guidance on thermoregulation for term and late preterm infants admitted to maternity wards during the first days of life is considerably less well defined (9). As a result, approaches to maintain normothermia in this population vary substantially between institutions and countries. For instance, in several Dutch hospitals, use of heated cots is standard of care to manage thermoregulation in newborns during the first days of life. In contrast, in most Belgian hospitals, normothermia is managed in a cot with blankets, without external heat sources. Proposed advantages of heated cots include the ability to easily adjust temperature following the individual need of each newborn and the awareness for adequate thermoregulation. However, these devices are more expensive, their sustainability is questionable, and it requires extra maintenance compared to care in a standard cot.

Consequently, there is a lack of evidence regarding the benefit of heated cots for maintaining normothermia and preventing hypothermia and hyperthermia in late preterm and term newborns cared for in maternity units. The aim of this study was to compare two thermoregulatory strategies and to evaluate whether heated cot use was more effective than standard care in maintaining normothermia during the first days of life.

Methods

Population

Inclusion criteria

This multicentre retrospective comparative study included healthy neonates (≥36 weeks; >2.2 kg) admitted to the maternity units of two non-university hospitals with different temperature regulation protocols. The Belgian centre constituted the control group, while the Dutch centre implemented a heated cot protocol. All infants born between December 2023 and February 2024 (defined as winter) and between June and August 2024 (defined as summer) were included in the analysis (Figure 1).

TABLE 1: Overview of patient characteristics.

Variables	Non-heated cot	Heated cot	p-value
N = 1371	N = 527	N = 844	
Born in summer, n (%)	285 (54%)	437 (52%)	0.438 (1)
Born in winter, n (%)	242 (46%)	407 (48%)	0.438 (1)
Sex, n (%)			0.076 (1)
female	271 (52%)	392 (46%)	
male	255 (48%)	452 (54%)	
GA, weeks			0.587 (2)
mean ± SD	39.59 ± 1.11	39.63 ± 1.28	
median (Q1, Q3)	39.71 (38.86, 40.43)	39.57 (38.79, 40.71)	
Delivery method, n (%)	*		0.001 (1)
assisted	45 (8.5%)	90 (11%)	
Caesarean	106 (20%)	234 (28%)	
vaginal	376 (71%)	520 (62%)	
Birthweight, kg			0.004 (2)
median (Q1, Q3)	3,426 (3,100, 3,692)	3,490 (3,135, 3,880)	
Birthweight category, n (%)	**		<0.001 (1)
LGA	43 (8.2%)	141 (17%)	
AGA	423 (80%)	590 (70%)	
SGA	61 (12%)	113 (13%)	
Feeding, (n = 1317) (%)			<0.001 (3)
breastfeeding	406 (77%)	557 (70.5%)	
formula feeding	61 (11.6%)	233 (29.5%)	
combination	60 (11.4%)	-	
Maternal diabetes, n (%)			0.3 (3)
no	492 (93%)	796 (94%)	
yes	35 (6.6%)	48 (5.7%)	
APGAR			
APGAR 1min (n = 1350)	8.73 ± 0.98	8.52 ± 1.50	0.090 (2)
APGAR 5min (n = 1350)	9,539 ± 0,651	9,623 ± 0,848	<0.001 (2)
APGAR 10min (n = 1062)	9,867 ± 0,367	9,821 ± 0,542	0.773 (2)
Temperature measurements during hospital stay			<0.001 (2)
mean ± SD	7,54 ± 2,87	7,47 ± 4,72	
median (Q1, Q3)	7 (6, 9)	6 (4, 10)	
Hospital hours (h)			<0.001
mean ± SD median	64,9 ± 20,6	25,7 ± 15,7	
Median (Q1, Q3)	67 (55, 79)	15.2 (5.9, 24.4)	

GA: gestational age, LGA: large for gestational age, SGA: small for gestational age; AGA: appropriate for gestational age. Statistical analysis (1) chi square test (2) Mann Withney U test (3) Fisher test. * Post hoc pairwise comparisons: difference in vaginal deliveries and Caesarean sections (p_adj=0.002). **Post hoc pairwise comparisons: difference in AGA and LGA (both p_adj<0.001), no difference for SGA (p_adj=0.98). p_adj values were adjusted for multiple post hoc comparisons using the Bonferroni method

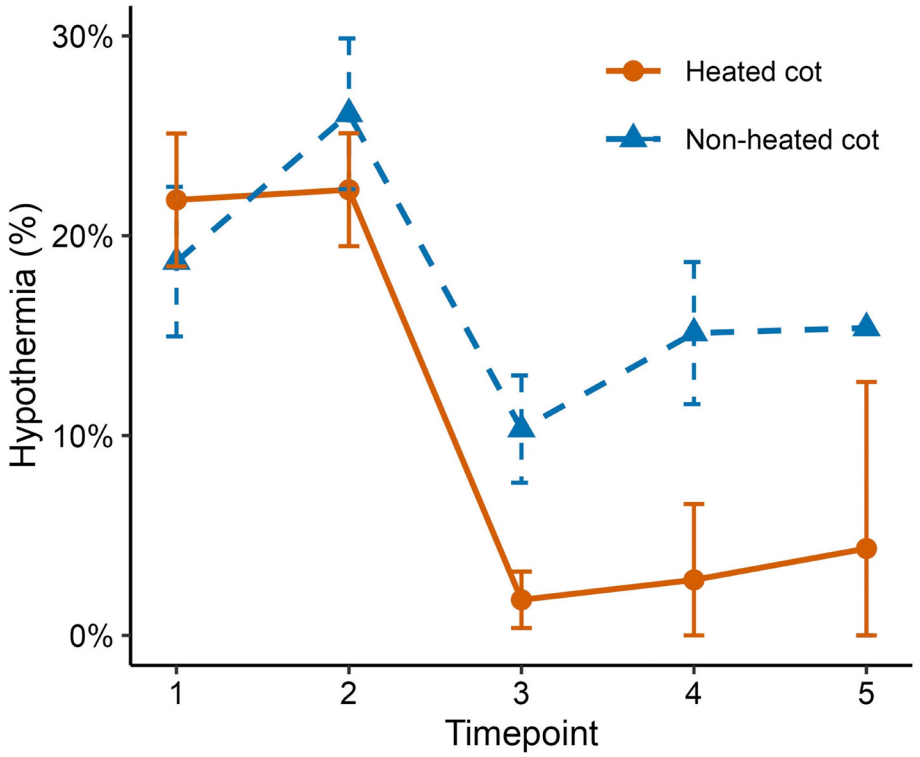


FIGURE 2: Percentages of hypothermia by timepoints with 95% confidence intervals. Solid red line = heated cot group. Dashed blue line = non-heated cot group. t1 (0–2 hours), t2 (2–24 hours), t3 (24–48 hours), t4 (48–96 hours), and t5 (>96 hours after birth).

Exclusion criteria

Neonates requiring neonatal intensive care (e.g., for prematurity, low birth weight, or suspected infection requiring antibiotics) or phototherapy were excluded.

Outcomes and definition

The primary research question was whether heated cot use was associated with a higher proportion of normothermic neonates during the first days of life compared with standard cot care. Secondary research questions examined the association of heated cot use with hypothermia, hyperthermia, hypoglycaemia, and postnatal weight loss. Study outcomes were defined a priori. Normothermia was defined, according to the World Health Organization, as all recorded temperatures remaining within 36.5–37.5 °C throughout the observation period (9). Temperature measurements were categorized across five postnatal time intervals: t1 (0–2 h), t2 (2–24 h), t3 (24–48 h), t4 (48–96 h), and t5 (>96 h). Hyperthermia was defined as any recorded temperature >37.5 °C (mild, 37.5–38.0°C; moderate, >38.0 °C or ≥2 temperatures >37.5 °C) and hypothermia any temperature <36.5 °C (mild, 36.0–36.5 °C; moderate, <36.0 °C or ≥2 temperatures <36.5 °C). Hypoglycaemia was defined as blood glucose <50 mg/dL before 48 h or <60 mg/dL after 48 h (17).

The exposure of interest was heated cot use (heated cot versus standard cot care). The following variables were collected a priori as potential confounders: Apgar score at 1, 5 and 10 minutes; mode of delivery (caesarean section versus vaginal); feeding type; postmenstrual age; birth weight; birth weight category; percentage of postnatal weight loss; length of hospital stay (hours); maternal diabetes; and neonatal blood glucose measurements. Birth weight category was defined as small for gestational age (SGA; birth weight <p10), appropriate for gestational age (AGA; birth weight p10–p90), or large for gestational age (LGA; birth weight >p90). The percentage of postnatal weight loss was calculated as the lowest weight recorded during admission relative to birth weight. Effect modifiers are described separately in the statistical analysis section.

Study interventions

In the control group (AZ Monica, Deurne, Belgium), infants were nursed in standard cots with skin-to-skin care and additional clothing. Temperature was checked after birth and monitored at least twice daily, or more frequently if an abnormal value was found (below 36.5 °C or above 37.5 °C). When hypothermia was observed, skin-to-skin care was encouraged; when this was not possible, the infant was covered with extra clothing and sheets. In the heated cot group (Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands), all infants were nursed on heated cots (Vab CosyTherm2) in addition to skin-to-skin care and routine temperature monitoring. The heat mattress is set at 37.5°C by default. If the temperature of the neonate is below 36.5°C, in the impossibility

TABLE 2: Overview of Temperature Outcomes.

2a. Overview of Normothermia, Hypothermia and Hyperthermia			
Variables	**Non-heated cot**	**Heated cot**	**p-value**
N = 1371	N = 527	N = 844	
Normothermia, n (%)	221 (41.9%)	414 (49.1%)	<0.001 (1)
Hypothermia, n (%)	240 (45.5%)	268 (31.8%)	<0.001 (1)
Mild hypothermia, n (%)	136 (25.8%)	139 (16.5%)	<0.001 (1)
Moderate hypothermia, n (%)	104 (19.7%)	129 (15.3%)	0.032 (1)
Hyperthermia, n (%)	110 (20.9%)	226 (26.8%)	<0,001 (1)
Mild hyperthermia, n (%)	127 (24.1%)	337 (39.9%)	<0.001 (1)
Moderate hyperthermia, n (%)	48 (9.1%)	171 (20.3%)	<0.001 (1)

2b. Temperature Outcomes per Timepoint				
Timepoint	**Temperature category**	**No heated cot**	**Heated cot**	**p-value**
1 (0-2h)	Normothermia	296 (71%)	382 (64.5%)	0.0315 (1)
	Hypothermia	78 (18.7%)	129 (21.8%)	0.2320 (1)
	Hyperthermia	43 (10.3%)	81 (13.7%)	0.1083 (1)
2 (2-24h)	Normothermia	369 (70.8%)	549 (65.8%)	0.0555 (1)
	Hypothermia	136 (26.1%)	186 (22.3%)	0.1097 (1)
	Hyperthermia	20 (3.8%)	120 (14.4%)	<0.001 (1)
3 (24-48h)	Normothermia	400 (81%)	279 (82.8%)	0.5057 (1)
	Hypothermia	51 (10.3%)	6 (1.8%)	<0.001 (1)
	Hyperthermia	45 (9.1%)	54 (16%)	0.0025 (1)
4 (48-96h)	Normothermia	313 (80.3%)	58 (80.6%)	0.9532 (1)
	Hypothermia	59 (15.1%)	2 (2.8%)	0.0045 (1)
	Hyperthermia	20 (5.1%)	13 (18.1%)	0.0001 (1)
5 (> 96h)	Normothermia	11 (84.6%)	20 (87%)	1.0000 (2)
	Hypothermia	2 (15.4%)	1 (4.3%)	0.5394 (2)
	Hyperthermia	NA	2 (8.7%)	0.5254(2)
Statistical analyses (1) Chi-square (2) Fisher's exact test.				

of skin-to-skin care, the heat mattress is built up to a maximum temperature of 40°C. At a temperature above 37.5°C, the heat mattress is reduced by 0.5°C. Temperature is measured rectally after birth and monitored every 3-4 hours for the first 24 hours of life.

In both groups infants wear disposable nappies, a cotton romper, clothing as per parents' choice and they are covered with cotton sheets and blankets. For each infant, all temperature measurements recorded during the maternity stay were included, from birth until discharge. The usual length of stay was 6–24 hours in the Dutch heated cot hospital and at least 48 hours in the Belgian control hospital.

For each infant, neonatal characteristics and temperature measurements were retrieved from the medical patient record in both centres. Temperatures were measured predominantly rectally, although the extent to which other methods were used could not be determined from the records. The frequency of measurements followed each centre's local protocol and the nursing staff's clinical judgement, and therefore differed between the two centres.

Statistics

Data collection

Data were collected using REDCap (Belgium) and CTcue (IQVIA, Amsterdam, the Netherlands). Analyses were performed in R version 4.5.2. A pilot sample of 100 infants per group was used for sample size estimation, yielding a required sample of 394 infants per group at α=0.05 and 80% power. The final study population exceeded this target sample size, as all available eligible patients within the prespecified study period were included.

TABLE 3: Odds ratios (OR) for normothermia, hypothermia and hyperthermia associated with heated cot use (1 vs 0)

Timepoint	OR	95 CI interval	p-value
Normothermia			
T1 (0-2h)	0.66	0.50–0.86	0.0024
T2 (2-24h)	2.51	1.99–3.17	<0.001
T3 (24-48h)	2.46	1.75–3.47	<0.001
T4 (48-96h)	3.48	2.00–6.05	<0.001
T5 (> 96h)	4.52	0.61–33.58	0.14
Hypothermia			
T1 (0-2h)	1.39	0.99-1.95	0.052
T2 (2-24h)	0.27	0.20–0.36	<0.001
T3 (24-48h)	0.06	0.02–0.15	<0.001
T4 (48-96h)	0.02	0.004–0.097	<0.001
T5 (> 96h)	0.04	0.003–0.611	0.021
Hypothermia			
T1 (0-2h)	1.51	0.96–2.37	0.078
T2 (2-24h)	1.43	0.81–2.51	0.214
T3 (24-48h)	1.01	0.63–1.63	0.958
T4 (48-96h)	1.95	0.91–4.18	0.087
T5 (> 96h)	NA	NA	NA
Stratified by timepoint adjusted for measurement intensity per timepoint.			

Descriptive statistics

Continuous variables were non-normally distributed on Q–Q plots, so groups were compared using the Mann–Whitney U, chi-square, or Fisher's exact test as appropriate, with significance at $p<0.05$.

Generalized Linear Mixed-Effects Model

For temperature-related outcomes, generalized linear mixed-effects models with a random intercept for each neonate were used to account for repeated measurements within patients. Heated cot use was the main fixed effect. Prespecified baseline characteristics: gestational age, birthweight, sex, mode of delivery, and birth month were evaluated as potential confounders using a change-in-estimate approach, with a change in the estimated effect of <5% considered not relevant. Maternal diabetes, 5-minute Apgar score, feeding status, and birthweight category (small, appropriate, or large for gestational age) were assessed in additional analyses. As none of these substantially changed the estimated association, they were not retained in the final models.

Timepoint was included as a categorical fixed effect in all models to account for temporal variation across t1–t5. Measurement intensity was defined as the number of temperature measurements per neonate standardized per defined time interval. Measurement intensity was included as a fixed effect in all models to account for differences in monitoring frequency between centres and between patients, which may relate to clinical instability. Moreover, the use of a heated cot may encourage more frequent temperature assessments. Final models included heated cot use, timepoint, and measurement intensity.

Secondary outcomes

Subgroup and interaction analyses were performed as exploratory analyses and were not adjusted for multiple comparisons. Effect modification of the association between heated cot use and normothermia, hypothermia, and hyperthermia by birthweight, gestational age, and birthweight category was assessed using likelihood ratio tests. Predicted probabilities were additionally estimated. The association between heated cot use and hypoglycaemia was evaluated at patient level using multivariable logistic regression restricted to neonates who underwent glucose monitoring, adjusted for birthweight, gestational age, sex, mode of delivery, and birth month. The effect of heated cot use on percentage postnatal weight loss was examined using multivariable linear regression among neonates with available weight-loss data, adjusted for the same baseline variables and duration of hospitalization. Sensitivity analyses included alternative definitions of hospital stay and additional adjustment for birthweight category.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Jeroen Bosch Ziekenhuis (JBZ), 's-Hertogenbosch, the Netherlands (AGB code 06011034), and Algemeen Ziekenhuis Monica VZW, Belgium (enterprise number BE 0459.768.815). Due to the observational nature of the study, the Ethics Committee has waived the need for parental consent for participation in the study.

Results

Descriptives

We analysed 1,371 neonates: 527 in the control group and 844 in the heated cot group (Table 1). Groups were comparable for season of birth, sex, gestational age and maternal diabetes. Birthweight category differed significantly, with fewer neonates appropriate for gestational age (AGA) and more neonates large for gestational age (LGA) in the heated cot group, while proportion infants small for gestational age (SGA) were similar. Mode of delivery also differed with more Caesarean sections and fewer vaginal deliveries in the heated cot group. Apgar scores differed statistically significant only at 5 minutes, but differences were clinically small. Birthweight differed modestly between groups and feeding practices were not comparable between centres. Median hospital stay was longer in the Belgian cohort than in the Dutch cohort (64.9 vs. 25.7 hours). The number of temperature measurements were similar between centres (Table 1).

Normothermia

The proportion of neonates classified as normothermic was significantly higher in the heated cot group than in the control group (49.1% vs. 41.9%, p = 0.01, Pearson's Chi-squared test) (Table 2). In a generalized linear mixed model adjusted for timepoint, heated cot use was associated with higher odds of normothermia (OR 1.36, 95% CI 1.18–1.58; p<0.001), which increased after adjustment for measurement intensity (OR 1.48, 95% CI 1.28–1.72; p<0.001). Measurement intensity was strongly associated with normothermia, with each one standard deviation increase in measurement intensity associated with lower odds of normothermia (OR 0.67, 95% CI 0.62–0.73; p < 0.001). When analysed by predefined time intervals (Table 3) and adjusted for measurement intensity per timepoint, a significant interaction between heated cot use and timepoint was observed (likelihood ratio test $\chi^2(4) = 45.88$, p < 0.001). The use of a heated cot was associated with lower odds of normothermia during the first 2 hours after birth. From 2 hours onwards, the association became positive and increased over time. Beyond 96 hours, the point estimate remained elevated, but with wide confidence intervals, reflecting limited data in this interval. Inclusion of baseline covariates within the first timepoint did not substantially change the estimated odds ratio for heated cot use.

Hypothermia

Hypothermia occurred more frequently in the non-heated cot group than in the heated cot group (45.5% vs. 31.8%, p<0.001). Both mild (25.8% vs. 16.5%, p<0.001) and moderate hypothermia (19.7% vs. 15.3%, p=0.038) were less common with heated cot use (Table 2). The highest proportion of hypothermia occurred between 2–24 hours of age (Figure 2). A generalized linear mixed model adjusted for timepoint and measurement intensity showed that heated cot use was associated with lower odds of hypothermia (OR 0.51, 95% CI 0.42–0.63; p<0.001). Adding measurement intensity improved model fit (likelihood ratio test $\chi^2(1)=22.59$, p<0,001). The association was strongly time-dependent (likelihood ratio test $\chi^2(4)= 120.7$, p < 0.001), although hypothermia odds at the first timepoint were paradoxically higher in the heated cot group, heated cot use was associated with consistently lower odds from timepoint 2 onward, with the strongest reduction at timepoint 4 (Table 3).

Hyperthermia

Hyperthermia was more frequent in the heated cot group than in the non-heated group (26.8% vs. 20.9%, p = 0.013), including both mild and moderate cases (Table 2). Heated cot use was associated with increased odds of hyperthermia (OR 1.72, 95% CI 1.28–2.31, p < 0.001). Adding timepoint and measurement intensity to the model significantly improved fit (likelihood-ratio test, $\chi^2(5) = 176.04$, p < 0.001). There was no significant interaction between heated cot use and timepoint (likelihood-ratio test, $\chi^2(4) = 7.98$, p = 0.09), indicating that the effect of heated cot use did not differ significantly across timepoints. In a sensitivity analysis adjusting for timepoint-specific measurement intensity, the per-timepoint odds ratios were attenuated and no longer reached statistical significance at any timepoint, although all point estimates remained in the same direction (OR ≥ 1). Estimates at timepoint 5 were unstable across all models, consistent with sparse data (Table 3).

Outcomes by birthweight, gestational age and birthweight category

No significant interaction was observed between heated cot use and either gestational age or birthweight for normothermia, hypothermia, or hyperthermia. For gestational age, likelihood ratio tests showed no evidence of effect modification for normothermia (χ^2 = 0.12, p = 0.73), hypothermia (χ^2 = 0.044, p = 0.83), or hyperthermia (χ^2 = 0.03, p = 0.86). Similarly, birthweight did not significantly modify the association between heated cot use and normothermia (χ^2 = 1.76, p = 0.18), hypothermia (χ^2 = 0.35, p = 0.55), or hyperthermia (χ^2 = 0.26, p = 0.61). Predicted probabilities nevertheless

suggested a greater absolute benefit of heated cot use for normothermia at lower birthweight and lower gestational age. For hypothermia, predicted probabilities were lower in the heated cot group across the birthweight and gestational age ranges, with a visually larger absolute difference at lower birthweight. For hyperthermia, predicted probabilities were consistently higher in the heated cot group, with visually steeper increases at higher birthweight and gestational age.

In contrast, birthweight category (SGA/LGA/AGA) significantly modified the association between heated cot use and both normothermia ($\chi^2 = 6.19$, $p = 0.045$) and hypothermia ($\chi^2 = 8.20$, $p = 0.017$), but not hyperthermia ($\chi^2 = 5.22$, $p = 0.074$). For normothermia, the association with heated cot use was significant only in SGA neonates. For hypothermia, lower odds were observed across all birthweight categories, with the strongest associations in LGA and SGA neonates (Figures 3–4).

Exploratory clinical outcomes

Glucose monitoring was performed more frequently in the heated cot group than in the standard care group (38.0% vs. 12.7%). Among neonates who underwent glucose measurement, the proportion with hypoglycaemia did not differ significantly between groups (123/321 [38.3%] vs. 18/67 [26.9%]; $p = 0.103$). In multivariable analysis, heated cot use was not significantly associated with hypoglycaemia (OR 1.70, 95% CI 0.87–3.30; $p = 0.118$), while it was strongly associated with a higher probability of glucose monitoring. Data on weight loss were less complete in the heated cot group than in the standard care group (40.5% vs. 97.0%). Median weight loss was lower in the heated cot group (5.07%, IQR 3.81–6.42) than in the standard care group (6.25%, IQR 5.06–7.71; $p < 0.001$). After adjustment for hospitalisation duration and baseline characteristics, heated cot use remained associated with lower weight loss (mean difference −0.88 percentage points, 95% CI −1.31 to −0.46; $p < 0.001$).

Discussion

This multicentre study compared thermoregulation in healthy term neonates nursed on heated versus standard cots. Heated cot use was associated with improved early postnatal thermoregulation; higher odds of normothermia, lower odds of hypothermia, but also with higher odds of hyperthermia. Trends toward favourable association were observed in vulnerable subgroups, such as lower gestational age, lower birth weight and SGA neonates.

The high burden of hypothermia underscores this relevance: overall hypothermia incidence (37%) exceeded studies using the same WHO definition (21%–23%) (8,19). Higher rates (28.4%–52.5%) rely on unclear definitions (2,18). Interpretation is complicated because measurements per neonate are rarely reported. We found higher measurement intensity associated with higher incidence: the first study, to our knowledge, to account for this.

Association between heated cot and temperature maintenance

The effect of heated cot use varied over time. Early after birth, it was associated with lower rates of normothermia, likely reflecting the transitional physiological instability of this period, the shorter duration and fewer measurements at timepoint 1, and more frequent skin-to-skin care that reduced thermal differences between groups (18). From two hours onwards, the association became progressively positive, with increasing odds of normothermia and decreasing odds of hypothermia. This pattern persisted after adjustment for measurement intensity, indicating it cannot be fully explained by differential monitoring.

Heated Cot Use and Increased Risk of Hyperthermia

Heated cot use was associated with significantly higher odds of hyperthermia. This effect was also time-dependent, with the highest odds at timepoints 1 and 2. In subgroup analyses, the effect appeared more pronounced at higher gestational age and birthweight, although the interaction terms were not significant. Nevertheless, significantly higher odds were observed in the AGA and LGA subgroups. Tveiten et al. similarly reported increased hyperthermia risk from 8 hours of age and in neonates with higher birth weight (18). These findings suggest that heated cot use in otherwise healthy newborns requires careful monitoring and may not be the optimal for this subgroup.

Heated Cot Use in Neonates with Increased Risk of Hypothermia

The effect of heated cots was more pronounced at lower gestational age and birth weight. SGA neonates in the heated cot group showed significantly higher normothermia and lower hypothermia, while effects in AGA and LGA were smaller or non-significant. Heated cots may be especially beneficial in high-risk subgroups prone to hypothermia (18,19).

Heated Cot Use and Early Neonatal Outcomes

As hypothermia is strongly associated with hypoglycaemia, effective temperature maintenance might be expected to reduce hypoglycaemia (8, 20). However, this study found no evidence that heated cot use was independently associated with less hypoglycaemia among neonates undergoing glucose monitoring. The unadjusted likely reflects more protocol-driven glucose measurements in the study cohort versus clinically guided monitoring in controls indicating detection bias. Heated cots were consistently associated with reduced weight loss, even after adjusting

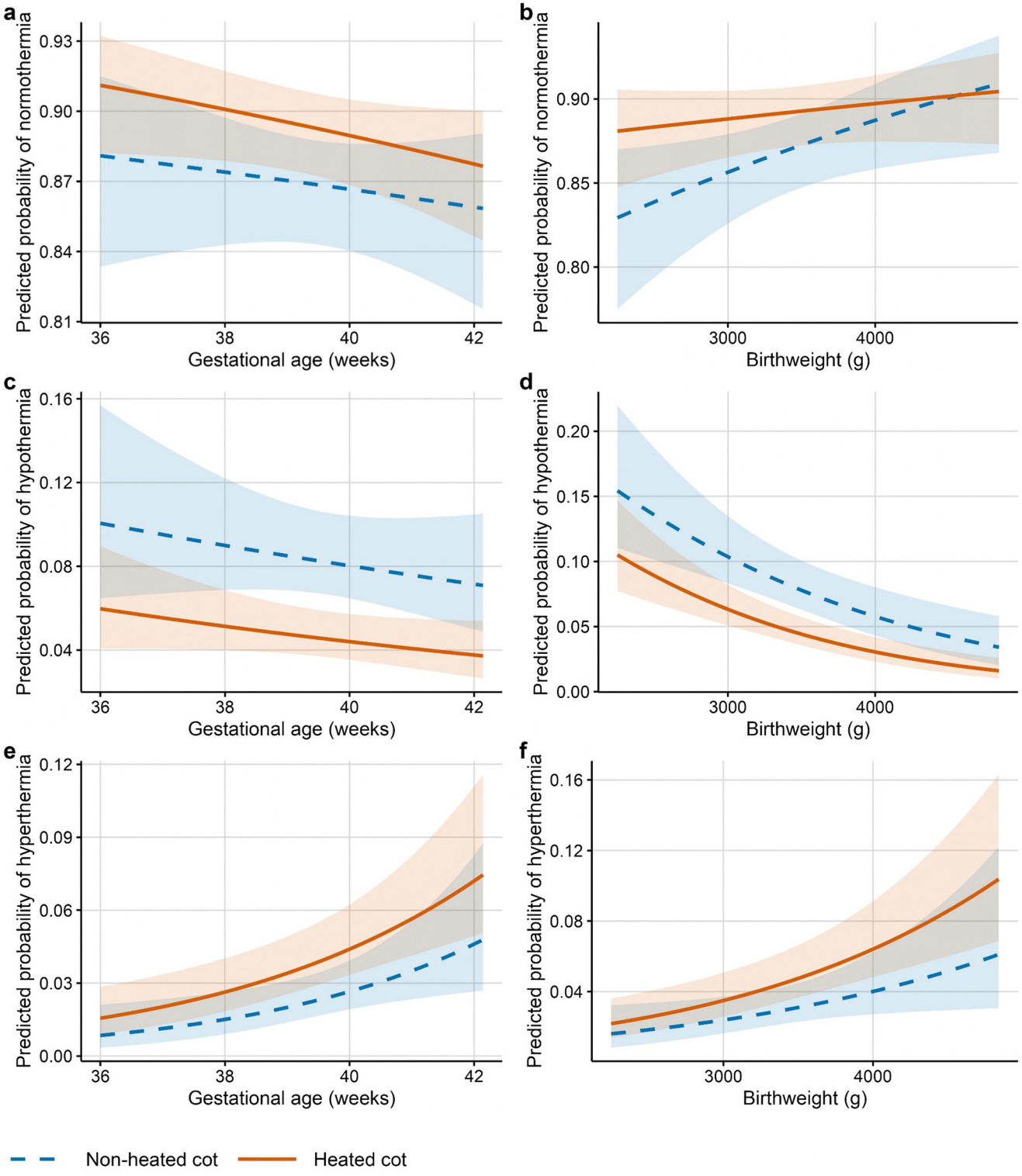


FIGURE 3: Predicted probability of normothermia (a, b), hypothermia (b, c) and hyperthermia (d, e) by gestational age, stratified by heated cot use. Predictions are derived from a generalized linear mixed model and adjusted for timepoint and measurement intensity to allow comparison at equal monitoring levels. Solid red line = heated cot group, Dashed blue line = non-heated cot group.

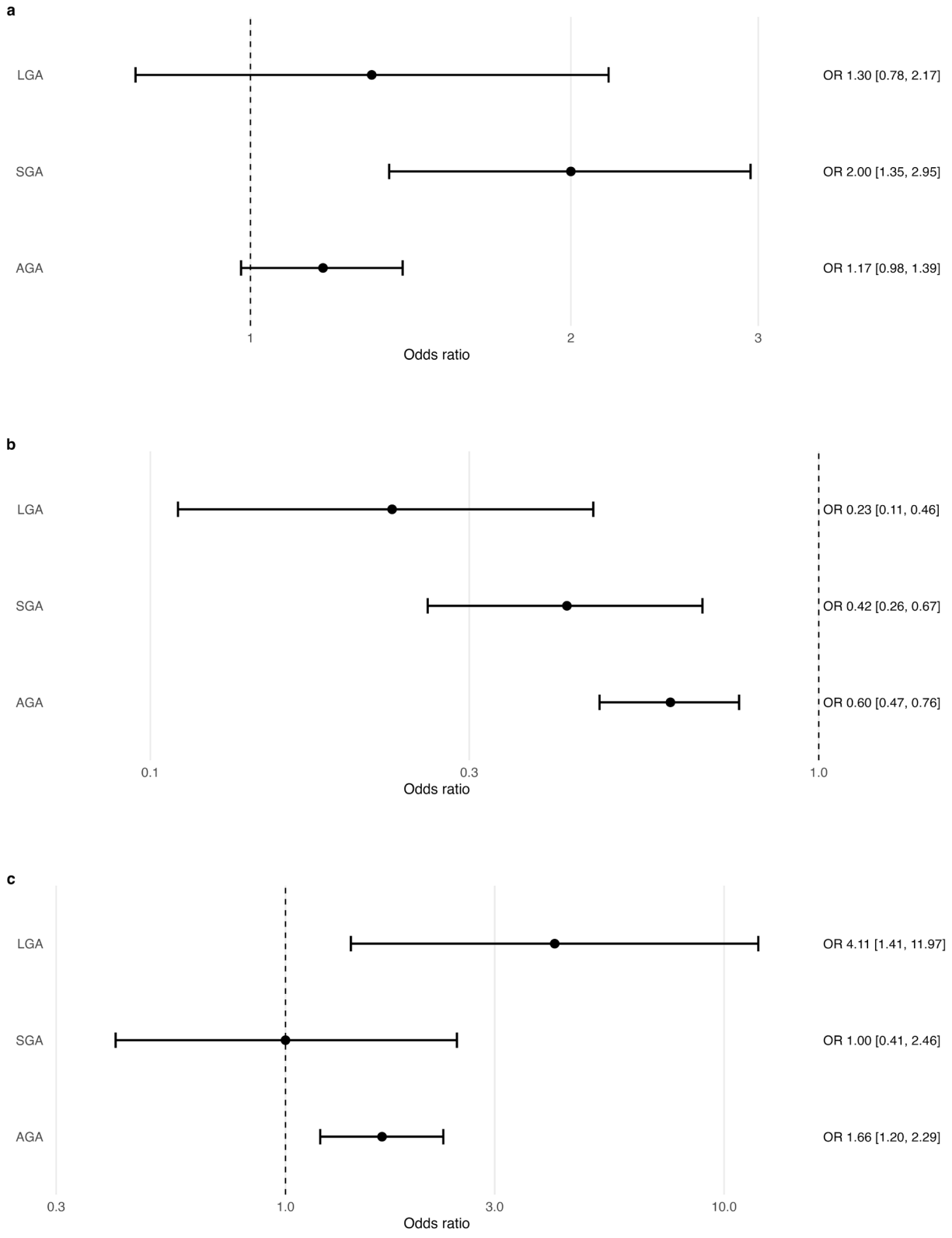


FIGURE 4: Forest plot with effect of heated cot versus no heated cot on birthweight categories regarding normothermia (a), hypothermia (b) and hyperthermia (c). Adjusted for mean timepoint and mean measurement intensity. Odds ratio with 95% confidence intervals are added. LGA: large for gestational age, SGA: small for gestational age, AGA: appropriate for gestational age.

for gestational age, birth weight, and hospitalization duration. This should be interpreted with caution, as the groups differed substantially in protocol-driven length of hospital stay. Further research is needed to determine clinical relevance beyond the early neonatal period.

Limitations

Several limitations should be acknowledged. First, the retrospective observational design limits causal inference, and subgroup analyses were exploratory and potentially underpowered, particularly for smaller categories. Second, although the cohorts were largely comparable, some differences should be acknowledged. The difference in birth weight reached significance but appears of limited clinical relevance, whereas the differences in AGA/LGA proportions are relevant, as LGA neonates may be intrinsically more prone to hyperthermia and SGA neonates to hypothermia (4,6,7,13,14,18,19). Third, the centres differed organisationally in ways for which adjustment was not possible: a higher proportion of home births and selective referral of higher-risk neonates in the Netherlands, combined with restricted chart availability for lower-risk births. The observed differences in mode of delivery are consistent with this, and residual selection bias cannot be excluded.

Thermoregulatory strategies were centre-specific and applied to all neonates independent of risk factors; consequently, heated cot exposure coincided with institutional and protocol variations. The two centres also differed in their thermal management protocols, as the heated cot centre prescribed more frequent measurements during the first 24 hours than the control centre. Despite a similar total number of measurements per patient, the marked difference in length of stay may therefore have affected the timing, distribution and intensity of monitoring. The heated cot centre was accompanied by a more intensive monitoring regimen, which may have heightened staff awareness of thermal care and prompted earlier intervention. A further methodological consideration is measurement intensity: neonates with more frequent temperature measurements have a higher probability of being classified as hypo- or hyperthermic. By accounting for repeated measurements within neonates and adjusting for measurement intensity, our analysis aimed to reduce this detection bias.

Finally, some data limitations restrict interpretation: glucose monitoring was not uniform, limiting hypoglycaemia comparisons, and weight loss data were incomplete, particularly in the heated cot group. Additionally, data on potentially relevant determinants of neonatal thermoregulation e.g. clothing, skin-to-skin contact, maternal temperature, epidural analgesia, and ethnicity, were unavailable. Room temperature may have been especially relevant, as it was adjustable according to parental preference but not recorded.

Conclusion

This multicentre study suggests that heated cot use is associated with improved thermal control compared with standard care, reflected by higher odds of normothermia and lower odds of hypothermia, but also by higher odds of hyperthermia. At the subgroup level, this favourable effect appeared most pronounced in SGA neonates, whereas heated cot care may be less suitable for LGA neonates, who appear more prone to hyperthermia. Findings on hypoglycaemia were inconclusive reflecting differing glucose monitoring practices, and the apparent reduction in weight loss should be interpreted cautiously given the substantially shorter, protocol-driven hospital stay in the heated cot group. Heated cot use was associated with a statistically and potentially clinically relevant improvement in thermoregulation. Routine implementation for the overall population does not appear justified based on this study alone, but targeted use in subgroups at increased risk of hypothermia, including SGA, low birth weight, and late preterm neonates, may offer added value, though this remains uncertain. Prospective studies, ideally randomized controlled trials, are warranted to confirm these findings, clarify metabolic and clinical effects, examine temporal temperature variability, and optimize thermal management protocols in routine neonatal care.

Statements and Declarations

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Competing interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Consent to Participate: Due to the observational nature of the study, the Ethics Committee has waived the need for parental consent for participation in the study

Use of Artificial Intelligence: Artificial intelligence tool (ChatGPT, open AI, version 5.4) was used exclusively for linguistic support, including improvement of grammar, wording, and readability. All study design decisions, analyses, interpretation of findings, and conclusions were made by the authors. The authors assume full responsibility for the final content of the manuscript.

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REVIEW ARTICLE

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Systematic Review on the Gastrointestinal Microbiome in the Diagnosis and Treatment of Anorexia Nervosa

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Keywords

Anorexia nervosa; Gut microbiome

Abstract

Introduction
Anorexia nervosa is a common eating disorder, with a lifetime prevalence of 0,8-6,3% in women and 0,1-0,3% in men. Recently, increasing literature has emerged on insights regarding the gastrointestinal microbiome in these patients. Scientific studies suggest a potential link between the composition of this microbiome and psychological traits such as body dissatisfaction, as well as the influence of this composition on weight evolution.

Objectives
This systematic literature review aims to present the available information on the gastrointestinal microbiome in patients with anorexia nervosa. Based on these findings, future research may focus on potentially externally modulating the gastrointestinal microbiome to enhance treatment and/or weight gain.

Methodology
The articles included in this literature review were obtained by consulting scientific databases (PubMed, Embase, CINAHL, and Google Scholar). Out of the 1.189 resulting articles, a selection procedure led to the inclusion of fourteen articles in this review.

Results
This literature review shows that the gastrointestinal microbiome of patients with anorexia nervosa at the time of diagnosis exhibits reduced richness (Chao1 index, alpha diversity) and an altered composition (beta diversity) compared to healthy individuals. After treatment, alpha-diversity seems to be increased. The microbiome composition evolves but does not normalize after treatment. The altered microbiome composition appears to have significant implications regarding weight gain.

Conclusions
This literature review highlights a clear deviation in both the composition and richness of the gastrointestinal microbiome in patients with anorexia nervosa compared to healthy individuals. External modulation of the microbiome offers a potential complementary therapeutic approach for these patients.

Introduction

Anorexia nervosa (AN) is a common eating disorder, affecting 0.8-6.3% of women and 0.1-0.3% of men worldwide at some point in their lives (1). In Belgium, data from 2022-2023 indicate that 13% of the population aged 10 to 64 years exhibits disordered eating behaviour, with the highest prevalence (18%) among adolescent girls (2). Despite growing knowledge about anorexia nervosa, it remains one of the most lethal psychiatric disorders, with an average mortality rate of 5% within the first four years after diagnosis (3). AN is characterized by an intense fear of gaining weight, a severely distorted body image and low self-esteem. These factors result in insufficient energy intake, leading to significantly low body weight relative to age, sex, growth trajectory and physical health. Two subtypes of anorexia nervosa can be distinguished: the restrictive type and the binge-eating/purging type. The restrictive type is defined by weight loss resulting from strict dieting, fasting and/or excessive physical activity. In contrast, the binge-eating/purging type involves recurrent episodes of binge eating and/or purging behaviours (e.g., vomiting or the use of laxatives) (4). Scientific studies have reported associations between the abundance of specific microorganisms and psychological traits related to anorexia nervosa, such as body dissatisfaction and a drive for thinness (4, 5). These findings offer new perspectives on the potential interaction between disordered eating behaviour and the gastrointestinal microbiome in patients with anorexia nervosa. The gastrointestinal microbiome refers to the community of microorganisms residing in the gut, which plays a crucial role in digestion, immunity and other psychological processes (6). The interaction between gut microorganisms and brain function can be explained by the gut-brain axis. This refers to a bidirectional communication system between

the gut and the brain. The gastrointestinal microbiome can influence brain function through various mechanisms, including the production of short-chain fatty acids and the synthesis of neurotransmitters. Conversely, signals from the brain can also influence gastrointestinal function and the composition of gut microorganisms (7). The gastrointestinal microbiome can be evaluated using various parameters. For the purposes of this literature review, alpha and beta diversity are key concepts. Alpha diversity describes the microbial composition within a single individual (8). Higher alpha diversity indicates a greater number of species, a more balanced distribution and/or greater phylogenetic diversity (i.e. how evolutionarily distinct the species are from one another) (8). This can be assessed using measures such as the Shannon Index (to evaluate the distribution) and the Chao1 Index (to estimate species richness) (9). Research has shown that a less balanced distribution of microorganisms is associated with more severe depressive symptoms (10). This suggests that an increase in alpha diversity among patients could be associated with clinical improvement. Conversely, beta diversity compares the microbiome composition between individuals. It reflects how distinct the gut microbial communities are between different people (8). A reduction in beta diversity between a healthy population and a patient group may indicate a shift in the microbial composition of patients toward the profile of healthy people. The aim of this literature review is to synthesize the current knowledge on the gastrointestinal microbiome in patients with anorexia nervosa. By critically analysing and comparing the existing literature, valuable insight may be identified for future research and potential therapeutic applications.

Materials and Methods

Protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). The primary objective of this review was to synthesize findings from studies investigating the gastrointestinal microbiome in patients with anorexia nervosa. In the included studies, the gastrointestinal microbiome was assessed through stool sample analyses from both patient (AN) and healthy control populations (HC).

Stool analyses

Most of the included studies employed Polymerase Chain Reaction (PCR) to analyse stool samples, specifically targeting the 16S or 23S rRNA gene. This technique uses the enzyme DNA polymerase, which synthesizes a complementary DNA strand based on an existing DNA template. Once amplification is complete, the DNA can be further analysed to identify the specific microorganisms present in the microbiome of the examined samples (12). In addition, Fouladi et al. utilized next-generation sequencing (NGS), specifically shotgun-metagenomic-sequencing (13). This analytical method involves extracting DNA from all cells within a community, fragmenting it into smaller pieces, and then individually sequencing and analysing these fragments (14).

Search strategy and study selection

A literature search was conducted to identify relevant articles for this review. For this purpose, database-specific search strings were developed, and the databases were consulted on October 18, 2024. The databases used for this review were PubMed, Embase, CINAHL and Google Scholar. The formulation of search strings was guided by Emtree (Embase) and MeSH (PubMed). Based on the synonym lists and hierarchical term structures provided by these tools, relevant alternative terms were identified and incorporated. These search strings were subsequently adapted to the syntax requirements of each database to yield the most relevant results (see supplementary material).

Inclusion and Exclusion criteria

The inclusion criteria for this review were all studies that were performed in humans with anorexia nervosa and studied the gastrointestinal microbiome using stool samples. Studies were excluded based on the following criteria: (a) study design: review articles or study protocols without results; (b) population: animal or in vitro models, or studies with a sample size smaller than five participants; (c) scope: insufficient specificity regarding the research topic; (d) accessibility; full-text not available.

Data extraction

Data extraction was performed manually by the researchers. The following information was collected: population characteristics (e.g., mean age, mean BMI, gender, sample size), method of faecal analysis, diagnostic criteria, reported findings related to the gastrointestinal microbiome, and relevant interpretations or recommendations.

Primary outcome

The primary outcome of this systematic review was to synthesize reported findings regarding the gastrointestinal microbiome in patients with anorexia nervosa, both at the time of diagnosis and after treatment. For this purpose, the microbiome of patients at diagnosis was compared with that of healthy individuals. Additionally, changes in the microbiome during treatment were assessed by comparing the gastrointestinal microbiome of patients after treatment with that at the time of diagnosis.

TABLE 1: Characteristics of the included studies.

Author	Year	Population (AN0/AN1/HC)[1]	BMI (kg/m²)			Age (years)			Duration disease	Duration treatment
			AN[0]	AN[1]	HC	AN[0]	AN[1]	HC		
Andreani et al. (27)	2024	57/50/34	15.99 (12.50;18.77)	18.88 (16.85;20.96)	20.94 (17.65;26.07)	16.25 (12;20.35)	16.52 (12.23;19.01)	16.56 (14.11;18.46)	15.25 (1.63;71.97) months	//
Armougom et al. (16)	2009	9/-/20	12.73 ± 1.602	-	20.68 ± 2.014	19 – 36	-	13 – 68	//	//
Borgo et al. (26)	2017	15/-/15	13.9 ± 2.1	-	22.1 ± 2.6	-	-	-	//	//
Fan et al. (5)	2023	77/-/70	15.6 ± 2.5	-	21.8 ± 1.9	23.5 ± 7.0	-	23.2 ± 4.4	5.5 years	//
Fouladi et al.(13)[2]	2022	93/78/98 UNC: 38/33/69 Denver: 55/45/29	(38) 15.74 ± 2.11 (55) 13.78 ± 1.74	(33) 18.28 ± 1.05 (45) 15.41 ± 1.10	(69) 21.98 ± 2.13 (29) 22.56 ± 1.60	(38) 23.2 ± 6.87 (55) 27.7 ± 7.41	(33) 22.6 ± 6.90 (45) 27.4 ± 6.68	(69) 23.6 ± 5.28 (29) 31.1 ± 5.64	//	(33) 32.37 ± 26.21 days (45) 17.66 ± 9.56 days
Kleiman et al. (15)	2015	16/10/12	16.2 ± 1.5	17.4 ± 0.9	21.5 ± 1.9	28.0 ± 11.7	//	29.8 ± 11.6	//	//
Mack et al. (24)	2016	55/44/55	15.3 ± 1.4	17.7 ± 1.4	21.6 ± 2.0	23.8 ± 6.8	//	23.7 ± 6.7	//	14.0 ± 6.8 weeks
Monteleone et al. (21)	2021	17/-/20	15.0 ± 1.8	-	20.3 ± 1.4	20.5 ± 3.1	-	23.0 ± 3.3	//	//
Monteleone et al. (22)	2020	21/16/20	14.6 ± 1.3	20.5 ± 0.7	20.3 ± 1.4	21.7 ± 4.2	22.3 ± 4.4	23.0 ± 3.3	//	20 weeks
Morita et al. (17)	2015	14/-/21	12.7 ± 1.5	-	20.5 ± 2.1	28.1 ± 10.7	-	31.5 ± 7.4	//	//
Mörkl et al. (19)	2017	18/-/26	15.29 ± 1.28	-	21.89 ± 1.73	22.44 ± 3.20	-	24.93 ± 3.75	3.14 ± 3.51 years	//
Prochazkova et al. (28)	2021	52/52/67	14.4 (13.4;15.9)	17.1 (15.5;18.1)	21.9 (19.9;23.7)	23 (19;27)	//	24 (22;28.5)	60 (36;126) months	51 (38.5;64) days
Schulz et al. (25)	2020	19/19/20	15.76 ± 2.03	18.8 ± 0.87	20.31 ± 2.35	15.77 ± 1.94	16.16 ± 1.99	16.35 ± 1.11	17.16 ± 16.12 months	4.05 ± 1.39 months
Yuan et al. (23)	2022	30/-/30	14.92 ± 2.54	-	20.89 ± 2.14	16 (13;22)	-	18 (13;24)	//	46 (17;58) days

[1] AN0 : patients with anorexia nervosa at time of diagnosis; AN1: patients with anorexia nervosa after treatment; HC: healthy controls.
[2] Fouladi et al.s' study was conducted at two centres. the UNC Center of Excellence for Eating Disorders and the Denver ACUTE.
-: not investigated
//: not specified

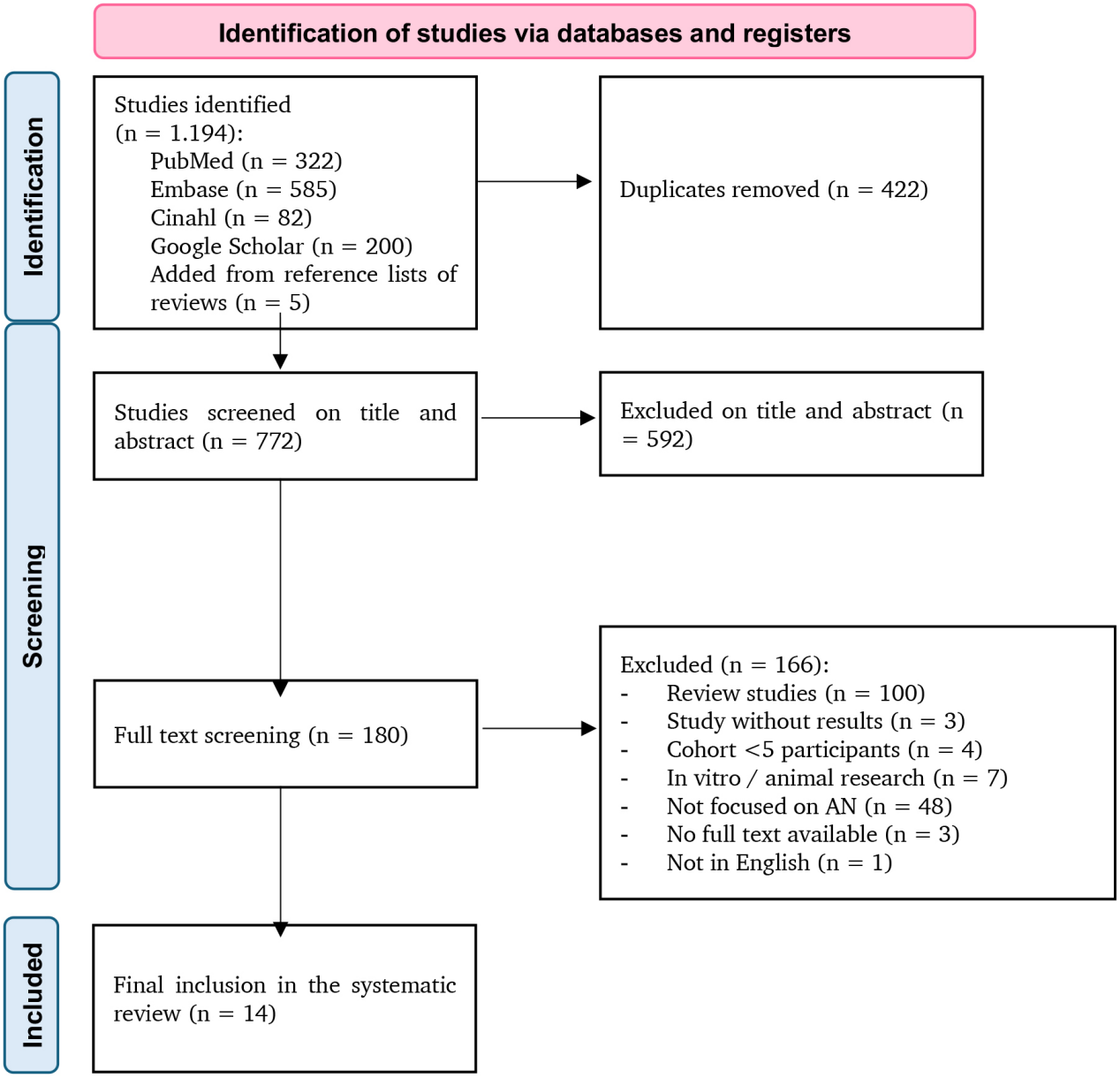


FIGURE 1: PRISMA flowchart.

Results

Study selection

The initial search across PubMed, Embase, CINAHL and Google Scholar yielded a total of 1,189 records. After removing duplicates (n = 422) and screening titles and abstracts, the full texts of the remaining articles were assessed for eligibility. Based on the pre-defined exclusion criteria, 166 articles were excluded during the full-text screening phase. Additionally, five relevant studies were identified through reference tracking of review articles. A detailed overview of the selection process is presented in the PRISMA flow chart (Figure 1).

Study characteristics

In total, fourteen studies were included in this systematic review. For the diagnosis of anorexia nervosa, most studies employed the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (4). Exceptions include the studies by Kleiman et al., Armougom et al., and Morita et al., which utilized DSM-4 criteria (15-18). In the study by Mörkl et al., the diagnosis was established based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (19, 20). When studies distinguished between the restrictive and binge-purge subtypes of anorexia nervosa, only data pertaining to the restrictive subtype were included in this review. The majority of the included studies focused exclusively on female patients and healthy female controls, which aligns with the epidemiological

TABLE 2: Alpha and beta diversity in AN (diagnosis) compared to HC.

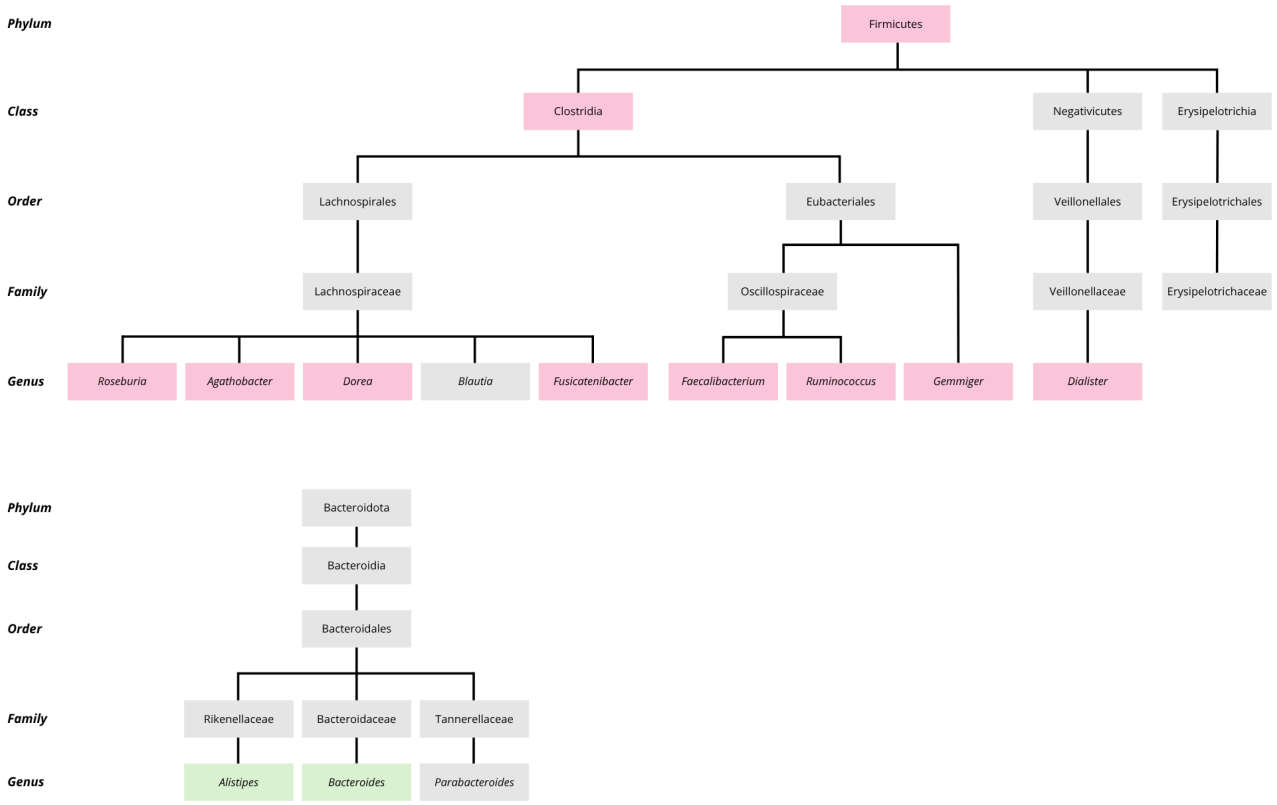
Author	Publication year	Population (AN/HC)	Stool analysis	Results	
				Alpha diversity	Beta diversity
Monteleone et al. (22)	2020	21/20	16S PCR		
Monteleone et al. (21)	2021	17/20	16S PCR		
Kleiman et al. (15)	2015	16/12	16S PCR		
Yuan et al. (23)	2022	30/30	16S PCR		
Schulz et al. (25)	2020	19/20	16S PCR		
Mörkl et al. (19)	2017	18/26	16S PCR		
Mack et al. (24)	2016	55/55	16S PCR		
Borgo et al. (26)	2017	15/15	16S PCR		
Andreani et al. (27)	2024	57/34	16S PCR		
Prochazkova et al. (28)	2021	52/67	16S PCR		
Fan et al. (5)	2023	77/70	16S PCR	/	
Fouladi et al. (13)	2022	93/98	NGS	/	

Alpha diversity (CHAO1-index)	
	Trend towards higher alpha diversity in AN (diagnosis) compared to HC
	No difference reported
	Trend towards lower alpha diversity in AN (diagnosis) compared to HC
	Alpha diversity is significantly lower in AN (diagnosis) compared to HC
Beta diversity	
	Microbiome composition differs between AN and HC
	Microbiome composition is significantly different between AN and HC

pattern of anorexia nervosa. Table 1 summarizes the characteristics of the included studies, including BMI (Body Mass Index) age and illness/treatment duration.

Gut microbiome of AN (diagnosis) compared to HC

The results concerning alpha and beta diversity from twelve included studies are summarized in Table 2. Two studies were excluded from this table due to the absence of explicit reporting on these outcome measures (16, 17). Table 2 is organized according to findings related to alpha-diversity in terms of richness, specifically based on the Chao1 index. This method of organization places the three top-listed studies in the table as those that reported a significantly lower alpha-diversity in patients with anorexia nervosa compared to healthy controls (15, 21, 22). Four studies subsequently reported a trend towards a lower alpha-diversity among patients, while one study reported no difference between the two groups (19, 23-26). Toward the bottom of the table, two studies reported an increase in alpha diversity in patients with anorexia nervosa relative to healthy individuals (27, 28). Finally Table 2 ends with two articles that did not report explicit findings regarding alpha-diversity, but that nonetheless provided relevant data on beta diversity (5, 13). Since the studies were sorted based on the results of the Chao1 index, beta diversity findings appear in a non-systematic order within the table. Nevertheless, Table 2 shows that in all twelve studies, the composition of the gastrointestinal microbiome (beta diversity) was found to differ – significantly or non-significantly – between patients with anorexia nervosa at the time of diagnosis and healthy controls. In addition, Figure 2 presents a concise summary of the relative abundance of specific microorganisms (families, genera, classes and phyla) in the gut microbiome of patients with anorexia nervosa compared to healthy controls. In line with Table 2, these data refer to the period around the time of diagnosis of the patients with anorexia nervosa. Figure 2 reveals that most of included microorganisms were found in lower abundance in the gut microbiome of patients compared to controls. Notably, all these included microorganisms that showed reduced presence in patients belonged to the Firmicutes phylum. In contrast, a few microorganisms from the Bacteroidota phylum were found in higher abundance in patients relative to healthy individuals. Fan et al. also reported several noteworthy correlations between specific microorganisms and psychological characteristics (5). For example, the absolute abundance of the genus *Parasutterella* was positively correlated with body dissatisfaction. Due to the selection procedure applied



	Not investigated
	Higher abundance in AN (diagnosis) compared to HC
	Lower abundance in AN (diagnosis) compared to HC

FIGURE 2: Abundances of microorganisms AN (diagnosis) compared to HC.

to determine which microorganisms were included in Figure 2, *Parasutterella* was not included. However, this genus was investigated by Monteleone et al. and Monteleone et al., both of which found a higher abundance of *Parasutterella* in patients with anorexia nervosa at the time of diagnosis compared to healthy controls (21, 22).

Gut microbiome of AN (after treatment) compared to AN (diagnosis)

Table 3 includes data from the seven studies that also conducted analyses after a defined treatment period. The structure of the table follows the same logic as Table 2, with studies ordered based on the changes in alpha diversity related to richness (Chao1 index) between the time of diagnosis and after treatment. At the top of Table 3 are two studies reporting a significant increase in alpha diversity of patients after treatment compared to the diversity levels of these patients at the time of diagnosis (24, 25). These are followed by two studies that reported a non-significant increase and two that observed a decrease in alpha diversity post-treatment (15, 22, 27, 28). The table ends with one study that did not provide explicit information on the Chao1 index but still contained relevant data regarding beta diversity (13). Furthermore, this table also clearly presents the data related to beta diversity. Only one study did not find changes in the composition of the gut microbiome after treatment compared to the gut microbiome at the time of diagnosis (25). Additionally, the study by Prochazkova et al. did not report explicit findings on compositional changes of the gut microbiome in patients with anorexia nervosa (28). The remaining five studies uniformly indicate that the composition of the gut microbiome undergoes changes during the course of treatment (13, 15, 22, 24, 27). Consistent to Figure 2, the data in Figure 3 provides relevant insights into the abundance of specific microorganisms before and after treatment. Figure 3 demonstrated that microorganisms belonging to the phylum Firmicutes are present in higher abundance following treatment, compared to their abundance at diagnosis. In contrast, the abundance of *Alistipes* and *Bacteroides* – both belonging to the phylum Bacteroidota – decreased over the course of treatment.

Discussion

This systematic review highlights consistent differences in both the richness and composition of the gastrointestinal microbiome between patients with

TABLE 3: Alpha and beta diversity in AN (after treatment, t_1) compared to AN (diagnosis, t_0).

Author	Publication year	Population AN (t_0/t_1)	Stool analysis	Results	
				Alpha diversity	Beta diversity
Schulz et al. (25)	2020	19/19	16S		
Mack et al. (24)	2016	55/44	16S		
Monteleone et al. (22)	2020	21/16	16S		
Kleiman et al. (15)	2015	16/10	16S		
Andreani et al. (27)	2024	57/50	16S		
Prochazkova et al. (28)	2021	52/52	16S		/
Fouladi et al. (13)	2022	93/78	NGS	/	

Alpha diversity (CHAO1-index)	
	Alpha diversity increased significantly in AN (after treatment) compared to AN (diagnosis)
	Trend towards higher alpha diversity in AN (after treatment) compared to AN (diagnosis)
	Trend towards lower alpha diversity in AN (after treatment) compared to AN (diagnosis)

Beta diversity	
	The difference in microbiome composition between AN and HC decreases after treatment, but does not fully recover
	The microbiome composition remains equally different between AN and HC after treatment

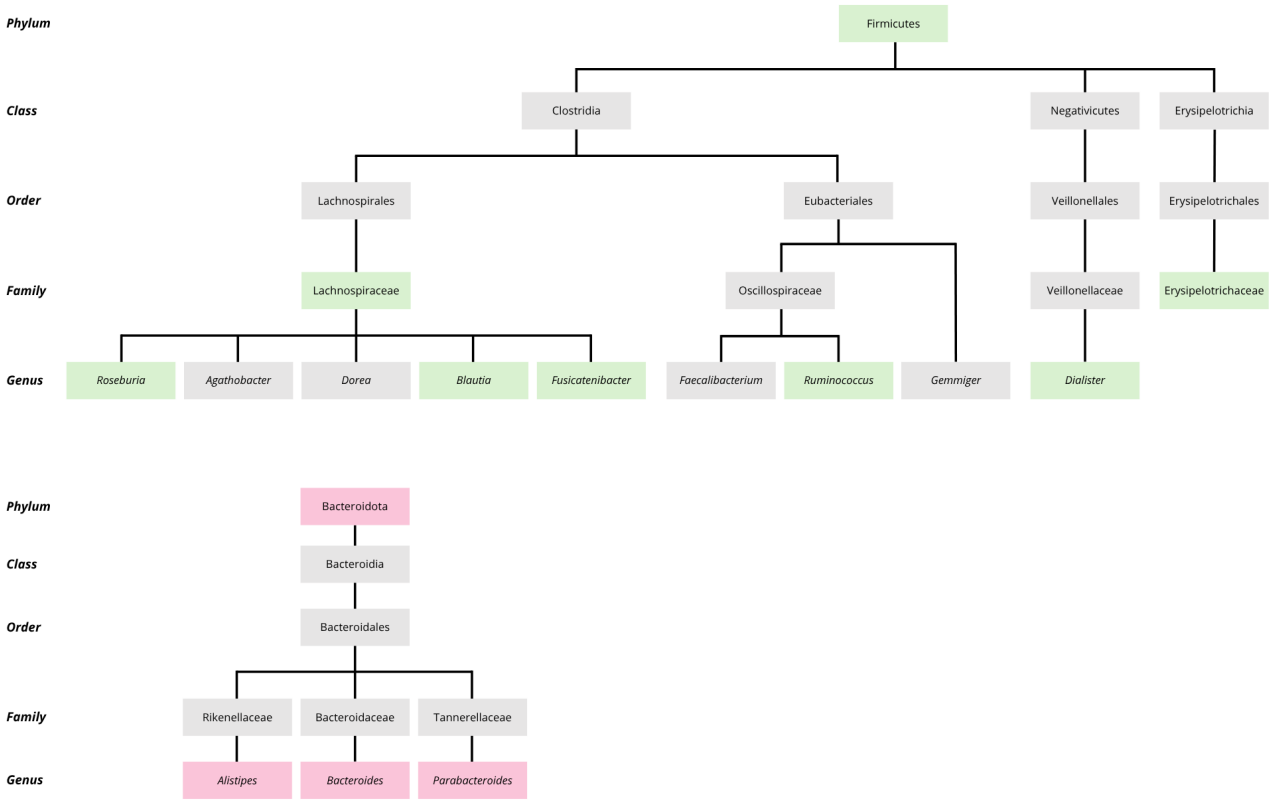
anorexia nervosa and healthy individuals, as well as within the patient group. This raises the question of whether well-founded hypotheses can be developed concerning the abundance of specific microorganisms in relation to the stage of illness and the treatment trajectory in patients with anorexia nervosa.

Gut microbiome at the time of diagnosis

The included studies show that the alpha diversity based on richness (Chao1 index) of the gastrointestinal microbiome is generally lower in patients with anorexia nervosa at the time of diagnosis compared to healthy individuals. Furthermore, this review indicated that the composition (beta diversity) of the microbiome also differs – either significantly or non-significantly – between patients at diagnosis and healthy controls. These microbiome alterations are also reflected in the analysis of the abundance of various microbial taxa. In addition, the findings suggest a potential correlation between a reduced abundance of microorganisms belonging to the phylum Firmicutes and anorexia nervosa, particularly at the time of diagnosis. Conversely, microorganisms belonging to the phylum Bacteroidota appear to be more abundant in patients compared to healthy controls. This suggests a possible association between Bacteroidota abundance and anorexia nervosa. Moreover, two studies report an increased presence of the genus *Parasutterella* in patients with anorexia nervosa relative to healthy individuals (21, 22). This microorganism has been linked to body dissatisfaction (5). Given its elevated abundance in patients with anorexia nervosa, *Parasutterella* might be hypothesized to play a role in disturbances in body image perception, which may have implications for the recovery process.

Gut microbiome after treatment

Comparing the composition and richness of the gastrointestinal microbiome in patients at the time of diagnosis with analyses conducted after treatment yields several noteworthy findings. Primarily, the majority of included studies report an increase in alpha diversity, as well as a shift in the microbiome composition (beta diversity) towards a profile more closely resembling that of healthy individuals. However, no study demonstrated that the microbiome composition of patients post-treatment becomes fully comparable to that of the healthy control group. Changes in the gastrointestinal microbiome composition following treatment are also reflected in the abundance analysis of specific microorganisms. These analyses show that the genera *Alistipes*, *Bacteroides* and *Parabacteroides*, as well as the phylum Bacteroidota, are less abundant in the microbiome of the patients after treatment. In line with the hypothesis suggested above – that microorganisms belonging to the phylum Bacteroidota may be associated with anorexia nervosa – these microorganisms are indeed found in reduced abundance after treatment and subsequent weight gain in patients. These findings suggest a potential relationship between microorganisms of the order Bacteroidales and the health and weight status of patients with anorexia nervosa. Furthermore, this study shows that microorganisms belonging to the phylum Firmicutes are less abundant in the gastrointestinal microbiome of these patients at diagnosis. After treatment, the abundance of these microorganisms increases. These observations also support a possible correlation between microbial composition and the nutritional and weight status of patients.



	Not investigated
	Higher abundance in AN (after treatment) compared to AN (diagnosis)
	Lower abundance in AN (after treatment) compared to AN (diagnosis)

FIGURE 3: Abundance of microorganisms in AN (after treatment, t_1) compared to AN (diagnosis, t_0).

Key insights

The study conducted by Menni et al., investigating a population of healthy women, reports an association between the families Oscillospiraceae and Lachnospiraceae and reduced long-term weight-gain, whereas the genus *Bacteroides* is linked to an increased risk of weight gain (29). When these findings are considered alongside the results of this literature review regarding the microbiome at diagnosis, a possible connection emerges. This review reports an elevated abundance of *Bacteroides* in patients with anorexia nervosa at the time of diagnosis. Given that *Bacteroides* has been associated with a higher risk of weight gain, it is plausible that this increased presence reflects a physiological response aimed at promoting weight gain in response to undernutrition. Conversely, several genera within the families Oscillospiraceae and Lachnospiraceae are found to be reduced at diagnosis, which might similarly be explained as a protective mechanism of the body in response to the underweight status. These hypotheses are further supported by the study of de Clercq et al., which demonstrated that faecal microbiota transplantation with a high abundance of the phylum Bacteroidota and a lower abundance of Firmicutes resulted in significant weight gain (30). After treatment, when patients typically exhibit less severe underweight, a decreased abundance of microorganisms belonging to the phylum Bacteroidota and an increased abundance of those belonging to Firmicutes are reported. These findings could also be interpreted within the framework of the aforementioned hypothesis, suggesting that at this stage, the body may have less need to actively stimulate weight gain. When comparing the findings of this systematic review with recent data from healthy individuals, the study by Yamamoto-Wada et al. provides crucial insights (31). This study, which excluded individuals with underlying diseases, demonstrated that the gut microbiota of underweight women (BMI < 17.5) differs significantly from that of normal-weight controls. Specifically, the underweight group exhibited a significantly lower alpha diversity. Although it should be noted that Yamamoto-Wada et al. utilized different diversity metrics than the Chao1 index employed in the current review – precluding a direct statistical comparison – the overarching trend consistently points toward reduced alpha diversity in low-BMI populations. Furthermore, the underweight group in their study showed a decreased abundance of taxa such as *Dorea*, *Fusicatenibacter* and *Agathobacter*. This aligns with the lower abundance of these bacteria observed

in patients with anorexia nervosa at the time of diagnoses, as discussed previously. These results allow us to cautiously suggest that certain microbial alternations are indeed linked to low body weight itself.

Strengths and limitations

A key strength of this systematic review is the comparison of findings from fourteen individual studies, providing a broader and deeper understanding of the gastrointestinal microbiome's composition and dynamics in patients with anorexia nervosa. This collective approach enhances the relevance of the findings and increases the likelihood of identifying consistent patterns, enabling better-supported hypotheses and informing future clinical research. However, several limitations should be considered when interpreting the results. The selection of the fourteen articles was based on strict exclusion criteria, which may have omitted relevant studies. For example, non-English publications were excluded, potentially overlooking important data from countries with different dietary cultures that could influence microbiome composition and diversity. Furthermore, animal studies were excluded, possibly missing valuable mechanistic insights. Additionally, the included studies vary in methodology, timing of sample collection, exclusion criteria, and potentially participants' diets, limiting comparability and reducing the overall reliability of combined conclusions. Most studies focused exclusively on female patients and controls, leaving possible sex differences underexplored. Only one study examined long-term microbiome changes, restricting conclusions about sustained effects. Finally, two studies – Andreani et al. and Prochazkova et al. – reported findings on alpha diversity at diagnosis and after treatment that contradict the other studies (27, 28). This may indicate the influence of other confounding factors, although no clear differences explaining these discrepancies were identified.

Clinical implementation

An underexplored aspect in current research on the gastrointestinal microbiome in patients with anorexia nervosa is the potential interaction between different types of food and the abundance of specific microorganisms. Scientific studies suggest a shift in microbial abundance in a direction that, based on the aforementioned hypotheses, would be favourable to promote weight gain in these patients when following a protein-rich or fat-rich diet (32-34). Conversely, a carbohydrate-rich diet might potentially limit weight gain (35). Considering that standard hypercaloric nutritional supplementation derives approximately half of its energy from carbohydrates, it could be suggested that this composition may not be optimal for stimulating weight gain in this patient population when taking the suggested microbiome's response into account (36). Regarding the effect of enteral nutrition on the gastrointestinal microbiome, no definitive conclusions can yet be drawn, as studies in patients with Crohn's disease have produced conflicting results (37). However, one study suggests that industrially prepared enteral nutrition may be favourable for promoting weight gain than blended diet when considering the microbiome's impact (38). A critical examination of the impact of various kinds of nutrition – whether standard diet, medical supplementation or enteral feeding – on the microbiome could provide valuable insights. A better understanding of the interplay between different types of food or nutrients and the gastrointestinal microbiome, combined with the aforementioned hypotheses, could contribute to more targeted treatment strategies and potentially shorten the recovery process.

Conclusion

This systematic review examined the relationship between the gastrointestinal microbiome and anorexia nervosa. The included studies indicate that patients with anorexia nervosa exhibit, at diagnosis, reduced microbial richness (Chao1 index, alpha diversity) and an altered composition (beta diversity) of the gastrointestinal microbiome compared to healthy individuals. Consistent with these findings, clear differences were also reported in the abundance of various microorganisms. Furthermore, this review shows that both the richness and composition of the microbiome undergo significant changes throughout treatment. Generally, this results in increased microbial richness and shifts in composition. However, these changes do not lead to a full normalization of the gastrointestinal microbiome toward the profile observed in healthy individuals. Additionally, Fan et al. demonstrated associations between specific microorganisms and psychological traits such as body dissatisfaction and the drive for thinness (5). Moreover, scientific research points to a potential influence of the gastrointestinal microbiome composition on weight evolution (29, 30). This review highlights the importance of the gastrointestinal microbiome as a promising yet underexplored factor in the treatment of anorexia nervosa. The observed microbial differences and their changes during treatment suggest a possible link to weight gain. Focused research on this relationship and intervention possibilities through nutrition could represent a crucial step toward improving therapeutic approaches.

COI statement

All authors certify that they have no conflicts of interest (COIs), including financial or other relationships with the product or its manufacturer. Moreover, the manufacturer had no influence on the design, methodology or reporting of this review.

Supplementary file: search strategy

PUBMED

Subject 1

("Feeding and Eating disorders"[MeSH] OR "Eating disorders"[tiab] OR "Eating disorder"[tiab] OR "Pathologic Eating Behavior"[tiab] OR "Disordered Eating Behavior"[tiab] OR "Disordered Eating Behaviour"[tiab] OR "Disordered Eating"[tiab] OR "Anorexia Nervosa"[MeSH] OR "Anorexia"[tiab] OR "Anorexia Nervosa"[tiab] OR "Binge-Eating Disorder"[MeSH] OR "Binge-Eating Disorder"[tiab] OR "Binge eating syndrome"[tiab] OR "Binge-eating syndrome"[tiab] OR "Bulimia Nervosa"[MeSH] OR "Bulimia"[tiab] OR "Bulimia Nervosa"[tiab])

Subject 2

"Gastrointestinal Microbiome"[MeSH] OR "Gastrointestinal Microbiome"[tiab] OR "Gastrointestinal Flora"[tiab] OR "Gastrointestinal Microflora"[tiab] OR "Gut Microbiome"[tiab] OR "Gut Microflora"[tiab] OR "Gut Microbiota"[tiab] OR "Gut bacteria"[tiab] OR "Intestinal Flora"[tiab] OR "Intestine Flora"[tiab] OR "Intestinal Microbiome"[tiab] OR "Intestinal Microbiota"[tiab] OR "Intestinal Microflora"[tiab] OR "bowel microbiota"[tiab] OR "Gastro Intestinal Flora"[tiab] OR "Gastrointestinal Microbiota"[tiab] OR "gastrointestinal tract flora"[tiab] OR "Gastrointestine Flora"[tiab] OR "Gastrointestine tract flora"[tiab] OR "Intestinal bacteria"[tiab] OR "Intestinal Bacterial Flora"[tiab] OR "Intestinal Canal Flora"[tiab] OR "Intestine Microbial Flora"[tiab] OR "Intestine Microflora"[tiab]

Combination:
(subject 1) AND (subject 2)

("Feeding and Eating disorders"[MeSH] OR "Eating disorders"[tiab] OR "Eating disorder"[tiab] OR "Pathologic Eating Behavior"[tiab] OR "Disordered Eating Behavior"[tiab] OR "Disordered Eating Behaviour"[tiab] OR "Disordered Eating"[tiab] OR "Anorexia Nervosa"[MeSH] OR "Anorexia"[tiab] OR "Anorexia Nervosa"[tiab] OR "Binge-Eating Disorder"[MeSH] OR "Binge-Eating Disorder"[tiab] OR "Binge eating syndrome"[tiab] OR "Binge-eating syndrome"[tiab] OR "Bulimia Nervosa"[MeSH] OR "Bulimia"[tiab] OR "Bulimia Nervosa"[tiab]) AND ("Gastrointestinal Microbiome"[MeSH] OR "Gastrointestinal Microbiome"[tiab] OR "Gastrointestinal Flora"[tiab] OR "Gastrointestinal Microflora"[tiab] OR "Gut Microbiome"[tiab] OR "Gut Microflora"[tiab] OR "Gut Microbiota"[tiab] OR "Gut bacteria"[tiab] OR "Intestinal Flora"[tiab] OR "Intestine Flora"[tiab] OR "Intestinal Microbiome"[tiab] OR "Intestinal Microbiota"[tiab] OR "Intestinal Microflora"[tiab] OR "bowel microbiota"[tiab] OR "Gastro Intestinal Flora"[tiab] OR "Gastrointestinal Microbiota"[tiab] OR "gastrointestinal tract flora"[tiab] OR "Gastrointestine Flora"[tiab] OR "Gastrointestine tract flora"[tiab] OR "Intestinal bacteria"[tiab] OR "Intestinal Bacterial Flora"[tiab] OR "Intestinal Canal Flora"[tiab] OR "Intestine Microbial Flora"[tiab] OR "Intestine Microflora"[tiab])

EMBASE

Subject 1

'eating disorder'/exp OR 'eating disorder':ti,ab,kw OR 'eating disorders':ti,ab,kw OR 'pathologic eating behavior':ti,ab,kw OR 'pathologic eating behaviour':ti,ab,kw OR 'disordered eating behaviour':ti,ab,kw OR 'disordered eating behavior':ti,ab,kw OR 'disordered eating':ti,ab,kw OR 'anorexia nervosa'/exp OR 'anorexia nervosa':ti,ab,kw OR 'anorexia':ti,ab,kw OR 'binge eating disorder'/exp OR 'binge eating disorder':ti,ab,kw OR 'binge eating syndrome':ti,ab,kw OR 'binge-eating syndrome':ti,ab,kw OR 'binge-eating disorder':ti,ab,kw OR 'bulimia'/exp OR 'bulimia':ti,ab,kw OR 'bulimia nervosa':ti,ab,kw

Subject 2

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Combination:
(subject 1) AND (subject 2)

('eating disorder'/exp OR 'eating disorder':ti,ab,kw OR 'eating disorders':ti,ab,kw OR 'pathologic eating behavior':ti,ab,kw OR 'pathologic eating behaviour':ti,ab,kw OR 'disordered eating behaviour':ti,ab,kw OR 'disordered eating behavior':ti,ab,kw OR 'disordered eating':ti,ab,kw OR 'anorexia nervosa'/exp OR 'anorexia nervosa':ti,ab,kw OR 'anorexia':ti,ab,kw OR 'binge eating disorder'/exp OR 'binge eating disorder':ti,ab,kw OR 'binge eating syndrome':ti,ab,kw OR 'binge-eating syndrome':ti,ab,kw OR 'binge-eating disorder':ti,ab,kw OR 'bulimia'/exp OR 'bulimia':ti,ab,kw OR 'bulimia nervosa':ti,ab,kw) AND ('intestine flora'/exp OR 'intestine flora':ti,ab,kw OR 'bowel microbiota':ti,ab,kw OR

'gastrointestinal flora':ti,ab,kw OR 'gastro intestinal flora':ti,ab,kw OR 'gastrointestinal microbiome':ti,ab,kw OR 'gastrointestinal microbiota':ti,ab,kw OR 'gastrointestinal tract flora':ti,ab,kw OR 'gastrointestine flora':ti,ab,kw OR 'gastrointestine tract flora':ti,ab,kw OR 'gut bacteria':ti,ab,kw OR 'gut microbiota':ti,ab,kw OR 'intestinal bacteria':ti,ab,kw OR 'intestinal bacterial flora':ti,ab,kw OR 'intestinal flora':ti,ab,kw OR 'intestinal canal flora':ti,ab,kw OR 'intestinal microbiota':ti,ab,kw OR 'intestinal microflora':ti,ab,kw OR 'intestine microbial flora':ti,ab,kw OR 'intestine microflora':ti,ab,kw OR 'intestine flora':ti,ab,kw)

CINAHL

Advanced Search: EBSCOhost (e-bronnen.be) – database: 'CINAHL Plus with Full Text'

Subject 1

(MH "eating disorders") OR (MM "eating disorders") OR (TI "eating disorders") OR (TI "eating disorder") OR (AB "eating disorders") OR (AB "eating disorder") OR (TI "pathological eating behavior") OR (TI "pathological eating behaviour") OR (AB "pathological eating behavior") OR (AB "pathological eating behaviour") OR (TI "disordered eating behavior") OR (TI "disordered eating behaviour") OR (AB "disordered eating behavior") OR (AB "disordered eating behaviour") OR (TI "disordered eating") OR (AB "disordered eating") OR (MH "anorexia") OR (MH "anorexia nervosa") OR (MM "anorexia") OR (MM "anorexia nervosa") OR (TI "anorexia") OR (TI "anorexia nervosa") OR (AB "anorexia") OR (AB "anorexia nervosa") OR (MH "binge eating disorder") OR (MM "binge eating disorder") OR (TI "binge eating disorder") OR (TI "binge-eating disorder") OR (TI "binge eating syndrome") OR (TI "binge-eating syndrome") OR (AB "binge eating syndrome") OR (AB "binge-eating syndrome") OR (AB "binge eating disorder") OR (AB "binge-eating disorder") OR (MH "bulimia") OR (MH "bulimia nervosa") OR (MM "bulimia") OR (MM "bulimia nervosa") OR (TI "bulimia") OR (TI "bulimia nervosa") OR (AB "bulimia") OR (AB "bulimia nervosa")

Subject 2

(MH "gut microbiota") OR (MM "gut microbiota") OR (TI "gut microbiota") OR (AB "gut microbiota") OR (TI "intestine flora") OR (AB "intestine flora") OR (TI "bowel microbiota") OR (AB "bowel microbiota") OR (TI "gastrointestinal flora") OR (AB "gastrointestinal flora") OR (TI "gastrointestinal microbiome") OR (AB "gastrointestinal microbiome") OR (TI "gastrointestinal microbiota") OR (AB "gastrointestinal microbiota") OR (TI "gastrointestinal tract flora") OR (AB "gastrointestinal tract flora") OR (TI "gastrointestine flora") OR (AB "gastrointestine flora") OR (TI "gastrointestine tract flora") OR (AB "gastrointestine tract flora") OR (TI "gut bacteria") OR (AB "gut bacteria") OR (TI "intestinal bacteria") OR (AB "intestinal bacteria") OR (TI "intestinal bacterial flora") OR (AB "intestinal bacterial flora") OR (TI "intestinal flora") OR (AB "intestinal flora") OR (TI "intestinal canal flora") OR (AB "intestinal canal flora") OR (TI "intestinal microflora") OR (AB "intestinal microflora") OR (TI "intestine microbial flora") OR (AB "intestine microbial flora") OR (TI "intestine microflora") OR (AB "intestine microflora")

Combination:
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GOOGLE SCHOLAR

Eating disorders and microbiome

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REVIEW ARTICLE

Belg J Paediatr. 2026;28(3):263-292

Efficacy and Safety of Therapeutic Options in Children and Adolescents With Persistent or Chronic Primary Immune Thrombocytopenia: A Systematic Review

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Keywords

Immune Thrombocytopenia, Paediatric, Chronic, Management

Abstract

Background

Currently, there is no consensus on the treatment of persistent and chronic primary immune thrombocytopenia (ITP) in children. This systematic review evaluates the safety and efficacy of current therapeutic options.

Methods

A comprehensive literature search was performed across MEDLINE/PubMed, Elsevier databases (EMBASE, Scopus), Web of Science (WoS; core collection), and Cochrane (CENTRAL). We included articles published between 1995 and 2026, reporting on safety and/or efficacy of therapies in children and adolescents (<18 years) with persistent or chronic primary ITP.

Results

Ninety-four studies were included. Watchful waiting resulted in a complete remission rate of 14-76%. Of note, thrombopoietin receptor agonists demonstrated the best efficacy/safety balance: acceptable and durable response rates (40-78%) with favourable safety profiles. Splenectomy also yields high complete response rates, but carries a risk of life-threatening complications. Besides, rituximab, sirolimus and mycophenolate mofetil show good efficacy but safety data are scarce. In contrast, first-line therapies (corticosteroids, IVIG and anti-D) provide only short-term benefit whereas cyclosporine A, dapsone and interferon-alpha demonstrate inconsistent efficacy in addition to relevant side effects.

Conclusions

The choice of therapeutic options in paediatric persistent and chronic ITP is extensive. While watchful waiting may be appropriate for many patients, thrombopoietin receptor agonists appear to offer the most favourable efficacy/safety balance when pharmacological treatment is indicated. Long-term safety evaluation and comparative studies focusing on patient-centred outcomes remain warranted.

Introduction

Primary immune thrombocytopenia (ITP) is an acquired, immune-mediated disorder characterized by isolated thrombocytopenia (platelet count < 100 × 10^9/L), and in contrast to secondary ITP, it is not caused by an underlying disease or medication use (1). The pathogenesis is complex, involving increased platelet destruction and/or impaired production, with contributions from humoral and T-cell–mediated cytotoxicity. Additionally, in some cases the concentration of endogenous thrombopoietin, which stimulates the growth and maturation of megakaryocyte progenitors, is lower than expected (2,3). Acute primary ITP occurs in 2–6 per 100,000 children annually and is usually self-limiting, though thrombocytopenia persists in 15–20% of cases (4-6). In 2009, consensus definitions for the duration of ITP have been established: 'newly diagnosed' (<3 months), 'persistent' (3–12 months) and 'chronic' (>12 months), as well as standardized criteria for treatment response (1). Although rare in children, major complications such as intracerebral haemorrhage can be life-threatening, with significant mortality rates (2,7–9). Other bleeding events, such as severe epistaxis, gastrointestinal bleeding and menorrhagia, can significantly affect quality of life, limit daily activities and cause psychological stress for patients and families (10). Therefore, ITP treatment aims to prevent severe bleeding episodes and maintain quality of life. However, the management of persistent and chronic ITP remains controversial, as second-line therapies vary in efficacy and safety profiles. Yet, watchful waiting may also be appropriate for some patients. Besides, the current treatment paradigm is shifting from an exclusive focus on the platelet count to clinically relevant endpoints such as bleeding complications and quality of life (11). This systematic review summarizes the safety and efficacy of treatment options for children and adolescents with persistent or chronic ITP, to guide clinical decision-making and optimize outcomes.

Materials and methods

Search strategy and study selection

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. It was registered in the International Prospective Register of Systematic Review (PROSPERO) and can be accessed at https://www.crd.york.ac.uk/PROSPERO/view /CRD42024574932.

A systematic search was conducted on September 5th, 2024, in PubMed/MEDLINE, Elsevier databases (EMBASE (https://www.embase.com, Scopus), Web of Science (WoS; Core Collection) and Cochrane (CENTRAL). A second search was performed on February 22nd, 2026, to guarantee a complete and up-to-date literature overview. The full search strategy is shown in Supplementary Table 1. Reference lists of relevant articles and reviews were screened manually for additional eligible studies.

We included original human studies (randomized controlled trials (RCTs), cohort studies, case series) published in English between 1995 and February 2026. Editorials and letter-format papers were considered, provided they reported small-scale studies. Eligible studies focused on children and adolescents (<18 years) with primary ITP lasting ≥3 months. Studies including both paediatric and adult data were considered only if paediatric results were available separately. We excluded studies limited to adults, those on secondary ITP, case reports or case series with fewer than 3 participants, and studies that did not report efficacy or safety outcomes. All records were imported into the Rayyan review management platform and duplicates were removed by manual screening. Two reviewers independently screened titles and abstracts per predefined criteria, while blinded to each other's decisions. Disagreements were resolved by consensus and/or by discussion with a third reviewer.

Data extraction and analysis

The following data were extracted: a) study details (title, authors, year, design); b) study population (sample size, age, sex, country, previous treatments if any); c) treatment details and outcomes (intervention type, dosage, efficacy, adverse events); d) information relevant to risk-of-bias assessment.

Quality and risk-of-bias assessment

Study quality was assessed using the JBI critical appraisal tool. Each item was rated "Yes", "No" or "Unknown" (insufficiently reported). Quality was expressed as the percentage of "Yes" responses (items 11–13 omitted for RCTs) and categorized as high quality/low risk of bias (≥80%), moderate quality/moderate risk of bias (50–79%) or low quality/high risk of bias (<50%). "Not applicable" items were excluded. "No" and "Unknown" were treated equivalently. Two reviewers independently performed the assessments, resolving discrepancies by discussion or consultation with a third reviewer.

Definitions

We defined complete remission (CR) as platelet count ≥ 100 x 10^9/L and clinically relevant partial remission (PR) as platelet count ≥ 30 x 10^9/L. The 2009 International Working Group (IWG) criteria were used to classify ITP duration: persistent (3–12 months) and chronic (>12 months) (1). The precise definitions for each study are provided in Table 1.

Results

Our searches identified 7,644 articles. After removing duplicates and selection based on eligibility criteria, 500 articles were identified for full text reading. Finally, 94 studies were included (Figure 1). A detailed summary of the efficacy and safety outcomes for each therapy is provided in Table 2.

Thrombopoietin-receptor agonists (TPO-RAs)

TPO receptor agonists bind to the c-Mpl receptor on the megakaryocytes, which causes change of the receptor and thus activation of the JAK2/STAT pathway. This increases megakaryocyte proliferation and platelet production, countering immune-mediated peripheral destruction (12).

Our search identified 15 articles studying eltrombopag in 926 patients (5 to 143 per study): 2 RCTs, 11 cohorts and 2 case series (11, 13-26). Two additional articles compared eltrombopag with romiplostim (27,28). Three non-RCTs had a prospective design. We also found 10 studies on romiplostim in 472 patients (4 to 203 per study): 2 RCTs, 5 cohorts and 3 case series (11,29–37). Five of these non-RCTs were prospectively designed (32–35,37). One RCT and 2 retrospective cohort studies examined avatrombopag in 164 children (34 to 75 per study) (38,39,40). Additionally, one retrospective cohort studied hetrombopag in 30 patients with persistent or chronic ITP (41).

Eltrombopag significantly increased the platelet count with 62-75% of patients achieving >50×10^9/L at least once, compared to 3-32% of those on placebo (13,14). The response lasted >6 weeks in 40% of patients (14). Quality of life showed minor improvements, albeit not statistically significant nor clinically relevant (13). Real-world data confirmed overall response rates of 54-89% (CR in 10-45%) (11,15-26). Similarly, 71% of patients treated with romiplostim achieved platelet counts >50×10^9/L at least once versus 20% with placebo. A durable response (≥6 weeks) occurred in 52% (30). In the non-RCTs overall response rates were 65-100%, which was durable in 44-78% (31–37). A direct

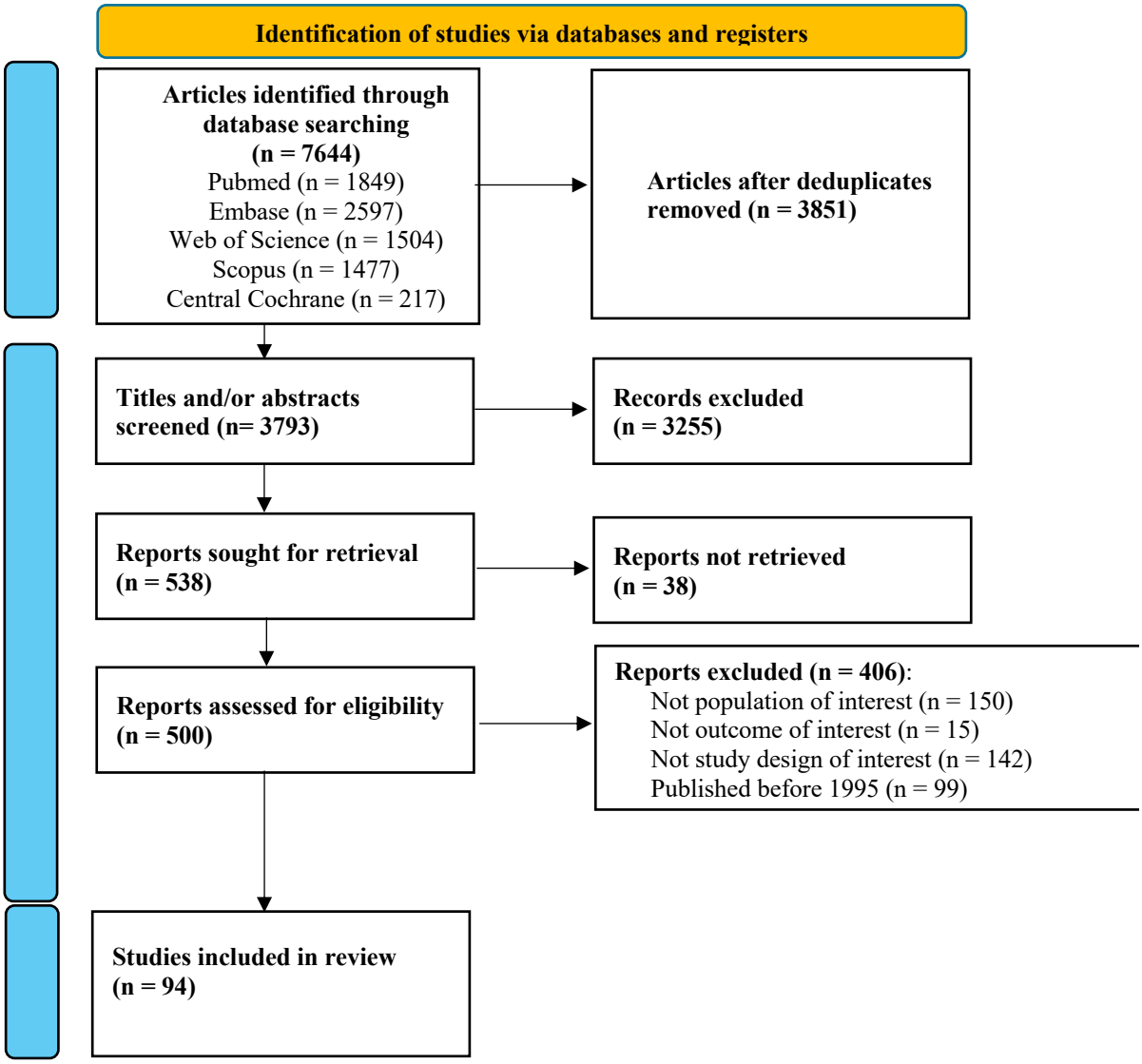


FIGURE 1: Selection process of articles following the Preferred Reporting Items for Systematic Meta-Analyses (PRISMA) flow diagram.

comparison between romiplostim and eltrombopag showed no statistical difference between both drugs (27,28). Avatrombopag led to an overall response of 61-88% which was sustained for 6 months in 33-55% (39,40). The RCT of Grace et al. demonstrated a durable platelet response in 28% of patients treated with avatrombopag, compared with 0% in the placebo group (38). Hetrombopag showed an overall response rate of 77%, including CR of 50%, and a durable overall response in 74% at 6 months (41).

The most common adverse events associated with eltrombopag were upper respiratory symptoms (20-30%) (13,14). Headache, gastrointestinal complaints and transient liver enzyme elevations were also reported (15-28). Most events were grade 1-2; grade 3-4 events occurred in 5% of patients on eltrombopag (13–18,20–26). For romiplostim, injection-site bruising (50%) and headache (43%) were most commonly reported, but also rash, oropharyngeal pain and upper respiratory symptoms occurred (29–37). Thrombocytosis was noted both on eltrombopag and romiplostim but no thromboembolic events were reported. No malignancies were described. Avatrombopag was associated with upper respiratory and gastrointestinal symptoms, headache, fatigue, fever and oropharyngeal pain. No thromboembolic events were reported (38–40). The study on hetrombopag reported upper respiratory tract infection, thrombocytosis, diarrhea, headache, vomiting, abdominal pain, itchy and dry skin, and dizziness (41).

Recombinant human thrombopoietin (rhTPO)

Recombinant human thrombopoietin has similar functioning to endogenous thrombopoietin, which accounts for megakaryocyte proliferation, differentiation and maturation, as well as platelet production (42).
We included 1 double-blind, placebo-controlled RCT on rhTPO in 56 children with chronic and persistent

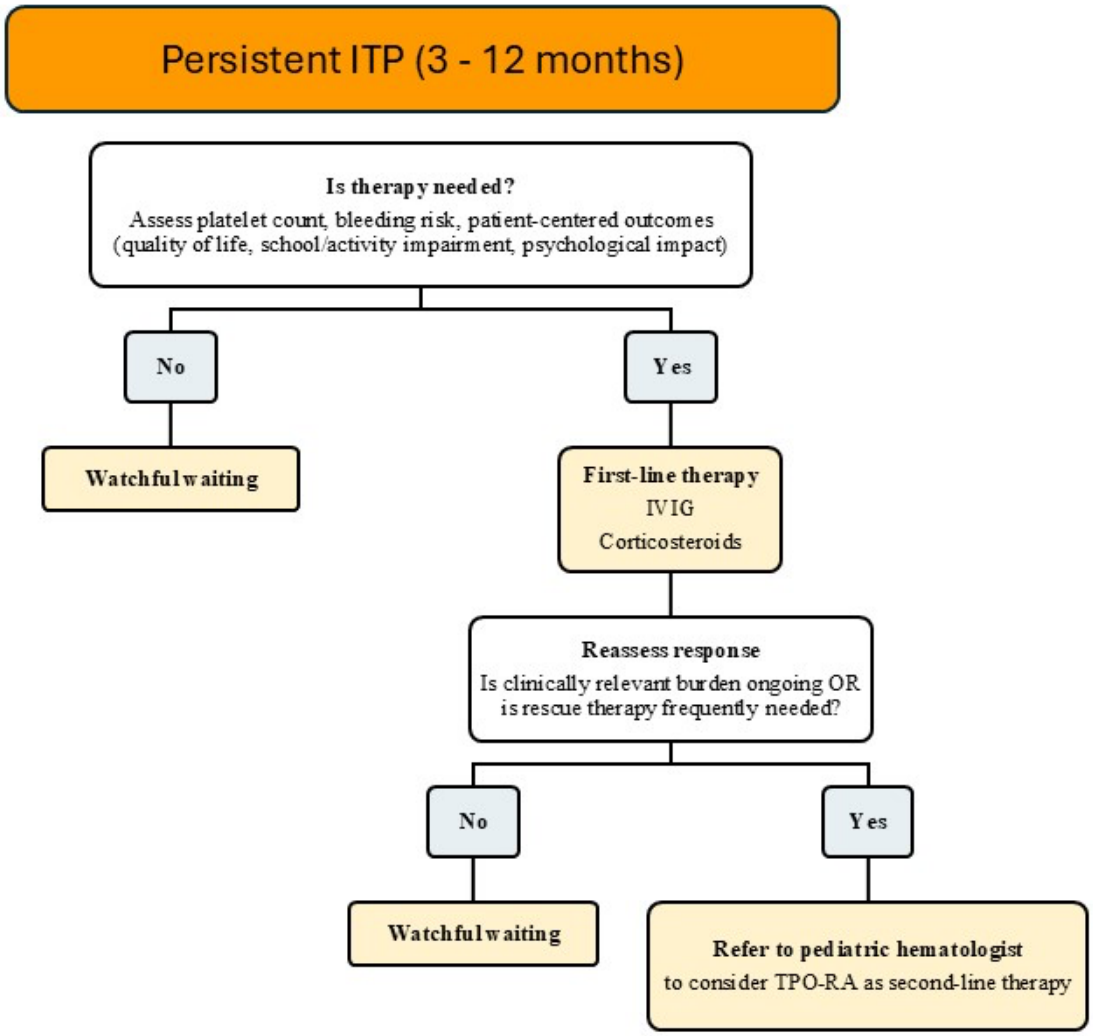


FIGURE 2: Proposed therapeutic algorithm for persistent immune thrombocytopenia. ITP: immune thrombocytopenia; IVIG: intravenous immunoglobulin; TPO-RA: thrombopoietin-receptor agonist.

ITP. An overall response rate of 59% was observed in the treatment group, compared to 13% in the placebo group. Epistaxis, cutaneous bleeding events and upper respiratory infection were most commonly reported adverse events (42).

Corticosteroids

Corticosteroids reduce autoantibody production, interfere with antibody binding and inhibit macrophage differentiation and phagocytosis (43). Ten studies evaluated corticosteroids in 164 patients (7 to 34 per study): 6 cohort studies and 4 case series (43–52). Most studies investigated high-dose dexamethasone whereas some used methylprednisolone or prednisone, or various types (43–52).

Dexamethasone increased platelet counts in most patients, but sustained responses were limited (43–48,50). Adams et al. reported that all 7 patients reached ≥ 30×10^9/L above baseline, though counts eventually declined (50). Similarly, Chen et al. observed PR in 6 of 7 patients, with only 1 maintaining the response after 12 months (45). Other studies reported responses during 6-12 months in 29–46% of patients, depending on the response criteria (43,46–48). Additionally, Ozer et al. evaluated monthly high-dose methylprednisolone (2 to 8 courses) and reported CR in 41%, maintaining counts of 20-100×10^9/L without mucocutaneous bleeding in 18% for 12 months (49). Finally, 3 other groups reported CR in 21-34% up till 14 years, though responses were not stratified by corticosteroid type (44,51,52).

The most common adverse events of corticosteroids were fatigue, weight gain, mood changes and gastro-intestinal complaints (43,45–47,49–51). Hypertension was rare (48). No significant differences were observed between corticosteroid types (51).

Intravenous immunoglobulin (IVIG)

Intravenous immunoglobulins modulate Fc receptor expression or affinity, block Fc receptor-mediated platelet phagocytosis and regulate immunity by influencing the cytokine network (53). We retrieved 4

articles studying IVIG in 77 patients (5 to 37 per study): 2 RCTs comparing IVIG to anti-D and steroids, or to steroids, 1 prospective observational cohort study comparing IVIG plus steroids, steroids alone, and watchful waiting, and 1 retrospective case series (44,52,54,55).
IVIG was not superior to anti-D or steroids (54). However, IVIG gave higher short-term but lower long-term responses than dexamethasone: all patients (n=8) achieved PR by day 3, but only 1 maintained CR >3 months (55). Similarly, 1 out of 6 patients receiving IVIG plus steroids remained in CR after 3 months (44). Headache was a common side effect (70%) and led to discontinuation in 1 patient. Aseptic meningitis occurred in 1 of 15 patients (7%) (54,55).

Anti-Rhesus immunoglobulins (anti-D)

Anti-D immunoglobulin binds to red blood cells, resulting in direct competition for macrophage clearance of the coated red blood cells and autoantibody-coated platelets, which reduces platelet destruction and raises platelet counts (56). We included 4 prospective and 2 retrospective studies, evaluating anti-D in 124 patients (6 to 34 per study): 3 cohort studies, 2 case series and 1 randomized, non-blinded trial comparing anti-D to IVIG (11,52,53,56-58). In persistent ITP, the overall response rate was 83% (PR 50%, CR 33%), while in chronic ITP, PR ranged from 0% to 44% and CR from 0% to 17% (50,52,53,56,58). No next-line treatment was given in 17% of patients and all patients had a sufficient increase in platelet counts (defined as ≥20 x10^9/L if symptomatic and ≥10 x10^9/L if asymptomatic) to protect against severe bleeding (11,57). Intravascular haemolysis with haemoglobin drops of 0.1 to 3.6 g/dL was reported in 3 papers (53,56,57). Other side effects included fever, chills, skin rash and haemoglobinuria.

Immunosuppressive and immune-modulating agents

Cyclosporine A

Cyclosporine inhibits interleukin-2 production and suppresses T-cell activation, and thereby decreases immune-mediated platelet destruction (59). We included 1 RCT comparing cyclosporine to sirolimus, 1 prospective interventional cohort study, 1 prospective case series and 2 retrospective observational studies, comprising 124 children (4 to 61 per study) (11,59-62). PR ranged from 20-46% and CR varied between 7% and 53% (59–62). Responses were durable during a median of 42 months following cessation (62). Hirsutism was the most common side effect (37 to 60% of patients) (60,62). Other adverse effects included hypertrichosis, transient hyperbilirubinemia, oral mycosis, fungemia, tremor, gum hypertrophy, mild gastrointestinal complaints, neutropenia, hypertension and renal impairment (59,60,62).

Rituximab

Rituximab is a monoclonal antibody that reduces autoimmune activity of CD20-positive B cells by complement- and antibody-mediated cytotoxicity, inhibition of lymphocyte proliferation and induction of apoptosis (63,64). Eight studies evaluated the effect and safety of rituximab in 202 patients (6 to 62 per study): 5 case series (3 prospective interventional, 2 retrospective observational, 1 prospective cohort and 1 retrospective cohort study (11,63-67). One prospective interventional cohort study studied rituximab administration prior to eltrombopag treatment versus eltrombopag monotherapy (68). PR and CR ranged from 17% to 67% and 0% to 68%, respectively (52,63–67) and no next-line therapy was needed in more than 50% (11). The response lasted for a median of 12 to 33 months (65–67). In the study comparing rituximab prior to eltrombopag with eltrombopag monotherapy, more patients receiving monotherapy achieved platelet counts ≥ 30x10/L and at least doubled their count at 1 month (85% vs 49%), whereas this difference was no longer observed at 12 months (88% vs 85%). CR was also more frequent in patients on monotherapy than those who received rituximab first (35% vs 9% at 1 month, 56% vs 48% at 12 months). Treatment cessation was achieved in 30% of the rituximab group versus none in the eltrombopag monotherapy group (68). Rituximab was generally well tolerated with mainly mild to moderate infusion reactions. Immunoglobulin levels could be reduced without major infections (64,66,68).

Sirolimus

Sirolimus is an mTOR-inhibitor and blocks cytokine-driven activation of lymphocytes (69). In a retrospective observational case series (n=12) on persistent ITP, PR was 8% and CR 75% (69). Additionally, an RCT comparing cyclosporine to sirolimus in 61 patients with chronic ITP reported a PR and CR of 50% after 6 months (60). No serious side effects were reported. One patient experienced haematuria, while several patients reported mild gastrointestinal complaints or upper respiratory symptoms (60,69).

Interferon alpha

Interferon alpha alters cytokine production, increases NK-cell activity and reduces secretion of autoantibodies (70,71). We identified 2 prospective case series, including 25 patients treated with interferon alpha (70,71). Hrstková et al. reported a PR of 27% and CR of 55%, for 18 to 30 months (70). In 82% of patients, a platelet count >150 x 10^9/L or an increase not reaching 150 x 10^9/L was seen. However, counts returned to baseline shortly after interferon discontinuation (71). Most patients reported flu-like symptoms during two weeks. Additionally, severe neutropenia (<1.0 ×10^9/L) was reported in one patient (71). Mildly elevated bilirubin and liver enzymes, without severe hepatotoxicity

occurred in another patient. No serious adverse effects were reported (70,71).

Mycophenolate mofetil

Mycophenolate mofetil is an inosine monophosphate dehydrogenase inhibitor, limiting de novo purine synthesis, necessary for lymphocyte proliferation, and antibody production (72). Only two studies investigated mycophenolate mofetil. A prospective case series (6 patients with persistent and chronic ITP) demonstrated that all responded to a combination of corticosteroids and mycophenolate mofetil (platelet counts >100 x10^9/L within 1 month). Steroids were tapered over 42 days and the response was maintained up to 12 months after discontinuation (72). In addition, a retrospective cohort study reported that almost half of the children did not need next-line therapies after the start of mycophenolate mofetil (11).

Dapsone

Dapsone induces low grade haemolysis, which likely interferes with platelet clearance by the reticulo-endothelial system (73). We identified 5 retrospective observational cohort studies, evaluating dapsone in 171 patients (10 to 45 per study) (11,73–76). The PR varied between 9 and 48%, whereas CR ranged from 24-49%. Response after 6-12 months of therapy (with or without cessation of dapsone) showed considerable variation, ranging from 0-40% (75,76). Common side effects included haemolysis, anaemia, skin rashes/ulceration, hepatitis and methemoglobinemia (74,75).

Daratumumab

Daratumumab is a humanized anti-CD38 monoclonal antibody that targets CD38-positive plasma cells, which are responsible for producing autoantibodies against platelet (77). We included 1 prospective interventional and 1 retrospective case series comprising 31 children (78,79). A response was seen in 82-90%, which was a CR in 73%. Relapse occurred in 55% at 6 months but retreatment led to CR in most of them. Most common side effects were infusion-related reactions, upper respiratory tract infection, thrombocytosis and 1 patient with secondary hypogammaglobulinemia (78,79)

Hydroxychloroquine

Hydroxychloroquine, commonly known as an antimalarial drug, modulates immunity and interferes with metabolic pathways due to inhibition of lysosomal functioning (80). Liu et al. conducted a retrospective cohort study, including 191 patients with chronic ITP. An overall response rate of 57% was achieved at 3 months, and was sustained in 41% at 12 months. Adverse effects were observed in 14% of patients, predominantly involving retinopathy, elevated liver enzymes and alterations in skin pigmentation (80).

Splenectomy

Splenectomy removes the primary site of platelet destruction and autoantibody-producing B cell formation (81). All 12 studies evaluating splenectomy were retrospective observational cohorts (11,81–89) with the exception of 2 case series (52,90). Sample sizes ranged from 6 to 288 per study (1,157 patients). Overall response rates ranged from 73 to 95% (PR 6-75%; CR 45-85%) (11,52,81–90). However, follow-up periods differed widely (1 month - 16 years). Pincez et al. evaluated the failure-free survival (FFS), defined as the time from splenectomy to second-line treatment (excluding steroids or IVIG) or death, whichever occurred first. FFS was 88% at 1 year, 84% at 2 years and 77% at 5 years post-splenectomy (85). Infectious complications were common, with overwhelming sepsis being reported in 6 patients of whom 4 died (81,82,85,87,88). Additionally, severe intracerebral haemorrhage occurred in 3 patients of which 2 were fatal (81,87,88). Aronis et al. reported transient thrombocytosis in all patients (81).

Watchful waiting

We included 7 articles evaluating watchful waiting in 613 patients (25 to 230 per study). Except for one case series, all were retrospective observational cohort studies (82,83,89,91–94). Follow-up duration ranged between 6 months and 25 years (82,83,89,91–94). PR was reported in 38% (92) and 66%, while CR ranged from 14% to 76% (82,83,89,92,93).

Other therapies

H. pylori eradication

H. pylori possibly induces autoantibody production by chronic immune response or by molecular mimicry between platelet surface antigens and virulent surface factors of the bacterium (95). Eight prospective interventional studies on H. pylori eradication included 237 children (3 to 84 per study): 3 case series, 3 cohort studies and 2 RCTs (95-102). The RCTs reported CR in 14% and 60% (eradication group) versus 11% and 18% (control group) (101,102). Similarly, CR in the other studies ranged from 13-80% (84,95–98,100). The treatment was well tolerated with only mild and transient side effects, not further specified (98,101).

Herbal formulations

Japanese and Chinese herbal formulations are hypothesized to modulate immune homeostasis, promote blood cell production and enhance glucocorticoid effects (103–105). We identified 1 retrospective case series of 44 children treated with cepharanthin, 1 RCT on 42 children treated with Guishao Shengxue decoction and 1 RCT on 216 patients receiving Huaiqihuang granule (103,104,106). Patients treated with cepharanthin showed median platelet counts

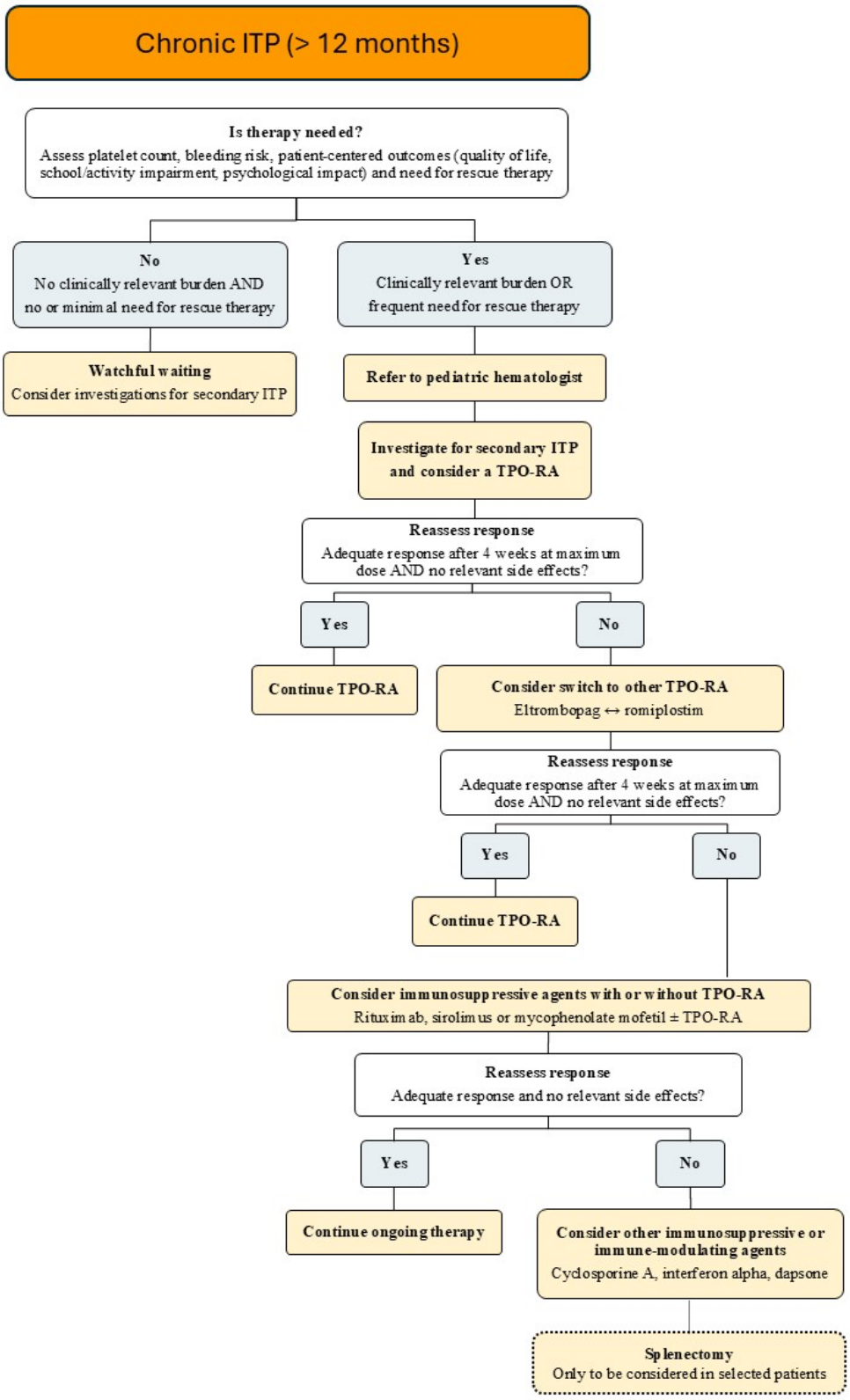


FIGURE 3: Proposed therapeutic algorithm for chronic immune thrombocytopenia.
ITP: immune thrombocytopenia; TPO-RA: thrombopoietin-receptor agonist.

increase from 21 to 59 x 10^9/L at 12 months and to 69 x 10^9/L at 24 months, with the greatest benefit in patients starting with platelet counts <20 x 10^9/L. Bleeding symptoms improved in 71-78% and steroids could be weaned (106). For Guishao Shengxue decoction, overall response rates were 95% and 71% in the treatment and placebo groups, respectively. Recurrence was reported in 4% of patients in the treatment arm versus 19% in the control arm (103). In the study on Huaiqihuang granule, overall response rates were 72% in the treatment group and 46% in the placebo group (104).

No serious adverse events occurred in the cepharantin and Guishao Shengxue decoction studies. One

patient treated with cepharanthin had transient hepatic dysfunction and Guishao Shengxue decoction was associated with nausea, fever and dizziness (though similar rates were reported in the control group) (103,106). Reported side effects in the Huaiqihuang granule study included diarrhoea, epistaxis, intracranial haemorrhage, gastrointestinal haemorrhage and gingival bleeding (104).

Escalating treatment strategy

Fu et al. retrospectively analysed 30 patients with chronic ITP who received stepwise treatment of high-dose dexamethasone, rituximab and eltrombopag (107). Nine patients received steroids alone, 4 received additional rituximab and 17 underwent triple therapy. Overall, 80% responded. The response persisted for ≥12 months in 37%. CR rates by treatment step were 33%, 75% and 29%, respectively (107).

Risk of bias and quality assessment

Detailed responses to each JBI checklist item are provided for each study type separately in Supplementary Tables 2-4. The methodological quality of the 27 case series was rated high for 21 (78%), moderate for 5 (18%) and low for 1 study (4%). Of the cohort studies (n=53), 9 were of high quality (17%), 38 of moderate (72%) and 6 of low quality (11%). Finally, 7 out of 14 RCTs (50%) had a high quality, 5 (36%) had a moderate and 2 (14%) had a low quality.

Discussion

Choosing the right treatment for a child with persistent or chronic ITP remains very challenging. By evaluating the efficacy and safety of the various options, this review aimed to support real-world clinical decision-making and provides an example of a therapeutic algorithm (Figure 2 and 3).

First of all, it is important to note that many patients with persistent ITP will recover and also a substantial proportion of patients achieve spontaneous remission more than 1 year after the initial diagnosis. Thus, the efficacy of therapies should be interpreted with caution, as it may be partially overestimated. Moreover, watchful waiting may be appropriate if significant bleeding is absent. If treatment is deemed necessary, first-line therapies (IVIG, corticosteroids, anti-D) are a reasonable option. However, as in acute ITP, these agents show short-term benefits, but relapse is common. Furthermore, the side effects and/or costs limit the long-term or repetitive usability.

This review reveals TPO-RAs (romiplostim, eltrombopag) as the second-line therapy with the most favourable balance between efficacy and safety, which is in line with the current treatment recommendations (108,10[9]). Sustained responses were observed in over half of patients and these drugs are well tolerated. However, long-term safety remains uncertain due to lack of existing data. Newer thrombopoietin receptor agonists, such as avatrombopag and hetrombopag, have further expanded the therapeutic landscape for ITP and demonstrate promising efficacy with favourable safety profiles. However, additional high-quality comparative studies and long-term follow-up data are needed to better define their relative positioning within second-line treatment strategies.

Alternative treatments, including rituximab, sirolimus, and MMF show promising efficacy but safety data are limited. On the other hand, cyclosporine A, dapsone, and interferon alpha demonstrate only modest or inconsistent efficacy with notable side effects, limiting their clinical use. Moreover, while splenectomy is effective in over 75% of patients, the risk of life-threatening infections and the irreversibility of the procedure urges us to consider splenectomy only as an option of last resort. Besides, although a link between H. pylori and chronic ITP has been suggested, response rates to eradication vary widely, reflecting differences in study populations and methodology. Screening may be considered in symptomatic patients, but is not recommended routinely in asymptomatic individuals. Finally, new therapeutic options are currently being studied: vitamin D as adjuvant treatment (NCT06073925), CAR-T cells (NCT06352281), obinutuzumab (NCT06094881), rilzabrutinib (NCT04562766) or efgartigimod (NCT07194850). Yet, we are awaiting the results of these emerging therapeutic strategies for children with chronic or persistent ITP.

Although this review provides a comprehensive overview of the currently available treatments for chronic and persistent paediatric ITP, several limitations should be considered. A key challenge is the inconsistent definitions for persistent and chronic ITP and treatment response, especially in studies conducted before the 2009 IWG consensus. This variability complicates direct comparisons. Besides, these IWG definitions do not fully reflect current patient-centred treatment goals, which emphasize quality of life and bleeding control rather than platelet count alone. Secondly, most included studies were retrospective cohort studies or case series, subject to inherent bias and only 3 of the included RCTs were considered high quality. Heterogeneity in study design further complicates comparisons and may explain variable response rates. This prompted us to a narrative synthesis, that guided the development of a therapeutic framework, which should be interpreted as a pragmatic synthesis of heterogeneous evidence rather than a definitive evidence-based pathway. Additionally, many studies lack long-term follow-up data, limiting assessment of response durability and long-term safety. Finally, given the limited number of studies on persistent ITP, lack of differentiation from chronic ITP and overlap between the former definition of chronic ITP (> 6 months) and current definition of persistent ITP (3-12 months), conclusions on the optimal treatment strategies for persistent ITP cannot be drawn.

Conclusion

The wide range of therapeutic options for persistent and chronic paediatric ITP makes selecting the most appropriate treatment challenging. Watchful waiting proves appropriate for many patients, whereas TPO-RAs appear to be the most favourable second-line treatment when pharmacological therapy is required. Future research should focus on monitoring of long-term safety and on comparing therapies while focusing on patient-centred outcomes.

Statements

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TABLE 1: Characteristics of included studies (Continued on next page)

Intervention	Study design	Year	N	Persistent or chronic	Definition of duration*	Definitions of efficacy*
Eltrombopag (13)	RCT	2015	67	Both		PLT >50x10^9/L at least once with no rescue therapy
Eltrombopag (14)	RCT	2015	92	Chronic		PLT >50x10^9/L with no rescue therapy for ≥ 6 weeks
Eltrombopag (15)	retrospective, observational cohort	2019	20	Chronic		
Eltrombopag (16)	retrospective cohort	2024	55	Both		PLT >30x10^9/L and more than a twofold increase compared to baseline and absence of bleeding events
Eltrombopag (17)	retrospective cohort	2020	71	Chronic		% of patients with PLT >30x10^9/L and >100x10^9/L at 1, 3, and 6 months of treatment
Eltrombopag (18)	retrospective, observational cohort	2020	60	Chronic		
Eltrombopag (19)	retrospective, observational cohort	2020	30	Chronic		
Eltrombopag (20)	prospective, observational cohort	2021	116	Both		
Eltrombopag (21)	retrospective, observational cohort	2023	56	Chronic		
Eltrombopag (22)	retrospective, observational cohort	2023	65	Chronic		
Eltrombopag (23)	retrospective, observational cohort	2023	143	Both		
Eltrombopag (24)	prospective, observational cohort	2023	30	Both		PLT >50x10^9/L for more than 75% of the tests
Eltrombopag (25)	prospective, interventional case series	2018	19	Both	Chronic if ≥ 6 months	
Eltrombopag (26)	retrospective case series	2024	13	Both	Not specified	complete: PLT >50x10^9/L with no rescue therapy for > 6 weeks; partial: response <6 weeks or requiring rescue therapy
Eltrombopag/ romiplostim (27)	retrospective cohort	2014	33	Both	Chronic if ≥ 6 months	PLT >50x10^9/L for at least 2 consecutive weeks
Eltrombopag/ romiplostim (28)	retrospective cohort	2024	33	Chronic		PLT >50x10^9/L
Romiplostim (29)	RCT	2011	18	Chronic		PLT >50x10^9/L
Romiplostim (30)	RCT	2016	62	Both	Chronic if ≥ 6 months	PLT >50x10^9/L with no rescue therapy in last 4 weeks
Romiplostim (31)	retrospective cohort	2014	7	Chronic	Not specified	PLT >30-50x10^9/L and low doses of romiplostim every 4-5 weeks
Romiplostim (32)	prospective, interventional cohort	2015	22	Chronic	Chronic if ≥ 6 months	PLT >50x10^9/L with no rescue therapy in last 4 weeks

TABLE 1: Characteristics of included studies (Continued on next page)

Romiplostim (33)	RCT	2019	66	Chronic	Chronic if ≥ 6 months	PLT >50x10^9/L
Romiplostim (34)	prospective, interventional cohort	2022	40	Both		PLT >50x10^9/L with no rescue therapy
Romiplostim (35)	prospective, interventional case series	2012	7	Chronic		PLT >50x10^9/L with no rescue therapy
Romiplostim (36)	retrospective case series	2014	4	Both		PLT >50x10^9/L and more than twofold increase compared to baseline, with no rescue therapy in last 8 weeks
Romiplostim (37)	prospective, interventional case series	2023	203	Both		PLT >50x10^9/L with no rescue therapy in last 4 weeks
Avatrombopag (38)	RCT	2025	75	Both		Durable platelet response: at least 6 out of 8 weekly PLT > 50×10^9/L during the last 8 weeks of the 12-week treatment period, in the absence of rescue therapy
Avatrombopag (39)	retrospective cohort	2024	34	Both		
Avatrombopag (40)	retrospective cohort	2025	55	Both		
Hetrombopag (41)	retrospective cohort	2025	30	Both		
Recombinant human thrombopoietin (42)	RCT	2024	56	Both		
Steroids (43)	prospective, interventional case series	1997	11	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L with no rescue therapy; partial: PLT 50-150x10^9/L with no rescue therapy; none: PLT <50x10^9/L or requiring rescue therapy
Steroids (45)	prospective, interventional cohort	1997	7	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L; partial: PLT 50-150x10^9/L; none: PLT <50x10^9/L
Steroids (46)	prospective, interventional cohort	1997	17	Chronic	Chronic if ≥ 6 months	normal PLT
Steroids (47)	prospective, interventional cohort	2002	13	Chronic	Not specified	complete: PLT >150x10^9/L; partial: PLT 50-150x10^9/L; none: PLT <50x10^9/L
Steroids (48)	prospective, interventional cohort	2010	13	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L; partial: PLT 50-150x10^9/L; minimal: PLT 20-30x10^9/L; none: unchanged PLT or increase but PLT <20x10^9/L
Steroids (49)	prospective, interventional cohort	2000	22	Chronic	Chronic if ≥ 6 months	complete: PLT >100x10^9/L; partial: PLT 20-100x10^9/L; none: PLT <20x10^9/L
Steroids (50)	prospective, interventional case series	1996	7	Both	Chronic if ≥ 6 months	PLT >30x10^9/L above pretreatment value
Steroids (51)	retrospective case series	2005	29	Chronic	Chronic if ≥ 6 months	complete: PLT between 180-250x10^9/L; partial: PLT between 70-110x10^9/L
Steroids/IVIG (44)	prospective, observational cohort	2006	12	Chronic	Chronic if ≥ 6 months	complete: PLT >100x10^9/L for >3 months off therapy and absence of abnormal bruising
Steroids/IVIG (54)	RCT	2006	37	Chronic	Chronic if ≥ 6 months	complete: PLT >100x10^9/L or 3 months off therapy
Anti-D (56)	prospective, interventional cohort	2009	20	Both		

TABLE 1: Characteristics of included studies (Continued on next page)

Intervention	Study design	Year	N	Persistent or chronic	Definition of duration*	Definitions of efficacy*
Anti-D (57)	prospective, interventional cohort	2010	30	Chronic	Chronic if ≥ 6 months	PLT >20x10^9/L in symptomatic patients and >10x10^9/L in asymptomatic patients
Anti-D (58)	prospective, interventional case series	2013	9	Chronic		
IVIG/anti-D (53)	RCT	2006	34	Chronic	Chronic if ≥ 6 months	PLT >50x10^9/L or doubling of baseline PLT with absence of bleeding
Steroids/IVIG/ anti-D (55)	RCT	2003	23	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L with no rescue therapy; partial: PLT >30x10^9/L and above pretreatment value
Cyclosporin/ sirolimus (60)	RCT	2020	61	Chronic		
Cyclosporin (59)	prospective, interventional case series	2002	14	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L; partial: PLT 50-150x10^9/L; none: unchanged PLT or >50x10^9/L with rescue therapy
Cyclosporin (61)	prospective, interventional cohort	2008	15	Chronic	Chronic if ≥ 6 months	complete: PLT >100x10^9/L for at least 2 months; partial: PLT >50x10^9/L and doubled; none: PLT < 50x10^9/L
Cyclosporin (62)	retrospective cohort	2016	30	Both		
Rituximab (63)	prospective, interventional case series	2014	18	Chronic		complete: PLT >100x10^9/L; partial: PLT 50-100x10^9/L; minimal: PLT 30-50x10^9/L; none: PLT <30x10^9/L
Rituximab (64)	prospective, interventional cohort	2008	6	Chronic	Not specified	complete: PLT >75x10^9/L; partial: PLT 30-75x10^9/L
Rituximab (65)	prospective, interventional case series	2011	12	Chronic		
Rituximab (66)	prospective, interventional case series	2005	24	Chronic	Chronic if ≥ 6 months	complete: peak PLT >150x10^9/L; partial: PLT between 50-100x10^9/L; minimal: >20x10^9/L above pretreatment value but <50x10^9/L; none: no increase
Rituximab (67)	retrospective case series	2006	19	Chronic	Chronic if ≥ 6 months	PLT >50x10^9/L for at least 7 days
Rituximab/ eltrombopag (68)	prospective, interventional cohort	2025	55	Both		
Sirolimus (69)	retrospective case series	2017	12	Persistent		complete: PLT >150x10^9/L for 2 months with ability to taper steroids; partial: improvement in PLT by ≥1 CTCAE grade for ≥2 months with same dose of steroids or stable PLT while tapering steroids by at least 50%
Interferon alpha (70)	prospective, interventional case series	2002	11	Chronic	Chronic if ≥ 6 months	Poor: PLT <30x10^9/L; fair: PLT 31-60x10^9/L; good: PLT 61-100x10^9/L; very good: PLT >100x10^9/L
Interferon alpha (71)	prospective, interventional case series	2001	14	Chronic		complete: PLT >150x10^9/L, partial: PLT increase but < 150x10^9/L; none: no increase or PLT increase <15% more than pretreatment value
Mycophenolate mofetil (72)	prospective, interventional case series	2017	6	Both		initial: PLT >100x10^9/L; complete: maintenance of initial response during >3 months while off steroids
Dapsone (73)	retrospective cohort	2020	29	Chronic		

TABLE 1: Characteristics of included studies (Continued on next page)

Dapsone (74)	retrospective cohort	2005	35	Chronic	Chronic if ≥ 6 months	complete: PLT >100x10^9/L; partial: PLT 50-150x10^9/L; none: PLT <50x10^9/L
Dapsone (75)	retrospective cohort	2014	12	Both		
Dapsone (76)	retrospective cohort	2024	45	Chronic		
Daratumumab (78)	prospective interventional case series	2025	20	Both		PLT >50×10^9/L without using rescue medication or increasing the dose of concomitant therapy during the 8 weeks after the first dose
Daratumumab (79)	retrospective case series	2025	11	Chronic		
Hydroxychloroquine (80)	retrospective cohort	2025	191	Chronic		
Splenectomy/none (82)	retrospective cohort	1995	92	Chronic	Chronic if ≥ 6 months	recovery = absence of purpura or abnormal bruising together with persistently normal PLT
Splenectomy/none (83)	retrospective cohort	2006	230	Chronic	Chronic if ≥ 6 months	normalization of PLT
Splenectomy (81)	retrospective cohort	2004	33	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L; partial: PLT 50-150x10^9/L
Splenectomy (84)	retrospective cohort	2006	90	Chronic	Chronic if ≥ 6 months	PLT >50x10^9/L
Splenectomy (85)	retrospective cohort	2022	120	Chronic		Failure-free survival defined as time from splenectomy to second-line treatment or death
Splenectomy (86)	retrospective cohort	2003	112	Chronic	Chronic if ≥ 6 months	complete: PLT >100x10^9/L with no rescue therapy for >2 months; partial: PLT >30x10^9/L with no rescue therapy for >2 months; none: PLT <30x10^9/L
Splenectomy (87)	retrospective cohort	2006	65	Chronic	Chronic if ≥ 6 months	complete: PLT >100x10^9/L with no rescue therapy; partial: PLT >30x10^9/L with no rescue therapy
Splenectomy (88)	retrospective cohort	2016	87	Both		
Splenectomy (90)	retrospective case series	2014	18	Chronic		
None (91)	retrospective case series	2004	62	Chronic	Chronic if ≥ 6 months	Complete: PLT >100x10^9/L for >3 months with no rescue therapy; partial: PLT >50x10^9/L for >3 months with no rescue therapy; none: PLT <50x10^9/L
None (92)	retrospective cohort	2012	44	Chronic	Chronic if ≥ 6 months	PLT >50x10^9/L
None (93)	retrospective cohort	2014	47	Chronic		group A: PLT>100x10^9/L; group B: PLT 50-100x10^9/L; group C: PLT <50x10^9/L
None (94)	retrospective cohort	2016	72	Both		
HP eradication (96)	prospective, interventional case series	2007	3	Chronic		
HP eradication (97)	prospective, interventional case series	2009	5	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L; partial: PLT 50-150x10^9/L
HP eradication (95)	prospective, interventional case series	2009	8	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L; partial: PLT >50x10^9/L above pretreatment values
HP eradication (98)	prospective, interventional cohort	2021	63	Chronic		complete: PLT >150x10^9/L; partial: PLT 50-150x10^9/L; none: PLT <50x10^9/L or <20x10^9/L above pretreatment value
HP eradication (99)	prospective, interventional cohort	2011	37	Chronic		complete: PLT >150x10^9/L; partial: PLT >50x10^9/L and >30x10^9/L above pretreatment values; none: PLT <50x10^9/L or <30x10^9/L above pretreatment value or need for rescue therapy

TABLE 1: Characteristics of included studies (End of table)

Intervention	Study design	Year	N	Persistent or chronic	Definition of duration*	Definitions of efficacy*
HP eradication (100)	prospective, interventional cohort	2021	55	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L; partial: improvement in PLT but <150x10^9/L; none: no improvement in PLT
HP eradication (101)	RCT	2009	16	Chronic	Chronic if ≥ 6 months	PLT >100x10^9/L for >3 months
HP eradication (102)	RCT	2015	22	Chronic	Chronic if ≥ 6 months	complete: PLT >150x10^9/L; partial: PLT 50-150x10^9/L and >20-30x10^9/L above pretreatment values; none: PLT <50x10^9/L or <20x10^9/L above pretreatment value
Guishao Shengxue Decoction (103)	RCT	2025	42	Both		
Huaiqihuang Granule (104)	RCT	2025	216	Chronic		
Cepharantin (106)	retrospective case series	2017	44	Chronic	Chronic defined as self-perpetuating, PLT at subnormal levels even during clinical remission	Excellent: PLT >100x10^9/L; good: increase of PLT, 50-100x10^9/L; fair: increase of PLT, 10-50x10^9/L; no change: less than 10x10^9/L different from pretreatment value; progression: decrease of PLT by >10x10^9/L
Escalating treatment regimen (107)	retrospective cohort	2021	30	Chronic		
Various drugs (11)	retrospective cohort	2020	392	Chronic		Complete: PLT >100x10^9/L; partial: PLT >30x10^9/L; none: PLT <30x10^9/L
Various drugs (52)	retrospective case series	2016	60	Chronic	Chronic if ≥ 6 months	Complete: PLT >150x10^9/L; partial: PLT >50x10^9/L; none: PLT <50x10^9/L
Various drugs (89)	retrospective cohort	2024	86	Chronic		

anti-D: anti-rhesus D immunoglobulins; HP: Helicobacter pylori; IVIG: intravenous immunoglobulins; N: number of patients; PLT: platelet count; RCT: randomized controlled trial; *Definitions consistent with International Working Group criteria when not explicitly stated

TABLE 2: Overview of the efficacy and safety of the different treatment options (Continued on next page)

Intervention	Efficacy*	Safety
Eltrombopag (13)	response in 62% (eltrombopag) versus 32% (placebo)	headache, upper respiratory tract infection, diarrhoea
Eltrombopag (14)	response in 40% (eltrombopag) versus 3% (placebo)	headache, nasopharyngitis, pyrexia, upper respiratory tract infection, cough, diarrhoea, vomiting
Eltrombopag (15)	complete response 35%; partial response 40%	mild thrombocytosis, rash
Eltrombopag (16)	overall response 60% durable at 6 months in 45%	elevated aminotransferase levels, headache, vomiting, hair loss, rash, stomach pain
Eltrombopag (17)	complete response 44%; partial response 68% at 6 months durable >50x10^9/L for at least 12 weeks in 40%	headache, thrombocytosis, oral aphthous ulcers, allergic urticaria, microcytic anaemia, transient elevated liver enzymes
Eltrombopag (18)	complete response 30%; partial response 89% at 12 months	transient increase in transaminases
Eltrombopag (19)	complete response 37%; partial response 37% at 12 weeks	vomiting, transient elevated transaminases
Eltrombopag (20)	complete response 46%; partial response 31%	increased indirect bilirubin, increased transaminases, increased alkaline phosphatase, thrombocytosis
Eltrombopag (21)	PLT >50x10^9/L at >75% of assessments in 60% after 6 months	headache, thrombocytosis, iron deficiency anaemia, microcytosis without anaemia, liver enzyme elevation
Eltrombopag (22)	overall response 81%	liver dysfunction, rash
Eltrombopag (23)	Persistent ITP: complete response 46%; partial response 36% Chronic ITP: complete response 43%; partial response 24%	not reported
Eltrombopag (24)	response in 47%	thrombocytosis, elevated liver enzymes
Eltrombopag (25)	complete response 11%; partial response 47%	thrombocytosis
Eltrombopag (26)	complete response 46%; partial response 23%	cholestatic hepatitis with bacteraemia
Eltrombopag/romiplostim (27)	response in 82%	Eltrombopag: mild headache, thrombotic event (a provoked deep-vein thrombosis at the site of an ankle fracture) Romiplostim: rash, nausea, headache
Eltrombopag/romiplostim (28)	response in 94% durable >6 months: 58% (eltrombopag); 44% (romiplostim)	transient thrombocytosis, liver toxicity, haemolysis, headache
Romiplostim (29)	response in 83% (romiplostim) versus 0% (placebo)	rash
Romiplostim (30)	response in 71% (romiplostim) versus 20% (placebo) durable >6 weeks: 52% (romiplostim) versus 10% (placebo)	contusion, epistaxis, headache, upper respiratory tract infection, vomiting, oropharyngeal pain, diarrhoea, nausea, pyrexia
Romiplostim (31)	response in 43%	
Romiplostim (32)	response in 96%	headache, upper respiratory tract infection, pyrexia
Romiplostim (33)	response in 94% durable >24 weeks without therapy in 23%	headache, contusion, upper respiratory tract infection
Romiplostim (34)	response in 65%	headache, body aches, oropharyngeal pain

TABLE 2: Overview of the efficacy and safety of the different treatment options (Continued on next page)

Intervention	Efficacy*	Safety
Romiplostim (35)	overall response 57%	
Romiplostim (36)	response in 100% durable >6 weeks in 75%	rash, irritability, sleep disturbances and alopecia
Romiplostim (37)	response in 88% durable >24 weeks in 5%	epistaxis, headache, nasopharyngitis, pyrexia, cough, petechiae, vomiting, and hematoma
Avatrombopag (38)	durable platelet response 28% (avatrombopag) versus 0% (placebo)	petechiae, epistaxis, ecchymosis, headache, cough, pyrexia, oropharyngeal pain, upper respiratory tract infection, haematoma; no deaths, thromboembolic events, or grade 3 or higher bleeding events
Avatrombopag (39)	overall response 88% at 12 weeks and 55% at 24 weeks	not reported
Avatrombopag (40)	eltrombopag-switch group: complete response 61%, partial response 19%, durable response at 6 months 48% hetrombopag-switch group: complete response 44%, partial response 22%, durable response at 6 months 33%	gastrointestinal symptoms, headache, fatigue; no thromboembolic events
Hetrombopag (41)	overall response 77%; complete response 50% durable overall response 74% at 6 months	upper respiratory tract infection, thrombocytosis, diarrhoea, headache, vomiting, abdominal pain, itchy and dry skin, dizziness
Recombinant human thrombopoietin (42)	complete response 15%; partial response 44% (recombinant human thrombopoietin) versus complete response 0%; partial response 13% (placebo)	epistaxis, skin and mucosal bleeding, upper respiratory tract infection; no liver or kidney toxicity, no thromboembolic events
Steroids (43)	complete response 9%; partial response 27% after 6 months	fatigue, mood changes, facial flushing, headache, irritability, stomach aches, aggressiveness, weight gain
Steroids (45)	complete response 29%; partial response 57%	myalgia, bone pain, acne, fatigue, weight gain, drowsiness
Steroids (46)	response 1 month after the 6th cycle 35%; durable >1 year 29%; no response 24%	fatigue, irritability, anxiety, abdominal pain, striae, acne, weight gain
Steroids (47)	complete response 23%; partial response 23% at 12 and 24 months	bloating, nausea, vomiting, insomnia, anxiety and depression, transient glucosuria
Steroids (48)	complete response 67%; partial response 17% after 1 cycle durable overall response after 4 cycles in 33%	hypertension
Steroids (49)	complete response 41%; partial response 18% at 12 months	weight gain, anxiety
Steroids (50)	response 100% but relapse in all patients; duration of response variable	fatigue, epigastric pain
Steroids (51)	complete response 34%; partial response 28%; failure 38%	
Steroids/IVIG (44)	steroids: complete response 25-29% IVIG: complete response 29-38% anti-D: complete response 38%	Steroids: hypertension, hyperglycaemia IVIG: aseptic meningitis Dapsone: not reported
Steroids/IVIG (54)	steroids: complete response 25% steroids + IVIG: complete response 8% no intervention: complete response 8%	not reported
Anti-D (56)	Persistent ITP: complete response 33%; partial response 50% Chronic ITP: complete response 12%; partial response 38%	low grade fever, haemolysis with drop in haemoglobin

TABLE 2: Overview of the efficacy and safety of the different treatment options (Continued on next page)

Anti-D (57)	response to provide prevention of hemorrhage in 100%	haemoglobin drop, haemoglobinuria, chills
Anti-D (58)	complete response 0%; partial response 44% at day 5 but 11% after 37 weeks	
IVIG/anti-D (53)	response 38% (IVIG) versus 39% (anti-D) on day 28	IVIG: aseptic meningitis with generalized seizures, headache, mild fever, rash anti-D: haemolysis with Hb drop, low-grade fever, rash
Steroids/IVIG/anti-D (55)	steroids: complete response 27% at day 3 (>6 months 18%); partial response 45% at day 3 (>6 months in 36%) IVIG: complete response 57% at day 3 (>6 months 14%); partial response 43% at day 3 (>6 months in 14%)	Steroids: moodiness, irritability, aggressiveness, altered mental state, depressive feelings, concentration difficulties, hyperactivity, sleeping disturbance, fatigue, increased appetite, dyspepsia, headache, facial flush, signs of Cushing syndrome, myalgia, and fever IVIG: headache
Cyclosporin/sirolimus (60)	cyclosporine: complete response 52%; partial response 45% at 6 months sirolimus: complete response 50%; partial response 50% at 6 months	cyclosporin: gum hypertrophy, hirsutism, GI symptoms sirolimus: respiratory infection, nausea, abdominal discomfort
Cyclosporin (59)	complete response 29%; partial response 21%	hypertrichosis, transient hyperbilirubinemia, oral mycosis, C. albicans fungemia
Cyclosporin (61)	complete response 7%; partial response 20%	not reported
Cyclosporin (62)	complete response 37%; partial response 20% durable in 23%	hirsutism, tremor, hypertension, impaired renal function, gum hypertrophy, neutropenia
Rituximab (63)	complete response 33%; partial response 11%; minimal response 6% at 4 weeks complete response 22%; partial response 17%; minimal response 6% at 6 months complete response 22%; partial response 17%; minimal response 17% at 36 months	not reported
Rituximab (64)	complete response 50%; partial response 33%	not reported
Rituximab (65)	complete response 63%; partial response 8%; minimal response 8%	infusion reactions (pruritus, urticaria, throat tightness), serum sickness leading to discontinuation in 2 patients, decreased immunoglobulin levels
Rituximab (66)	response 68%; durable in 37%	urticaria, fever and chills
Rituximab (67)	complete response 0%; partial response 67%	cough, rash, muscle cramps, headache, angioedema
Rituximab/eltrombopag (68)	rituximab plus eltrombopag: overall response 49%; durable response at 12 months 85%; successful treatment cessation in 30% with PLT remaining >30x10^9/L for at least 3 months eltrombopag alone: overall response at 1 month 85%; durable response at 12 months 88%; no successful treatment cessation	rituximab plus eltrombopag: infusion-related reactions, neutropenia, anaemia; no persistent hypogammaglobulinemia eltrombopag alone: thrombocytosis, elevated bilirubin
Sirolimus (69)	complete response 75%; partial response 8%	haematuria
Interferon alpha (70)	very good response 46%; good response 9%; fair response 9%; poor response 36% at 3 months very good response 55%; good response 0%; fair response 27%; poor response 18% at 18-30 months	fever, flu-like symptoms, mildly elevated bilirubin and liver enzymes
Interferon alpha (71)	complete response 43% (>3 months 29%); partial response 43% (>6 weeks 0%); no response 7%; worsening PLT below pretreatment values in 7% after one course	flu-like symptoms, neutropenia
Mycophenolate mofetil (72)	complete response 100% (6/6)	not reported

TABLE 2: Overview of the efficacy and safety of the different treatment options (Continued on next page)

Intervention	Efficacy*	Safety
Dapsone (73)	complete response 24%; partial response 48%	methemoglobinemia, skin ulceration
Dapsone (74)	complete response 49% (>6 months: 31%); partial response 17%	haemolysis, rash
Dapsone (75)	complete response 46%; partial response 9%; no response 46% durable >6 months: 0%	skin rash, hepatitis, anaemia
Dapsone (76)	complete response 40%; partial response 24% at 12 months	methaemoglobinemia
Daratumumab (78)	overall response 90%	infusion-related reactions, upper respiratory tract infection
Daratumumab (79)	complete response 73%; partial response 9% at week 1 durable response 91% at 3 months, 55% at 6 months	infusion-related reactions, thrombocytosis, secondary hypogammaglobulinemia
Hydroxychloroquine (80)	overall response 57% at 3 months durable response 41% at 12 months	retinopathy, elevated liver enzymes, changes in skin pigmentation
Splenectomy/none (82)	recovery post-splenectomy 78% compared to 61% after 15 years if no intervention	death due to OPSI
Splenectomy/none (83)	response post-splenectomy 73% compared to 27% after 0.5-10 years if no intervention	not reported
Splenectomy (81)	complete response 85%; partial response 6%; durable in 75% at 6 months to 4 years	death due to OPSI, transient thrombocytosis
Splenectomy (84)	response 75%	infectious episodes and death
Splenectomy (85)	failure-free survival: 1 year in 88%; 2 years in 84%; 5 years in 77%	severe bacterial infections, thrombosis, death
Splenectomy (86)	complete response 45%; partial response 30% after 5-16 years	OPSI
Splenectomy (87)	complete response 62%; partial response 15%; no response 9% at 6 months; relapse 14%	subphrenic effusion, death due to OPSI
Splenectomy (88)	overall response 93%; durable in 72% at 54 months	infection including OPSI, thrombosis
Splenectomy (90)	complete response 78%; partial response 17% durable in 50% after 82 months	not reported
None (91)	complete response 45%; PLT > $50x10^9$/L in 11%	not reported
None (92)	response 46% (39% if non-splenectomized; 75% if splenectomized)	not reported
None (93)	PLT >$100x10^9$/L in 45% PLT 50-$100x10^9$/L in 21% PLT <$50x10^9$/L in 34%	not reported
None (94)	complete remission at 2 years 50%; at 5 years 76%	
HP eradication (96)	complete response 75%; partial response 25%	not reported
HP eradication (97)	complete response 67%; partial response 33% after 3 months	not reported
HP eradication (95)	partial response 100%; relapse 20%	not reported
HP eradication (98)	complete response 63%; partial response 42%	not reported

TABLE 2: Overview of the efficacy and safety of the different treatment options (End of table)

HP eradication (99)	complete response 21%; partial response 18%	not reported
HP eradication (100)	complete response 13%; partial response 53%	not reported
HP eradication (101)	response 14% (HP eradication) versus 11% (no intervention)	not reported
HP eradication (102)	complete response 60% (HP eradication) versus 18% (no intervention)	not reported
Guishao Shengxue Decoction (103)	overall response 95% (Guishao Shengxue Decoction) versus 71% (placebo)	nausea, fever, dizziness
Huaiqihuang Granule (104)	overall response 72 % (Huaiqihuang granule) versus 46% (placebo) at 24 weeks	diarrhoea, epistaxis, intracranial haemorrhage, gastrointestinal haemorrhage, gingival bleeding
Cepharantin (106)	median PLT increase to 58.5 $x10^9$/L after 12 months and to 69$x10^9$/L after 24 months; PLT increase by >10$x10^9$/L in 54%	hepatic dysfunction
Escalating treatment regimen (107)	dexamethasone alone: complete response 33% dexamethasone plus rituximab: complete response 50% dexamethasone plus rituximab and eltrombopag: complete response 29%	not reported
Various drugs (11)	no intervention: response in 61% hydroxychloroquine: response in 54% rituximab: response in 52% azathioprine: response in 55% mycophenolate mofetil: response in 47% vinblastine: response in 25% anti-D: response in 17% vincristine: response in 0% dapsone: response in 20% colchicine: response in 47% romiplostim: response in 54% eltrombopag: response in 40% splenectomy: response in 84%	not reported
Various drugs (52)	steroids: complete response 21%; partial response 44% IVIG: complete response 20%; partial response 0% anti-D: complete response 17%; partial response 0% 6-mercaptopurine: complete response 0%; partial response 8% rituximab: complete response 0%; partial response 50% splenectomy: complete response 83%; partial response 0%	not reported
Various drugs (89)	no intervention: response in 29% splenectomy: complete response in 70% after 3 years rituximab, dapsone, danazole, vincristine: no response rate reported	

anti-D: anti-rhesus immunoglobulins; HP: Helicobacter pylori; ITP: immune thrombocytopenia; IVIG: intravenous immunoglobulins;
OPSI = overwhelming post-splenectomy sepsis; PLT = platelet counts; *response reported according to the definition in the respective publication

Supplementary TABLE 1: Search strategy

Pubmed

("purpura, thrombocytopenic, idiopathic"[Mesh]) OR ("idiopathic thrombocytop*"[tiab] OR "immune thrombocytop*"[tiab] OR "autoimmune thrombocytop*"[tiab] OR werlhof*[tiab] OR ITP[tiab])

AND

("child"[Mesh] OR "adolescent"[Mesh] OR "pediatrics"[Mesh]) OR (child*[tiab] OR adolescen*[tiab] OR juvenile[tiab] OR youth*[tiab] OR teen*[tiab] OR paediatric*[tiab] OR pediatric*[tiab] OR minor*[tiab] OR infan*[tiab])

AND

(chronic[tiab] OR persistent[tiab] OR refractory[tiab])

AND

("safety" [Mesh:NoExp] OR "adverse effects" [Mesh:NoExp] OR "watchful waiting" [Mesh] OR "rituximab"[Mesh] OR "thrombopoietin"[Mesh] OR "splenectomy" [Mesh] OR "tyrosine kinase Inhibitors"[Mesh] OR "immunoglobulins, intravenous"[Mesh] OR "steroids" [Mesh] OR "vincristine"[Mesh] OR "vinblastine"[Mesh] OR "mycophenolic acid" [Mesh] OR "immunosuppressive agents" [Mesh]) OR (efficacy[tiab] OR safety[tiab] OR adverse*[tiab] OR side*[tiab] OR treatment[tiab] OR therapy[tiab] OR "second-line"[tiab] OR "watchful waiting"[tiab] OR observation*[tiab] OR rituximab [tiab] OR thrombopoietin*[tiab] OR TPO[tiab] OR TPO-RA*[tiab] OR romiplostim[tiab] OR eltrombopag[tiab] OR avatrombopag [tiab] OR lusutrombopag[tiab] OR splenectomy[tiab] OR immune*[tiab] OR cyclophosphamide[tiab] OR cyclofosfamide[tiab] OR cyclosporine[tiab] OR azathioprine[tiab] OR dapsone[tiab] OR "protein tyrosine kinase inhibitor*"[tiab] OR "tyrosine protein kinase inhibitor*"[tiab] OR TKI[tiab] OR "tyrosine kinase inhibitor*"[tiab] OR "intravenous antibod*"[tiab] OR immunoglobulin*[tiab] OR "intravenous IG"[tiab] OR IVIG[tiab] OR anti-D[tiab] OR "anti rh"[tiab] OR rhesus*[tiab] OR steroid*[tiab] OR cortico*[tiab] OR vincristine[tiab] OR vinblastine[tiab] OR danazol[tiab] OR mycophenol*[tiab] OR cellcept[tiab] OR immunosuppress*[tiab] OR "immuno suppress*" [tiab] OR immunodepress*[tiab])

Embase

'idiopathic thrombocytopenic purpura'/exp OR 'autoimmune thrombocytopenia'/de OR ('idiopathic thrombocytop*' OR 'autoimmune thrombocytop*' OR 'immune thrombocytop*' OR 'werlhof*' OR 'ITP'):ti,ab,kw

AND

'child'/de OR 'infant'/de OR 'adolescent'/de OR 'juvenile'/de OR 'minor (person)'/exp OR ('child*' OR 'infant*' OR 'adolescent*' OR 'juvenile' OR 'youth*' OR 'teen*' OR 'pediatric*' OR 'paediatric*' OR 'minor*'):ti,ab,kw

AND

('chronic' OR 'persistent' OR 'refractory'):ti,ab,kw

AND

'safety'/de OR 'adverse event'/de OR 'side effect'/de OR 'watchful waiting'/exp OR 'second-line treatment'/exp OR 'rituximab'/exp OR 'thrombopoietin'/exp OR 'thrombopoietin receptor'/exp OR 'romiplostim'/exp OR 'eltrombopag'/exp OR 'avatrombopag'/exp OR 'lusutrombopag'/exp OR 'splenectomy'/exp OR 'cyclophosphamide'/exp OR 'cyclosporine'/exp OR 'azathioprine'/exp OR 'protein tyrosine kinase inhibitor'/de OR 'immunoglobulin'/de OR 'rhesus D antibody'/exp OR 'steroid'/de OR 'corticosteroid'/de OR 'vincristine'/exp OR 'vinblastine'/exp OR 'danazol'/exp OR 'mycophenolate mofetil'/exp OR 'immunosuppressive agent'/de OR ('efficacy' OR 'safety' OR 'adverse*' OR 'side*' OR 'treatment' OR 'therapy' OR 'second-line' OR 'watchful waiting' OR 'observation' OR 'rituximab' OR 'thrombopoietin*' OR 'TPO' OR 'TPO-RA*' OR 'romiplostim' OR 'eltrombopag' OR 'avatrombopag' OR 'lusutrombopag' OR 'splenectomy' OR 'immune*' OR 'cyclofosfamide' OR 'cyclophosphamide' OR 'cyclosporine' OR 'azathioprine' OR 'dapsone' OR 'protein tyrosine kinase inhibitor*' OR 'tyrosine protein kinase inhibitor*' OR 'TKI' OR 'tyrosine kinase inhibitor*' OR 'immunoglobulin*' OR 'intravenous antibod*' OR 'intravenous IG' OR 'IVIG' OR 'anti-D' OR 'anti rh' OR 'rhesus*' OR 'cortico*' OR 'steroid*' OR 'vincristine' OR 'vinblastine' OR 'danazol' OR 'mycophenol*' OR 'cellcept' OR 'immunosuppress*' OR 'immuno suppress*' OR 'immunodepress*'):ti,ab,kw

Web of science

TS=("idiopathic thrombocytop*" OR "immune thrombocytop*" OR "autoimmune thrombocytop*" OR "werlhof*" OR "ITP")

AND

TS=("child*" OR "adolescen*" OR "juvenile" OR "youth*" OR "teen*" OR "paediatric*" OR "pediatric*" OR "minor*" OR "infan*")

AND

TS=("chronic" OR "persistent" OR "refractory")

AND

TS=("efficacy" OR "safety" OR "adverse*" OR "side*" OR "treatment" OR "therapy" OR "second-line" OR "watchful waiting" OR "observation*" OR "rituximab" OR "thrombopoietin*" OR "TPO" OR "TPO-RA*" OR "romiplostim" OR "eltrombopag" OR "avatrombopag" OR "lusutrombopag" OR "splenectomy"

OR "immune*" OR "cyclophosphamide" OR "cyclofosfamide" OR "cyclosporine" OR "azathioprine" OR "dapsone" OR "protein tyrosine kinase inhibitor*" OR "tyrosine protein kinase inhibitor*" OR "TKI" OR "tyrosine kinase inhibitor*" OR "intravenous antibod*" OR "immunoglobulin*" OR "intravenous IG" OR "IVIG" OR "anti-D" OR "anti rh" OR "rhesus*" OR "steroid*" OR "cortico*" OR "vincristine" OR "vinblastine" OR "danazol" OR "mycophenol*" OR "cellcept" OR "immunosuppress*" OR "immuno suppress*" OR "immunodepress*")

Scopus

TITLE-ABS("idiopathic thrombocytop*" OR "immune thrombocytop*" OR "autoimmune thrombocytop*" OR "werlhof*" OR "ITP") OR AUTHKEY("idiopathic thrombocytop*" OR "immune thrombocytop*" OR "autoimmune thrombocytop*" OR "werlhof*" OR "ITP")

AND

TITLE-ABS("child*" OR "adolescen*" OR "juvenile" OR "youth*" OR "teen*" OR "paediatric*" OR "pediatric*" OR "minor*" OR "infan*") OR AUTHKEY("child*" OR "adolescen*" OR "juvenile" OR "youth*" OR "teen*" OR "paediatric*" OR "pediatric*" OR "minor*" OR "infan*")

AND

TITLE-ABS("chronic" OR "persistent" OR "refractory") OR AUTHKEY("chronic" OR "persistent" OR "refractory")

AND

TITLE-ABS("efficacy" OR "safety" OR "adverse*" OR "side*" OR "treatment" OR "therapy" OR "second-line" OR "watchful waiting" OR "observation*" OR "rituximab" OR "thrombopoietin*" OR "TPO" OR "TPO-RA*" OR "romiplostim" OR "eltrombopag" OR "avatrombopag" OR "lusutrombopag" OR "splenectomy" OR "immune*" OR "cyclophosphamide" OR "cyclofosfamide" OR "cyclosporine" OR "azathioprine" OR "dapsone" OR "protein tyrosine kinase inhibitor*" OR "tyrosine protein kinase inhibitor*" OR "TKI" OR "tyrosine kinase inhibitor*" OR "intravenous antibod*" OR "immunoglobulin*" OR "intravenous IG" OR "IVIG" OR "anti-D" OR "anti rh*" OR "rhesus*" OR "steroid*" OR "cortico*" OR "vincristine" OR "vinblastine" OR "danazol" OR "mycophenol*" OR "cellcept" OR "immunosuppress*" OR "immuno suppress*" OR "immunodepress*") OR AUTHKEY("efficacy" OR "safety" OR "adverse*" OR "side*" OR "treatment" OR "therapy" OR "second-line" OR "watchful waiting" OR "observation*" OR "rituximab" OR "thrombopoietin*" OR "TPO" OR "TPO-RA*" OR "romiplostim" OR "eltrombopag" OR "avatrombopag" OR "lusutrombopag" OR "splenectomy" OR "immune*" OR "cyclophosphamide" OR "cyclofosfamide" OR "cyclosporine" OR "azathioprine" OR "dapsone" OR "protein tyrosine kinase inhibitor*" OR "tyrosine protein kinase inhibitor*" OR "TKI" OR "tyrosine kinase inhibitor*" OR "intravenous antibod*" OR "immunoglobulin*" OR "intravenous IG" OR "IVIG" OR "anti-D" OR "anti rh" OR "rhesus*" OR "steroid*" OR "cortico*" OR "vincristine" OR "vinblastine" OR "danazol" OR "mycophenol*" OR "cellcept" OR "immunosuppress*" OR "immuno suppress*" OR "immunodepress*")

Central (cochrane)

#1 [mh "purpura, thrombocytopenic, idiopathic"]
#2 (("idiopathic" NEXT thrombocytop*) OR ("immune" NEXT thrombocytop*) OR ("autoimmune" NEXT thrombocytop*) OR (werlhof*) OR "ITP"):ti,ab,kw

#3 = #1 OR #2

#4 [mh "child"] OR [mh "adolescent"] OR [mh "pediatrics"]

#5 ((child*) OR (adolescen*) OR "juvenile" OR (youth*) OR (teen*) OR (paediatric*) OR (pediatric*) OR (minor*) OR (infan*)):ti,ab,kw

#6 = #4 OR #5

#7 ("chronic" OR "persistent" OR "refractory"):ti,ab,kw
#8 [mh ^"safety"] OR [mh ^"adverse effects"] OR [mh "watchful waiting"] OR [mh "rituximab"] OR [mh "thrombopoietin"] OR [mh "splenectomy"] OR [mh "tyrosine kinase inhibitors"] OR [mh "immunoglobulins, intravenous"] OR [mh "steroids"] OR [mh "vincristine"] OR [mh "vinblastine"] OR [mh "mycophenolic acid"] OR [mh "immunosuppressive agents"]

#9 ("efficacy" OR "safety" OR (adverse*) OR (side*) OR "treatment" OR "therapy" OR "second-line" OR "watchful waiting" OR (observation*) OR "rituximab" OR (thrombopoietin*) OR "TPO" OR (TPO-RA*) OR "romiplostim" OR "eltrombopag" OR "avatrombopag" OR "lusutrombopag" OR "splenectomy" OR (immune*) OR "cyclophosphamide" OR "cyclofosfamide" OR "cyclosporine" OR "azathioprine" OR "dapsone" OR ("protein tyrosine kinase" NEXT inhibitor*) OR ("tyrosine protein kinase" NEXT inhibitor*) OR "TKI" OR ("tyrosine kinase" NEXT inhibitor*) OR (intravenous NEXT antibod*) OR (immunoglobulin*) OR "intravenous IG" OR "IVIG" OR "anti-D" OR "anti rh" OR (rhesus*) OR (steroid*) OR (cortico*) OR "vincristine" OR "vinblastine" OR "danazol" OR (mycophenol*) OR "cellcept" OR (immunosuppress*) OR (immuno NEXT suppress*) OR (immunodepress*)):ti,ab,kw

#10 = #8 OR #9

#11= #3 AND #6 AND #7 AND #10

Supplementary TABLE 2: JBI Critical Appraisal checklist for case series

	Clear criteria for inclusion?	Condition measured in a standard, reliable way?	Valid methods for identification of condition?	Consecutive inclusion of participants?	Complete inclusion of participants?	Clear reporting of demographics?	Clear reporting of clinical information?	Outcomes or follow-up results clearly reported?	Presenting site(s)/clinic(s)/ demographic information clearly reported?	Appropriate statistical analysis?
Leblebisatan et al. (25)	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Lopes et al. (26)	N	Y	Y	U	U	Y	Y	Y	Y	Y
Mokhtar et al. (35)	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
Marquinez-Alonzo et al. (36)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Grainger et al. (37)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kuhne et al. (43)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Adams et al. (50)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Ferrara et al. (51)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Sabhan et al. (52)	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Sirachainan et al. (58)	Y	Y	Y	N	U	Y	Y	Y	Y	Y
Perrotta et al. (59)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Ansari et al. (63)	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Citak et al. (65)	Y	Y	Y	U	Y	Y	Y	Y	N	NA
Wang et al. (66)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Parodi et al. (67)	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Jasinski et al. (69)	Y	Y	Y	U	U	Y	Y	Y	Y	N
Hrstkova et al. (70)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Donato et al. (75)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Panigrahi et al. (72)	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Sun et al. (78)	Y	Y	Y	Y	Y	N	Y	Y	N	NA
Hu et al. (79)	Y	Y	Y	Y	Y	Y	Y	Y	N	NA
Ramenghi et al. (84)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Jayabose et al. (91)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ferrara et al. (95)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Neefjes et al. (96)	Y	Y	Y	N	N	N	N	Y	N	N
Maghbool et al. (97)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yamazaki et al. (106)	Y	Y	Y	N	U	Y	Y	U	Y	Y
Y = yes; N = no; U = unclear; NA = not applicable										

Supplementary TABLE 3: JBI Critical Appraisal checklist for cohort studies (Continued on next page)

	Groups similar and recruited from same population?	Exposure measured similarly for exposed and unexposed groups?	Exposure measured in a valid and reliable way?	Confounding factors identified?	Strategies to deal with confounding factors stated?	Participants free of outcome at start of study (or at the moment of exposure)?	Outcomes measured in a valid and reliable way?	Follow up time reported and long enough for outcomes to occur?	Follow up complete, and if not, reasons to loss to follow up described and explored?	Strategies to address incomplete follow up utilized?	Appropriate statistical analysis?
Ducassou et al. (11)	NA	NA	N	N	N	Y	Y	Y	Y	NA	Y
Cheng et al. (15)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Yang et al. (16)	NA	NA	Y	N	NA	Y	Y	Y	N	N	Y
Giordano et al. (17)	NA	NA	Y	Y	N	Y	Y	Y	Y	Y	Y
Richert-Przygonska et al. (18)	NA	NA	Y	N	N	Y	Y	Y	Y	Y	Y
Chen et al. (19)	NA	NA	Y	U	N	Y	Y	Y	Y	N	Y
Cheng et al. (20)	NA	NA	Y	Y	Y	Y	Y	N	Y	Y	Y
Giordano et al. (21)	NA	NA	Y	N	N	Y	Y	Y	Y	Y	Y
Wang et al. (22)	NA	NA	Y	N	NA	Y	Y	Y	Y	N	Y
Wang et al. (23)	NA	NA	Y	N	N	Y	Y	Y	Y	Y	Y
Dong et al. (24)	NA	NA	Y	Y	Y	Y	Y	N	Y	Y	Y
Ramaswamy et al. (27)	NA	NA	Y	Y	N	Y	Y	Y	Y	Y	Y
Obrisca et al. (28)	NA	NA	Y	Y	N	Y	Y	N	Y	N	Y
Seidel et al. (31)	NA	NA	Y	Y	N	Y	Y	Y	Y	N	Y
Bussel et al. (32)	Y	Y	Y	N	U	Y	Y	Y	Y	Y	Y
Tarantino et al. (33)	NA	NA	Y	N	N	Y	Y	Y	Y	NA	NA
Mareddy et al. (34)	NA	NA	Y	N	NA	Y	Y	Y	N	N	Y
Wang et al. (39)	NA	Y	Y	U	N	Y	Y	Y	Y	NA	Y
Hu et al. (40)	Y	Y	Y	N	N	Y	Y	Y	Y	NA	Y
Wang et al. (41)	NA	NA	Y	N	N	Y	Y	Y	Y	NA	Y
Ruggiero et al. (44)	NA	NA	N	N	N	Y	Y	Y	Y	NA	Y
Chen et al. (45)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Borgna-Pignatti et al. (46)	NA	NA	Y	N	N	Y	U	N	N	N	Y
Wali et al. (47)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Yadav et al. (48)	NA	NA	Y	N	N	Y	Y	N	N	N	N
Özer et al. (49)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Naithani et al. (56)	NA	NA	Y	N	N	Y	Y	U	Y	NA	Y
Yetgin et al. (57)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Choudhary et al. (61)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Liu et al. (62)	NA	NA	Y	N	NA	Y	Y	Y	Y	N	Y
Rao et al. (64)	NA	NA	Y	N	N	Y	Y	Y	U	U	Y
Ma et al. (68)	N	Y	Y	N	N	Y	Y	Y	N	N	Y
Khera et al. (73)	NA	NA	Y	N	N	Y	Y	Y	N	N	Y
Damodar et al. (74)	NA	NA	Y	Y	Y	Y	Y	N	U	N	Y
Patel et al. (75)	NA	NA	Y	N	NA	Y	Y	Y	N	N	Y

Supplementary TABLE 3: JBI Critical Appraisal checklist for cohort studies (End of table)

	Groups similar and recruited from same population?	Exposure measured similarly for exposed and unexposed groups?	Exposure measured in a valid and reliable way?	Confounding factors identified?	Strategies to deal with confounding factors stated?	Participants free of outcome at start of study (or at the moment of exposure)?	Outcomes measured in a valid and reliable way?	Follow up time reported and long enough for outcomes to occur?	Follow up complete, and if not, reasons to loss to follow up described and explored?	Strategies to address incomplete follow up utilized?	Appropriate statistical analysis?
Bharadwaj et al. (76)	NA	NA	Y	N	N	Y	Y	Y	N	N	Y
Liu et al. (80)	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Aronis et al. (81)	NA	NA	NA	Y	Y	Y	Y	Y	N	N	U
Reid et al. (82)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Donato et al. (83)	NA	NA	NA	Y	Y	Y	U	Y	N	N	U
Pincez et al. (85)	NA	NA	NA	Y	Y	Y	Y	Y	N	N	Y
El-Alfy et al. (86)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Wang et al. (87)	NA	NA	NA	N	N	Y	Y	Y	N	N	N
Ahmed et al. (88)	NA	NA	NA	N	N	Y	Y	N	N	N	Y
Koc et al. (89)	Y	Y	Y	N	N	Y	Y	Y	NA	NA	Y
Kim et al. (90)	NA	NA	NA	N	N	Y	Y	N	U	U	Y
Kato et al. (92)	NA	NA	NA	N	N	Y	Y	Y	Y	NA	Y
Shim et al. (93)	NA	NA	Y	N	N	Y	Y	Y	U	U	Y
Kim et al. (94)	NA	NA	NA	Y	Y	Y	Y	Y	U	N	Y
Hodeib et al. (98)	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Russo et al. (99)	NA	NA	Y	N	N	Y	Y	Y	Y	Y	Y
Ahmed et al. (100)	Y	Y	Y	N	N	Y	Y	Y	Y	U	Y
Fu et al. (107)	NA	NA	Y	N	NA	Y	Y	N	Y	NA	Y
Y = yes; N = no; U = unclear; NA = not applicable											

Supplementary TABLE 4: JBI Critical Appraisal checklist for randomized controlled trials

	True randomization for assignment of participants?	Allocation to treatment groups concealed?	Treatment groups similar at baseline?	Participants blind to treatment assignment?	Those delivering treatment blind to treatment assignment?	Treatment groups treated identically other than the intervention of interest?	Outcome assessors blind to treatment assignment?	Outcomes measured in the same way for groups?	Outcomes measured in a reliable way?	Follow-up complete and if not, differences adequately described and analysed?	Participants analysed in the groups to which they were randomized?	Appropriate statistical analysis?	Trial design appropriate and any deviations accounted for?
Bussel et al. (13)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Grainger et al. (14)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Elalfy et al. (29)	U	N	Y	U	U	Y	U	Y	Y	Y	Y	Y	U
Tarantino et al. (30)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Grace et al. (38)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Ma et al. (42)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
El Alfy et al. (53)	N	N	U	N	N	U	N	Y	Y	U	U	Y	N
El Alfy et al. (54)	U	U	Y	U	U	Y	U	Y	Y	U	Y	U	N
Hedlund-Treutiger et al. (55)	Y	N	Y	N	N	Y	N	Y	Y	N	Y	Y	Y
Mousavi-Hasanzadeh et al. (60)	Y	U	Y	U	U	N	U	Y	Y	Y	Y	Y	Y
Treepongkaruna et al. (101)	Y	N	Y	N	N	Y	N	Y	Y	U	Y	Y	Y
Brito et al. (102)	Y	U	Y	N	N	Y	U	Y	Y	Y	Y	Y	Y
Wang et al. (103)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Han et al. (104)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y = yes; N = no; U = unclear; NA = not applicable													

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Congenital Erosive and Vesicular Dermatosis (CEVD): A Rare Case and Review of the Literature

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Keywords

Erosive and Vesicular Dermatosis; CEVD; Scar

Abstract

Congenital erosive and vesicular dermatosis (CEVD) is a rare neonatal dermatosis characterized by erosive and vesicular lesions that develop at or shortly after birth and heal with reticulated scarring. The presented case highlights a localized erosive-vesicular eruption followed by cribriform scarring, clinically suggestive of CEVD. Recognition of the CEVD phenotype is important while maintaining a broad differential diagnosis that includes congenital infections, trauma, anetoderma of prematurity, and inherited blistering disorders.

Introduction

Congenital erosive and vesicular dermatosis (CEVD) is a rare neonatal condition characterized by erosive or vesicular lesions present at birth or developing shortly thereafter, which typically heal with reticulated scarring (1–4). Its pathogenesis remains unclear, though it is believed to represent an acquired in utero condition rather than a genetic disorder (1,5,6). Proposed mechanisms include intrauterine infection (e.g., herpetic infections), amniotic adhesions, or developmental defects in foetal skin healing (2,7,8).

Case presentation

A 3-month-old male infant was referred to our paediatric dermatology clinic for evaluation of several vesicular and erosive lesions located on the scrotum and lower abdomen. Shortly after birth, an erosion covered by some yellow vesicles was observed on the scrotum (figure 1). However, no swab was taken to confirm a herpes infection. Around the same period, a spontaneous abdominal erosion without preceding blister formation was also noted by the parents (figure 2). Both lesions were treated with chlorhexidine and healed within a few days. Physical examination revealed a linear, vertically oriented, non-inflammatory, atrophic macule on the lower abdomen (figure 3). The scrotal skin was completely healed, with no residual erythema or active lesions. The prenatal, perinatal, and postnatal courses were unremarkable. The infant was born at term by vaginal delivery. There was no birth or instrumentational trauma during delivery. Growth and neurodevelopment were normal. There was no family history of dermatologic disorders. The patient's 3-year-old brother had a subtle hypopigmented linear scar on his hand, reportedly secondary to a healed infantile erosion, and a history of self-limiting autoimmune neutropenia (figure 4). Maternal serologic testing demonstrated positive IgG antibodies for cytomegalovirus (CMV), while toxoplasmosis serology was negative. A previous miscarriage had been reported, although no amniotic adhesions were observed on ultrasound. Maternal Herpes simplex virus (HSV) testing was negative.

Discussion

CEVD is present at birth and is frequently reported in premature infants, with erosions, vesicles, and bullae may affect a large body surface area (2). Lesions present in the neonatal period heal within 10 days to 3 months. The clinical presentation of a linear, reticulated, non-inflammatory macule following the early erosive lesions is characteristic, but should be interpreted in the context of the clinical course and exclusion of important mimics (1,3,4,9). The precise pathogenesis of CEVD remains uncertain; current evidence favours an acquired intrauterine process rather than a hereditary disorder (5,6,10). Proposed mechanisms include intrauterine infections such as Herpes simplex virus or *Candida albicans*,



FIGURE 1: Initial vesicular lesion with an underlying erosion observed on the scrotum shortly after birth.



FIGURE 2: A subtle erosive lesion was noted on the right thorax and abdomen shortly after birth, without preceding trauma.



FIGURE 3: Around 3 months of age a cribriform scar developed at the sites of the erosive lesions previously noted on the thorax and abdomen.



FIGURE 4: A similar cribriform scar on the right third digit of the patient's brother.

amniotic adhesions, or disturbances in foetal wound healing (2,7,11,12).

Approximately one-third of reported CEVD cases demonstrate features suggestive of intrauterine infection, such as chorioamnionitis or discoloured amniotic fluid (4,9). CEVD does not follow a Mendelian pattern of inheritance, and genetic analyses for *TP63* and *POCRN*, have not established a causative variant (5, 14, 16). Familial recurrence is rare (9, 14); however, the subtle scar observed in the sibling in the present report is nonspecific and cannot be taken as evidence of familial CEVD. Although cases in full-term infant have been reported, CEVD is strongly associated with prematurity (17).

The differential diagnosis of CEVD includes intrauterine or congenital infections (e.g., herpes simplex virus, varicella-zoster virus, bacterial infections), congenital or perinatal trauma, anetoderma of prematurity, and a range of developmental, inflammatory, and genetic dermatoses such as epidermolysis bullosa, aplasia cutis congenita, focal dermal hypoplasia or aplasia, incontinentia pigmenti, dyskeratosis congenita, congenital ichthyosis, linear scleroderma, popliteal pterygium syndrome, atrophoderma of Pasini and Pierini, and vascular or vasospastic disorders including acrodermatitis chronica atrophicans and poikiloderma congenitale (3,4,6,12,15-17). Accordingly, a thorough perinatal workup comprising targeted infectious testing, bacterial and fungal cultures when clinically indicated, and, when appropriate, histopathologic evaluation may assist in ruling out alternative diagnoses (4,8,12). In a premature infant, anetoderma of prematurity would warrant particular consideration when an atrophic lesion is already visible early in the clinical course.

Since the supple, reticulated scarring pattern is considered highly characteristic, the diagnosis is often established clinically after relevant alternative diagnoses have been excluded (1,3,9). Histopathologic findings early in the disease process of CEVD can include epidermal necrosis, subepidermal vesiculation, and an eroded epidermis (3). Older lesions demonstrate scar formation, decreased hair follicles, and absent eccrine glands. At subsequent follow-up visits, associated findings should be carefully assessed, including signs of hyperthermia, alopecia, nail abnormalities, ocular involvement, neurological development, and hearing function (18,19). Lesions resolve rapidly during the first month, and further episodes are uncommon. (1,2,9).

Our patient presented with atypical clinical features, including postnatal recognition of lesions (reported in only a few cases) and the limited skin involvement, suggesting a mild disease expression (15,17). Also a sibling that had similar scars is rare and only descripted in two other cases (4,10).

Conclusion

This case illustrates a localized presentation of CEVD. The observation of a similar lesion in a sibling may reflect shared perinatal or environmental influences rather than a hereditary predisposition. Recognizing CEVD is essential to distinguish it from congenital infections and genetic blistering disorders, thereby avoiding unnecessary investigations and providing appropriate reassurance to families regarding its typically benign course and favourable prognosis.

Statement

Informed consent for publication of this case report and the accompanying clinical photographs was obtained.

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An Obstructing Ileal Duplication Cyst Masked by Campylobacter Gastroenteritis: a Rare Case Report

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Keywords

Enteric duplication cyst; Campylobacter; Enteritis; Ileum; Paediatric surgery

Abstract

Enteric duplication cysts are rare congenital anomalies. We report an 8-month-old girl presenting with symptoms of acute gastroenteritis and a stool PCR positive for *Campylobacter*. Clinical deterioration prompted additional imaging, revealing mechanical small bowel obstruction caused by a thick-walled pelvic structure. Subsequent explorative laparoscopy uncovered an ileal enteric duplication cyst. A segmental ileal resection was performed, and histopathology confirmed the diagnosis. The patient recovered uneventfully and was discharged on day 10. This case highlights the diagnostic challenge posed by the coexistence of infectious gastroenteritis and surgical pathology, emphasizing the need for clinical reassessment and a low threshold for further investigations.

Introduction

Enteric duplication cysts (EDC) are rare congenital anomalies of the gastrointestinal tract, estimated to occur in 1 in 4.500 live births (1). These anomalies are defined by a cystic or tubular structure that shares an epithelial lining, a smooth muscular wall, and a common blood supply with the adjacent segment of intestine (2). Clinical presentation is variable and depends on size, location, and complications, which may include bleeding, perforation, or bowel obstruction (3). Acute infectious gastroenteritis, on the other hand, is a frequent cause of abdominal symptoms in the paediatric population and is often diagnosed clinically or confirmed with stool testing (4). The overlap in symptomatology between infectious and surgical abdominal conditions, including fever, vomiting, diarrhoea, and abdominal tenderness, can complicate early diagnosis. The identification of a causative pathogen may further narrow clinical focus towards a single explanation, introducing the risk of diagnostic anchoring and potentially delaying recognition of a concurrent surgical pathology.

Case report

An 8-month-old full-term girl presented to our clinic with a general malaise, accompanied by vomiting, anorexia, and a fever of 38.3°C. According to her caregiver, she had experienced more than six episodes of mucous stools over the previous 12 hours.
Her past medical history was unremarkable, except for an episode of laryngitis stridulosa 2 months earlier. She had no prior history of abdominal surgery. On clinical examination, the patient appeared alert but irritable. Abdominal assessment revealed a hyperperistaltic, non-distended abdomen with mild abdominal tenderness. Cardiopulmonary examination was normal except for mild tachycardia (170 beats/min). Skin turgor was preserved, with no evidence of dehydration. Neurological examination revealed no signs of meningeal irritation. Laboratory tests were normal except for an elevated C-reactive protein (CRP) of 71.8 mg/L (reference value: <5 mg/L); white blood cell count was within the normal range at 10.8 × 10^3/μL (reference 6.0–17.5 × 10^3/μL). As acute gastroenteritis was initially suspected, the patient was started on intravenous fluid therapy. Within 24 hours after admission, the patient's fever persisted, reaching a

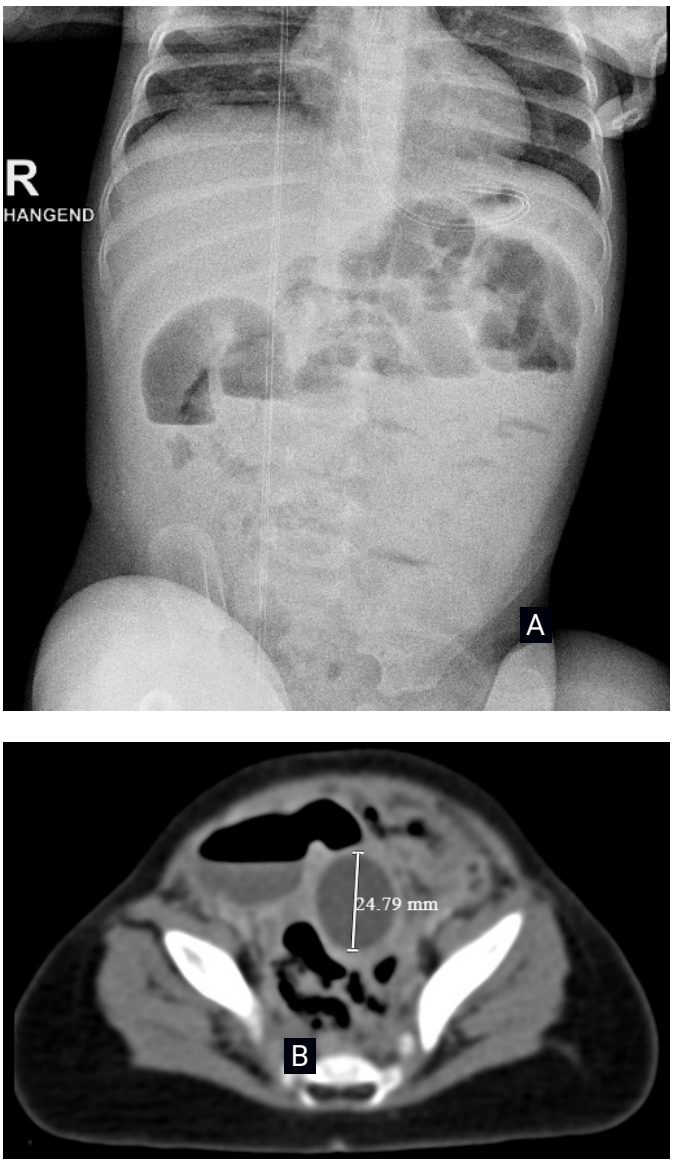


FIGURE 1: Plain abdominal radiograph demonstrating multiple dilated small bowel loops with air-fluid levels (A), and axial abdominal computed tomograph showing a 2.4 cm fluid-filled, thick-walled pelvic structure (B).

maximum temperature of 38.9 °C, and her abdomen became increasingly tender with guarding. Given the evolving concern for an acute abdomen, additional imaging was performed and empiric antibiotic therapy was initiated with amoxicillin/clavulanic acid at a dose of 100/10 mg/kg/day divided into three doses. On day one of hospitalization, azithromycin (one 10 mg/kg/day) was subsequently added following a positive stool PCR for *Campylobacter*. Blood and urinary cultures were negative. Abdominal ultrasound was performed as the first-line investigation and demonstrated dilated small bowel loops and free intraperitoneal fluid, but did not reveal a definitive cause. A subsequent plain abdominal radiograph demonstrated multiple dilated small bowel loops with air-fluid levels, supporting the suspicion of mechanical obstruction (Figure 1A). Complementary computed tomography (CT) confirmed preterminal small bowel dilatation. It showed a 2.4 cm fluid-filled, thick-walled pelvic structure, without signs of ileocolic intussusception (Figure 1B). Given the clinical deterioration and imaging findings suggestive of mechanical obstruction, the paediatric surgical team proceeded with urgent diagnostic laparoscopy under general anaesthesia. Perioperative exploration revealed a cystic lesion within the mesentery of the preterminal ileum, closely adherent to the adjacent bowel wall, consistent with an enteric duplication cyst. This lesion created a clear transition point with proximal small bowel dilatation and distal ileal collapse, identifying it as the cause of the mechanical small bowel obstruction. No evidence of bowel perforation, volvulus, or intussusception was observed. A segmental ileal resection, including the cystic lesion, was performed via a small laparotomic approach (Figure 2). Intestinal continuity was restored with an end-to-end anastomosis. Histopathology confirmed a 27 mm x 27 mm enteric duplication cyst with full-thickness involvement of the bowel wall. The lesion was focally lined by a single-layered columnar mucinous epithelium, and the lamina propria contained glands of antral type (Figure 3). Postoperatively, azithromycin was discontinued after a total of five days of therapy, while amoxicillin/clavulanic acid was continued for a total of two weeks because of the increased risk of bacterial translocation secondary to mechanical small bowel obstruction. CRP increased after surgery, peaking at 167 mg/L on postoperative day 1 before rapidly declining. The patient received total parenteral nutrition for five days and had an uneventful recovery, allowing discharge 10 days after surgery.

Discussion

This case underscores the need for a critical and cautious diagnostic approach when evaluating infants with evolving abdominal symptoms. The coexistence of an infectious and a surgical pathology, *Campylobacter* enteritis and an ileal enteric duplication cyst (EDC), increased the risk of diagnostic anchoring. Similar associations between enteric duplication cysts and concomitant gastrointestinal infections have only rarely been reported, highlighting the diagnostic challenge posed by overlapping clinical presentations (5,6). An important consideration raised by this case is whether the *Campylobacter* infection actively precipitated obstruction in an otherwise quiescent duplication cyst. Several mechanisms are plausible. First, mucosal and submucosal oedema induced by infection could have narrowed the intestinal lumen adjacent to the cyst. Second, increased peristaltic activity during acute enteritis may have promoted kinking at the transition point. At last, reactive mesenteric lymphadenopathy and oedema could have altered bowel positioning, further impairing luminal passage. Imaging played a pivotal role in establishing the diagnosis. Ultrasound, the first-line modality in paediatric abdominal complaints, revealed dilated bowel loops and free fluid but failed to delineate the cyst. This limitation has been reported in emergency settings, where bowel gas and inflammation obscure the "double wall" or



FIGURE 2: Laparotomic image of the ileal duplication cyst, showing a dilated (left) and collapsed (right) small intestine.

"gut signature" sign that is typically pathognomonic for duplication cysts (3). A subsequent plain abdominal radiograph demonstrated multiple dilated bowel loops with air-fluid levels, supporting the suspicion of mechanical obstruction. Complementary CT further characterized the obstruction by identifying a thick-walled, fluid-filled pelvic lesion while excluding intussusception. However, given the patient's progressive clinical deterioration and signs of an acute abdomen, urgent surgical exploration was indicated irrespective of the precise underlying aetiology. In retrospect, the additional diagnostic value of CT should therefore be carefully weighed against the radiation exposure associated with imaging during infancy. MRI is rarely used as a first-line modality due to the need for sedation in infants, though lesions typically show low T1- and high T2-weighted signal intensity when performed (3). At last, surgical resection remains the treatment of choice for symptomatic EDCs. Because the cyst and native bowel share a wall and blood supply, segmental resection with primary anastomosis is generally required. Endoscopic approaches carry a higher risk of incomplete cyst removal, which leaves residual tissue that increases the likelihood of recurrence or malignant changes (7).

Conclusion

Enteric duplication cysts are rare but important causes of bowel obstruction in infants. Their nonspecific presentation can mimic or be masked by infectious gastroenteritis. Careful clinical reassessment, judicious use of imaging, and timely surgical intervention are essential to ensure accurate diagnosis and optimal patient outcomes. Clinicians should maintain a high index of suspicion for surgical pathology in infants with atypical or worsening abdominal symptoms, even in the context of confirmed infectious gastroenteritis.

Statements

The authors have no conflicts of interest to declare concerning the topic discussed in this manuscript. Informed consent was obtained from the patient's legal guardians for publication of this case report and accompanying images.

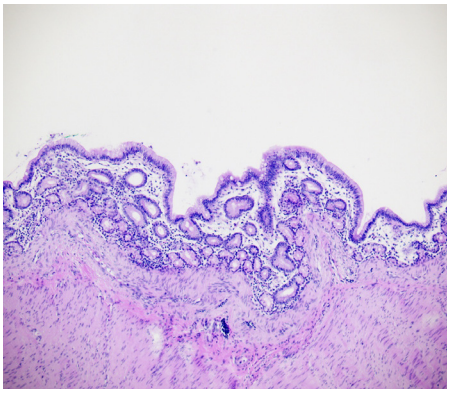


FIGURE 3: Hematoxylin and eosin staining (original magnification 10X) with high-power view; the cyst wall is lined by gastric mucosa and glands, with smooth muscle.

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CASE REPORT

Belg J Paediatr. 2026;28(3):303-308

Cervical Dystonia as an Underrecognised Feature of Gaucher Disease Type 3: Successful Treatment With Botulinum Toxin in Two Paediatric Siblings

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Keywords

Gaucher disease; Cervical dystonia; Movement disorders; Botulinum toxin

Abstract

Cervical dystonia is an uncommon but significant manifestation of Gaucher disease type 3, where abnormal neck postures are often reported without detailed characterisation. We describe two brothers with genetically confirmed disease who developed severe retrocaput in early childhood, causing major gait, balance, and social difficulties. Both showed typical neurological signs, including supranuclear gaze palsy, parkinsonian features, and pyramidal involvement; one also had juvenile myoclonic epilepsy. Due to severe dystonia, botulinum toxin injections were performed under ultrasound and electromyography guidance with light sedation. Both improved clearly and durably, underscoring the need to recognise treatable dystonia in this condition.

Introduction

Gaucher disease (GD) is the most common lysosomal storage disorder and results from biallelic pathogenic variants in *GBA1*, leading to deficient β-glucocerebrosidase activity and accumulation of glucosylceramide within lysosomes (1). The clinical spectrum is traditionally divided into three phenotypes based on neurological involvement: GD1, the non-neuronopathic form; GD2, the acute neuronopathic form with early and rapidly progressive neurological decline; and GD3, the chronic neuronopathic form with a heterogeneous course (2,3). In the latter form, horizontal supranuclear gaze palsy and oculomotor apraxia are the most characteristic neurological signs, although epilepsy, cognitive impairment, cerebellar ataxia, pyramidal signs, and parkinsonian features may also occur (1,2,4). A range of hyperkinetic movement disorders has also been reported in association with *GBA1* pathogenic variants, including dystonic tremor, hyperkinetic involuntary movements, blepharospasm, and even presentations evocative of rapid-onset dystonia-parkinsonism (4,5). Despite these observations, cervical dystonia remains insufficiently characterised in GD. Several reports refer to "abnormal cervical posture" or "retroflexion of the neck", particularly in GD3, but the dystonic nature of these postures is rarely documented (2,4). Only isolated descriptions of dystonia-like neck movements exist in GD3 (6). As a result, the true prevalence of cervical dystonia in GD3 is likely underestimated. Botulinum toxin type A (BoNT-A) is the first-line treatment for cervical dystonia in adults and is increasingly used in paediatric dystonia, although evidence remains limited and largely based on expert opinion (7,8). No published data exist regarding its use in GD, and the management of dystonia in this disease remains empirical. The multisystemic involvement of GD3, including respiratory vulnerability and skeletal deformities, raises additional concerns regarding procedural safety and optimal injection strategies (9). We report two brothers with genetically confirmed GD3 who developed severe cervical dystonia with prominent retrocaput in their early childhood and were treated successfully with BoNT-A injections performed under combined ultrasound (US) and electromyographic (EMG) guidance with paediatric sedation. To our knowledge, this is the first report documenting the efficacy and tolerability of BoNT-A for cervical dystonia in GD3.



FIGURE 1: **Cervical dystonia in two brothers with Gaucher disease type 3:** pre- (1,3) and post-treatment (2,4) images. Panels 1 and 2 show Patient A; panels 3 and 4 show Patient B. A marked improvement in head posture is observed one month after botulinum toxin injections. Note that no standardised dystonia rating scale (e.g. TWSTRS) was available for objective assessment, which represents a limitation of this report.

Case report

The two patients are brothers aged 5 and 4 years at the time of assessment. Patient A (eldest child) was diagnosed with GD3 in infancy after targeted Sanger sequencing was performed because of early systemic symptoms, including hepatosplenomegaly. The same homozygous pathogenic *GBA1* variant (c.1448T>C,

p.Leu483Pro) was subsequently confirmed in patient B, his younger brother, who later developed similar systemic manifestations. Early developmental milestones in both children were marked by systemic involvement consistent with GD3 (splenomegaly, hepatomegaly and thrombocytopenia), and neurological features progressively emerged during early childhood, including horizontal supranuclear gaze palsy and oculomotor apraxia, parkinsonian features, pyramidal signs, and global language delay. The phenotype of patient B is more severe, with additional features including juvenile myoclonic epilepsy and stridor. Cervical dystonia appeared around the age of 2, during gait acquisition, and was initially described by caregivers as "a tendency for the head to fall backward". This gradually evolved into a constant retrocaput associated with variable torticollis. The posture was not painful but severely interfered with balance, gait, and social interaction. During ambulation, the head was consistently pulled backward, forcing compensatory trunk flexion and limiting visual exploration. Clinical examination confirmed sustained involuntary activation of deep cervical extensors, consistent with a dystonic mechanism rather than pyramidal imbalance or orthopaedic restriction. This clinical impression was supported by electromyographic assessment, which demonstrated spontaneous and sustained activity in the cervical extensor muscles. Given the severity of the dystonia, BoNT-A treatment was proposed. Because of age, anxiety, and difficulty maintaining posture during the injections, both children underwent the procedure under light paediatric sedation. Nitrous oxide inhalation was used as the primary agent, occasionally supplemented with mild intravenous sedation when necessary. This approach ensured comfort, minimised movement, and allowed precise targeting of deep cervical muscles. All injections were performed using combined US and EMG guidance. US allowed visualisation of deep cervical muscles and vascular structures, while EMG confirmed dystonic overactivity and ensured accurate targeting of hyperactive muscle fibres. IncobotulinumtoxinA (Xeomin®) was used in all sessions. In patient A, the first session consisted of 50 units injected into both semispinalis capitis muscles, followed three months later by 80 units, extending the injection pattern to include the right sternocleidomastoid and splenius capitis muscles, taking into account a component of torticollis. In patient B, 50 units were administered during the first session into the bilateral semispinalis capitis and the left splenius capitis. One month after the first injection (Figure 1), patient B showed moderate improvement, maintaining a neutral head position while seated, although retrocaput persisted during gait examination. After the second injection, improvement became more marked, as he maintained a straight head and neck position approximately half of the time, including during ambulation. Patient A exhibited a more robust response. Two months after the first injection, he consistently maintained a neutral head position, with only a mild residual left torticollis during walking. Functional gains included improved gait stability, enhanced social interaction, and increased autonomy during play activities. No adverse effects were observed in either child, and the therapeutic effect persisted for at least three months. The accompanying video (Video 1) illustrates the clinical presentation and treatment response, with pre-injection recordings and follow-up segments three months after the first botulinum toxin injection in both patients.

Discussion

The clinical signs observed, notably the abnormal posture of the head, are consistent with dystonia. According to the most recent consensus definition, dystonia is defined as a movement disorder characterised by sustained or intermittent muscle contractions causing abnormal, often repetitive movements or postures, which are typically patterned and may be task-specific or exacerbated by voluntary action (10,11). Unlike adult idiopathic cervical dystonia, paediatric cervical dystonia is frequently secondary to underlying neurogenetic disorders (12,13). In the present cases, the persistent and stereotyped retrocaput associated with involuntary activation of deep cervical extensor muscles, its progressive emergence during motor development, and its marked interference with gait and balance are fully consistent with this definition. The absence of pain, fixed orthopaedic limitation, or signs suggestive of predominant pyramidal imbalance further supports a dystonic rather than structural or compensatory mechanism. Together, these elements strengthen the clinical diagnosis of cervical dystonia and support its inclusion within the neurological phenotype of GD3 (10,11). These two cases illustrate that cervical dystonia may be an overlooked neurological manifestation of GD3, a condition more commonly characterised by oculomotor dysfunction, epilepsy, and pyramidal signs (1,2). Besides, dystonic features such as dystonic tremor, blepharospasm, and dystonia-parkinsonism presentations have been reported in all subtypes of *GBA1*-related disorders suggesting that dystonia may be more prevalent than currently appreciated (4,5). BoNT-A is well established as first-line therapy for cervical dystonia in adults and is increasingly used in children, with evidence supporting its efficacy and safety despite the low level of available data (7, 8). Our observations align with these findings, showing meaningful functional improvement without adverse effects. The deep cervical muscles involved in retrocaput require precise targeting, and inaccurate injections may expose the patient to the risk of dysphagia or neck weakness, particularly in children with multisystemic disease. The use of combined US and EMG guidance enhances accuracy and reduces complications, an approach particularly valuable in rare diseases where anatomical variations or compensatory postures may complicate injection planning (7 9). Pain and anxiety during intramuscular injections are major concerns in children. Nitrous oxide is a well-established option for

procedural sedation, offering rapid onset, good tolerability, and minimal respiratory depression (14). In our cases, sedation facilitated optimal positioning and allowed safe access to deep cervical muscles. Given the potential respiratory vulnerability in GD, careful anaesthetic planning is essential, and a multidisciplinary approach is recommended (9,15). These observations suggest that cervical dystonia in GD3 may be more prevalent than currently recognised and that targeted chemodenervation using BoNT-A can provide significant functional benefits. Early identification and treatment may help reduce functional impairment and potentially limit secondary complications directly related to dystonia. Although this report describes only two cases, both patients have now received repeated BoNT-A injections every three months, corresponding to the period of efficacy. Besides, for more than five years of follow-up, we observed a sustained efficacy of the treatment and good tolerability. Larger studies or multicentre registries would help establish standardised protocols.

Conclusion

Cervical dystonia is a possible but overlooked neurological manifestation of GD3, and possibly of other paediatric neurogenetic disorders. In these two paediatric siblings, BoNT-A injections performed under combined US and EMG guidance, with appropriate paediatric sedation, resulted in significant and sustained improvement in head posture, gait, and quality of life. The treatment was well tolerated, with no adverse effects. These observations suggest that, as in many types of focal dystonia, botulinum toxin is a valuable therapeutic option and should be considered in cases of GD3 with dystonic features, while highlighting the importance of recognising dystonia as part of the neurological phenotype. Further studies are needed to better characterise dystonia in GD and to develop evidence-based treatment guidelines.

Statements

Informed consent: the patients' father has given his written consent for the use of the patients' photographs and videos for the purpose of this scientific work.
Conflict of interest statement: The authors declare no conflicts of interest.
Funding: No external funding was received for this work.

Supplementary Video 1 –
***Cervical dystonia* in Gaucher disease type 3.**
The video material supporting the findings of this study can be available on demand (main author).

- Segment 1-1: Patient A before botulinum toxin injection, showing severe retrocaput during gait.
- Segment 1-2: Patient A three months after the first injection, with significant improvement in head posture.
- Segment 2-1: Patient B before injection, showing sustained cervical extension during ambulation.
- Segment 2-2: Patient B two months after injection, with improvement of the retrocaput component and residual mild torticollis.

https://www.youtube.com/watch?v=xO0RiSM_Q_c

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9h → 13h Matinée

9h Plantons le décor
- 112 : Pompiers, ambulances, quelle est votre urgence ?
- Périple aux urgences pédiatriques à travers les yeux d'un enfant.
- Zéro stress, zéro douleur.
- FLASH : La médecine d'urgence dans la poche.

11h10 Top 5 des urgences
- Douleurs thoraciques et malaises : ces plaintes qui nous embêtent.
- Les boutons d'urgence ?!
- Gare à la bosse !
- Trop petit, trop chaud.
- FLASH : La médecine d'urgence dans la poche (gauche !).

13h Pause lunch – visite des stands

14h → 18h Après-midi

14h • *« Pediavox : les actualités pédiatriques belges ».*

14h20 Vague à l'âme
- Quand le vase déborde.
- Place aux accompagnants..
- La communication thérapeutique, ça se soigne

16h20 Quand la clinique ne suffit pas
- To scan or not to scan ?
- Hocus POCUS.
- Examens complémentaires : alliés ou ennemis ?

18h • Fin de la réunion scientifique.

Renseignements :
- Secrétariat scientifique : Dr F. Mascart francoise.mascart@chc.be
- Secrétariat administratif : Dr F. Kanen kanen.francois@hotmail.be
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Belg J Paediatr. 2026;28(3):309-318

Isolated Foetal Ascites Associated with a Urachal Cyst and Posterior Urethral Valves: A Case Report and Literature Review

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Keywords

Prenatal diagnosis; Foetal ascites;
Urachal remnants; Posterior urethral valves

Abstract

Background
Prenatal detection of isolated ascites in combination with an abdominal cyst poses a diagnostic challenge. The diagnosis of urachal remnants may be particularly difficult, as imaging findings can mimic other urinary tract anomalies. Furthermore, their rarity has resulted in a lack of clear evidence-based management guidelines.

Methods
A literature review was conducted to understand this clinical presentation. The Medline database (PubMed) was searched using the MeSH terms "Ascites/congenital," "Urachal Cyst," and "Urethral Obstruction/congenital." A total of 979 publications were screened.

Results
Urachal cysts are rare embryological remnants that are often asymptomatic and may regress spontaneously, supporting conservative management in selected paediatric cases. In contrast, posterior urethral valves require prompt diagnosis using voiding cystourethrography, followed by valve ablation. Long-term follow-up of these patients is essential, as up to 20% of affected patients may progress to end-stage renal disease.

Discussion
Early recognition of this rare combination of findings may facilitate timely diagnosis of posterior urethral valves and guide appropriate postnatal management. In this case, the urachal cyst may have acted as a pressure-relieving "pop-off" mechanism. This might explain the absence of hydronephrosis and could have potentially protected the renal function. Clinical follow-up will be necessary to determine whether this presumed pressure-relief mechanism translates into a more favourable long-term renal prognosis.

Introduction

This report describes the unique presentation of a neonate with antenatally detected isolated ascites and bladder wall thickening in combination with an abdominal cyst. Prenatal imaging suggested a urachal cyst, given its position between the bladder dome, and the anterior abdominal wall at the level of the umbilical insertion. However, the diagnosis of urachal remnants remains challenging, as imaging findings may resemble other urinary tract anomalies. The associated ascites and bladder wall thickening raised suspicion of uroperitoneum secondary to a suspected lower urinary tract obstruction. During further diagnostic evaluation, this neonate was eventually diagnosed with posterior urethral valves (PUV), a finding that was essential for therapeutic decision making and clinical follow-up. The coexistence of these conditions suggests a potential pathophysiological relationship, which will be further explained in this report. A narrative review of the literature was performed to further analyse this clinical presentation, with particular emphasis on the prenatal presentation of intra-abdominal cysts, the differential diagnosis of isolated ascites and the current evidence regarding the therapeutic management of posterior urethral valves and urachal cysts. The aim of this case representation is to guide clinicians in the diagnostic process, as a timely diagnosis is crucial in these patients to support optimal medical management.

Case presentation

The mother of this patient was referred to a tertiary hospital at 33 weeks of pregnancy due to the presence of isolated foetal ascites. Until then, the pregnancy had been uncomplicated. The family history was negative and the parents were non-consanguineous. Specialist ultrasound showed clear ascites and a cystic echolucent structure between the bladder and umbilical cord insertion (Figure 1). The bladder wall appeared thickened, without apparent keyhole sign,

TABLE 1: Comparison of biochemical parameters in blood, urine, and ascitic fluid on day 1.

	Blood	Urine	Ascites	Unit
Glucose	68	Negative	84	mg/dL
Albumin	38	/	12,4	g/L
Creatinine	0,91	20,2	0,90	mg/dL
Leukocytes		105	64	/microL
Erythrocytes		12	<1000	/microL

and there was a normal appearance of both kidneys without hydronephrosis. The anal canal and rectum were visible and appeared normal. Cardiac function was normal, with no evidence of hydrops fetalis or foetal anaemia. There were no features suggestive of a lymphatic disorder. The differential diagnosis included urinary ascites (secondary to bladder rupture or rupture of a urachal cyst), and, less likely, intestinal perforation secondary to bowel obstruction. A primary caesarean section was performed at 36 weeks 4 days of gestation because of breech presentation and anticipated respiratory compromise resulting from increased intra-abdominal pressure, as reflected by diaphragmatic elevation. Antenatal corticosteroids were administered to minimize the risk of transient tachypnoea of the neonate. The neonate demonstrated a good adaptation, showed no dysmorphic features and had a birthweight of 3000 grams (percentile 61). Spontaneous micturition was observed immediately after birth, although the quality of the urinary flow was not documented. The neonate was intubated because of restricted lung expansion due to the abdominal distention. An indwelling catheter was placed after birth by the paediatric urologist. Initial urine output showed transient polyuria during the first hours (6,3 mL/kg/hour), which subsequently normalized (approximately 3 mL/kg/hour). Due to abdominal distension causing respiratory compromise, paracentesis was performed, draining 350–400 mL of ascitic fluid. Following paracentesis, the infant was successfully extubated on day 2. Analysis of the ascitic fluid demonstrated a creatinine concentration comparable to serum (Table 1). Postnatal ultrasonography demonstrated a thickened bladder wall and an anechoic cyst anterior to the bladder consistent with a urachal cyst, without other abnormalities of the urinary tract (Figure 2). Initial voiding cystography on day 1 excluded urinary leakage or bladder perforation. The ascites drain was clamped on day 2, after stabilization of the abdominal circumference, and removed on day 7, with no recurrence of ascites during follow-up. Enteral feeding was initiated on day 4, with spontaneous meconium passage, and full enteral feeding was achieved by day 8. After starting enteral feeding, chylomicrons were not detected. MRI of the abdomen on day 5 confirmed the urachal cyst and bladder wall thickening, without additional abnormalities (Figures 3a and 3b). Biochemical analyses showed normal values for transaminases, coagulation, albumin and ferritin (differential diagnosis of gestational alloimmune liver disease). Metabolic testing showed normal results. Additionally, molecular karyotyping and a targeted metabolic gene panel were performed, both yielding normal results. Repeat voiding cystourethrography on day 7 demonstrated dilatation of the posterior urethra proximal to the level of obstruction suggestive of PUV, with active vesicoureteral reflux grade 1. Subsequently, a cystoscopy on day 10 confirmed the presence of PUV and a urachal opening with a cystic remnant. Valve ablation was postponed because of a narrow urethral meatus. The neonate was discharged on day 12 with an indwelling urinary catheter and antibiotic prophylaxis. At the age of 5 weeks, endoscopic resection of the PUV was successfully performed, after which the catheter could be removed. The patient is regularly seen by the paediatric nephrologist and urologist. As of the latest follow-up, there have been no episodes of urinary tract infection.. Follow-up ultrasonography demonstrated persistent bladder wall thickening without hydronephrosis. Biochemical parameters remained within the normal range. During a second cystoscopy at four months of age, no residual urethral valves were observed; only a small cyst was seen in the median cranial portion of the bladder.

Discussion

Antenatal diagnostic work-up and follow-up

In this case the antenatally diagnostic process was based on the visualization of an abdominal cyst in combination with isolated ascites. Most abdominal cystic lesions are detected during the second or third trimester of pregnancy (1). To further optimize the diagnostic workup of a foetal abdominal cyst, several important considerations should be taken into account. An important remark is that a pelvic cyst seen early during gestation, could be a sign of a dilated distal rectum in foetuses with an anal atresia. Therefore, careful evaluation of the perianal muscular complex remains essential to exclude the possibility of an anal atresia (2). The differential diagnosis of foetal abdominal cysts is summarized in Table 2 (1,3,4). In this case a urachus cyst was already suspected antenatally due to the anatomical relationship between the cyst, the anterior abdominal wall at the level of

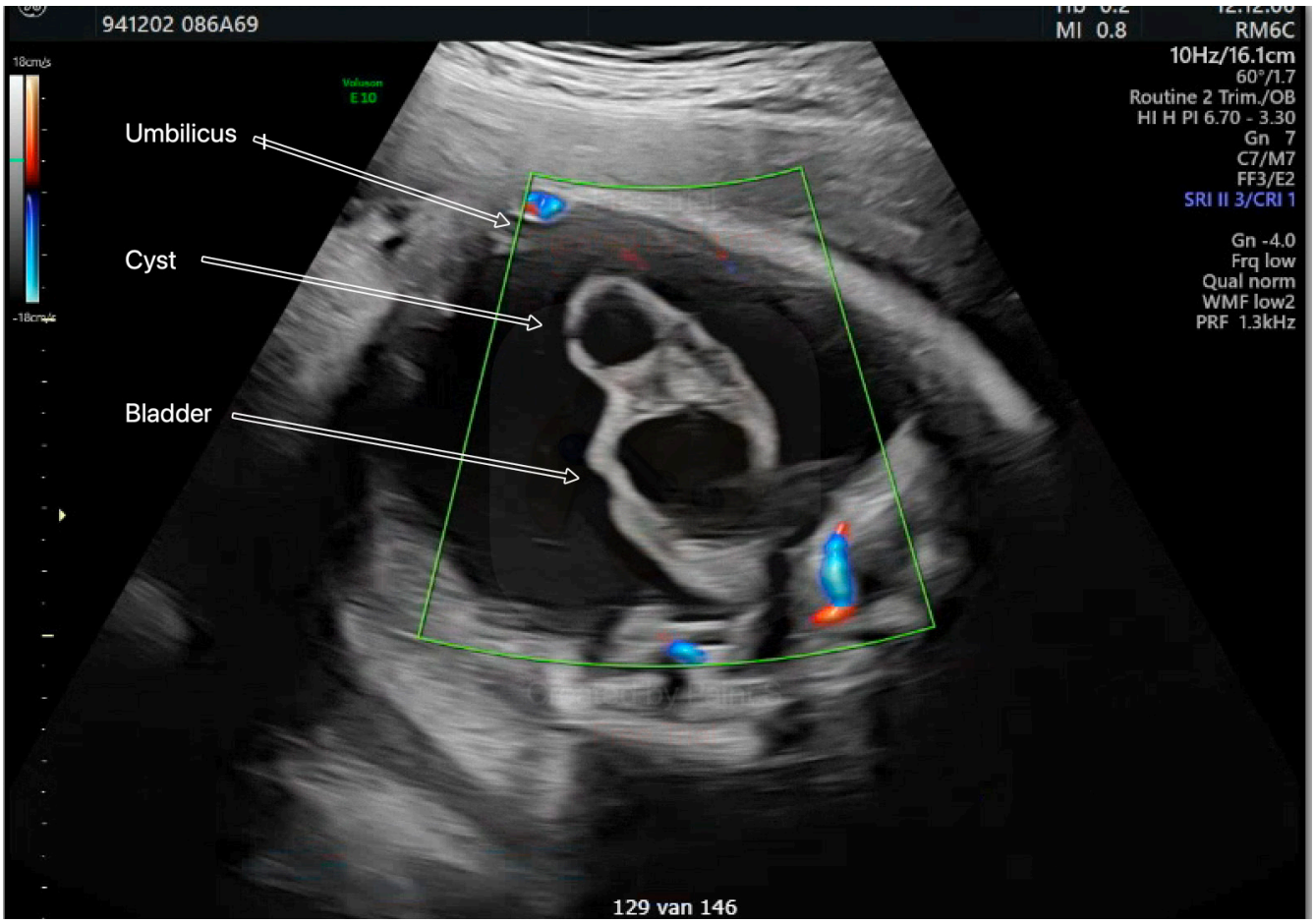


FIGURE 1: Antenatal ultrasound with abdominal cyst (between the bladder wall and the umbilical cord insertion), thickened bladder wall and clear ascites.

the umbilical insertion, and the bladder. The urachus represents an embryological connection between the bladder and the allantois, which normally undergoes obliteration during foetal development or in the early neonatal period (5). Failure of this involution results in the persistence of a urachal remnant, which may present as one of the following anomalies: a patent urachus with a persistent lumen between the bladder and umbilicus; a vesico-urachal diverticulum presenting as a blind pouch connected to the bladder; a urachal cyst containing a small patent lumen with two closed ends; and an umbilical–urachal sinus, which communicates with the umbilicus but not with the bladder (6). The most common anomaly is the urachal cyst, with an estimated incidence of approximately 1 in 5,000 births (7). Diagnosis may be challenging, as imaging findings can resemble other anomalies such as bladder diverticulum or incomplete bladder duplication (8). Postnatal imaging modalities including ultrasound and voiding cystourethrography may assist in establishing the diagnosis (6).

Foetal MRI may serve as the next step in the diagnostic approach of foetal abdominal cysts. Hügele et al. demonstrated that foetal MRI has superior diagnostic performance compared with ultrasound, increasing the diagnostic accuracy for foetal abdominal cystic lesions from 51% to 73.4% when added to the assessment (9). The recommended diagnostic workup and differential diagnosis for foetuses presenting with isolated ascites are summarized in Table 3 (10–12). In our case, a thorough prenatal evaluation was performed to determine both the cause of the ascites and the aetiology of the cyst. Although foetal MRI has superior diagnostic performance in the evaluation of foetal abdominal cysts, it was not performed in this case due to the clear visualization of the lesion on ultrasonography and MRI was therefore considered unlikely to provide additional diagnostic value. In addition to imaging, genetic analysis testing was performed in this patient. Previous authors have stated that an isolated abdominal cyst is not, in itself, an indication for genetic testing, which should therefore be reserved for foetuses with additional structural abnormalities (4). In our case, parental carrier screening for cystic fibrosis was performed and yielded negative results. However, cystic fibrosis testing is not routinely indicated in the absence of sonographic features suggestive of meconium peritonitis, such as calcifications. Nevertheless, it may be considered given the relatively high carrier frequency in the Caucasian population.

Prenatal follow-up was primarily guided by the presence of both the foetal ascites and the cyst. Depending on the underlying aetiology, potential complications associated with a foetal abdominal cyst include bowel



FIGURE 2: Postnatal ultrasound of the abdominal cyst located anterocranial from the roof of the urinary bladder extending towards the umbilicus without clear connection with the bladder (measuring 1 cm AP x 1.6 cm LL x 2.3 cm CC)

obstruction (particularly if an intestinal cyst is detected), development of polyhydramnios and preterm labour. Therefore, serial ultrasound and follow-up is necessary (1). In addition, the presence of ascites also has implications on prenatal management. Current recommendations advise ultrasound follow-up at 1–2-week intervals to monitor foetal growth, progression of ascites and amniotic fluid volume (10). Current evidence on intrauterine treatment of ascites remains controversial. In the past, intrauterine paracentesis or abdominal-amniotic shunting was considered where foetal development was compromised due to the amount of ascites (10). However, due to the rapid reaccumulation of ascites, intrauterine paracentesis didn't prevent complications (13). In patients presenting with a combination of these clinical entities, thorough evaluation is essential to support effective collaboration among neonatologists, gynaecologists, and paediatric surgeons. This multidisciplinary approach is crucial to provide optimal parental counselling, as well as guiding obstetric and neonatal care (3,4).

Relationship between posterior urethral valves, foetal ascites and a urachal cyst

Antenatally there was already a suspicion of lower urinary tract obstruction. Due to the thickened bladder wall, the diagnosis of PUV was re-evaluated by performing repeat voiding cystourethrography on the seventh day. When PUV is suspected, voiding cystourethrography should be performed as soon as possible to confirm the diagnosis (14).Voiding cystourethrography was able to confirm the presence of PUV despite the absence of hydronephrosis. Posterior urethral valves represent the most common cause of congenital obstructive uropathy (15). When urinary tract obstruction is suspected, antenatal evaluation should include assessment of amniotic fluid volume and detailed ultrasonographic examination, with the "keyhole sign" representing the classic sonographic hallmark. It is also possible to detect the presence of a urachal remnant by using voiding cystourethrography, especially when the urachal remnant presents as a diverticulum. However, when the remnant presents as a urachal cyst containing a small patent lumen with two closed ends, voiding cystourethrography can be insufficient to detect this remnant. In this patient, MRI of the abdomen was needed to confirm the diagnosis. Due to the presentation of ascites, a broad diagnostic approach was provided in our patient during admission on the neonatology ward. At present, there are no guidelines recommending the use of genetic analyses such as next generation sequencing to detect metabolic diseases in neonates presenting with ascites. However, it is currently standard clinical practice to perform a gene panel to investigate treatable metabolic diseases. This was performed due to the important therapeutic consequences and clinical outcome when a treatable metabolic cause is detected.

The coexistence of the following clinical entities (ascites, urachal cyst and posterior urethral valves) may

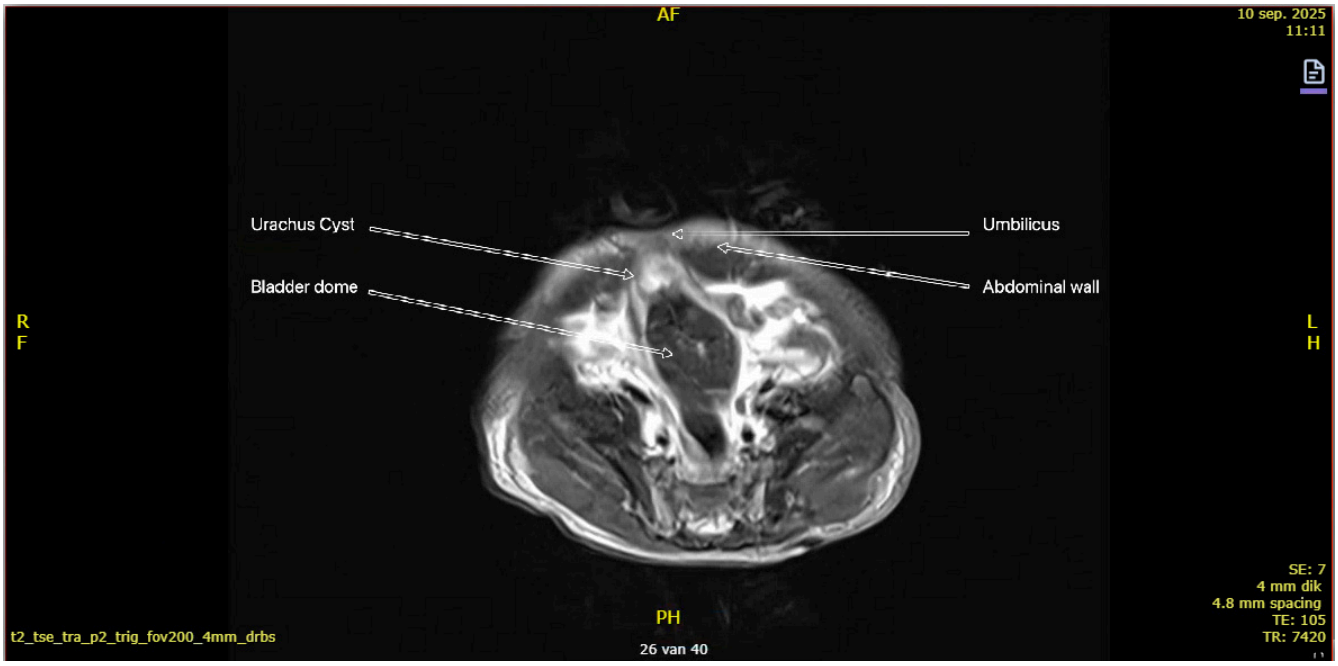
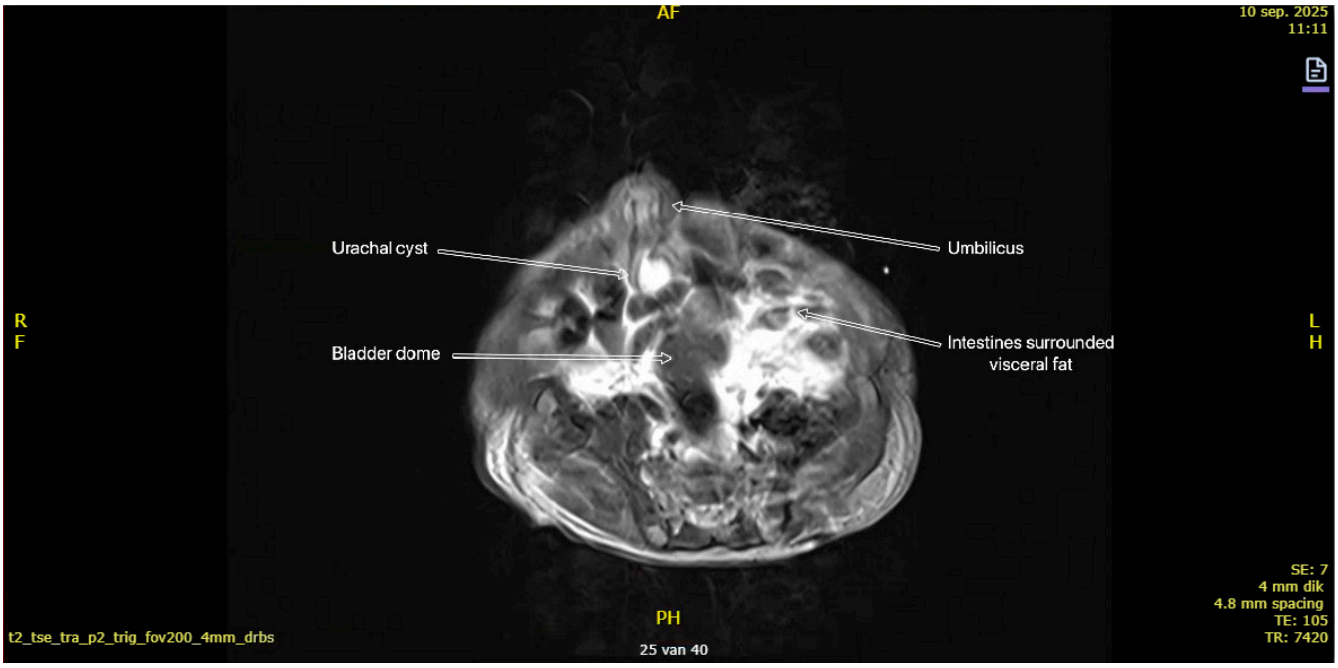


FIGURE 3a & b: MRI of the abdomen demonstrating the urachal cyst.



explain the unusual clinical presentation observed in this patient. There is a known association between PUV and the presence of a patent urachus (14). A case of a neonate with urinary ascites and posterior urethral valves without hydronephrosis was already reported by Prat et al. A hypothesized mechanism is the 'pop-off' mechanism (14–16). This mechanism is seen when increased pressure proximal to the obstruction could lead to forniceal or calyceal rupture, resulting in urinary ascites (which is life threatening when occurring in neonates) or a perinephric urinoma (in cases of extraperitoneal urinary extravasation). Several compensatory mechanisms have also been described, such as large bladder diverticula and urinary extravasation, which are known mechanisms to buffer high pressures in the urinary tract in utero and may therefore preserve renal function (15). It is also plausible that the urachal cyst functioned as a pressure-relieving pathway, limiting the transmission of increased intravesical pressure to the upper urinary tract. In this scenario, pressure generated by the urethral obstruction may have decompressed through the urachal remnant rather than resulting in hydronephrosis. The urinary ascites may therefore have resulted from partial rupture of the cyst or from transudation of urine into the peritoneal cavity. If ascitic fluid consists predominantly of urine, elevated concentrations of creatinine and urea would typically be expected. However, the biochemical composition of urinary ascites may be altered by partial resorption of fluid

TABLE 2: Differential diagnosis of foetal abdominal cysts (1,3,4).

Organ system	Lesion	Frequency	Characteristics
Embryological malformation	Urachal cysts	Rare	
Endocrinological	Adrenal (haemorrhagic) cysts		
Genital	Ovarian cysts	Most frequently in female foetuses	Location to the side of the bladder
	Hydrometrocolpos		
Intestinal	Intestinal duplication cysts	Most frequent	
	Hepatic cysts	Frequent	
	Biliary cysts	Frequent	
	Meconium pseudocysts	Frequent	Calcifications
	Mesenteric cysts	Frequent	
	Splenic cysts	Frequent	
	Bowel dilatations	Frequent	
	Choledochal cyst		Relationship of the cyst to the hepatic artery
	Pancreatic cyst		
	Anorectal anomalies		Pelvic cysts
Oncological	Cystic tumours, such as neuroblastoma	Rare	
Pulmonary	Intra-abdominal extra lobar bronchopulmonary sequestration with cystic changes		
Urological	Renal cysts		

across the peritoneum. The peritoneal membrane can act as a dialysis membrane between urine and plasma (17,18). As urine contains higher osmolarity and higher concentrations of creatinine, urea, and potassium, whereas plasma contains higher sodium levels, an "autodialysis" phenomenon may occur, allowing diffusion of water and sodium into the peritoneal cavity (17,19,20). Consequently, creatinine levels in urinary ascites are generally lower than in urine but remain higher than serum creatinine levels (20). Nevertheless, it remains controversial that the 'pop-off' mechanism seen with urinary extravasation is indeed kidney protective. The systematic review conducted by Khondker et al. demonstrated that urinary extravasation was not statistically significant associated with a renal protective effect (16). Illustration 1 schematically illustrates the proposed pressure-relieving pathway that may have functioned as a pop-off mechanism.

Further management of our patient is guided by the guidelines on congenital lower urinary tract obstruction and the current evidence on the management of urachal anomalies. The guidelines of the European Association of Urology and European Society for Paediatric Urology state the importance of immediately postpartum management consisting of prompt bladder drainage and initiation of antibiotic prophylaxis, when lower urinary tract obstruction is suspected. Given the potentially life-threatening nature of this condition, close monitoring in a neonatal intensive care setting is required, including regular assessment of renal function and electrolyte levels (14). Once the diagnosis is confirmed, definitive treatment consists of endoscopic valve ablation. Despite optimal management, approximately 20% of patients may progress to end-stage renal disease, highlighting the need for lifelong monitoring (14).

Due to the rarity of urachal anomalies, evidence-based management guidelines remain limited. Urachal cysts are frequently asymptomatic but may occasionally lead to complications such as infection, peritonitis, enteric fistula formation, or, rarely, malignant transformation. Both benign and malignant tumours have been reported, including teratoma, mucinous tumours, giant cell tumours, rhabdomyosarcoma, and yolk sac tumours (8). Management options include surgical excision or conservative follow-up. Increasing evidence supports conservative management in asymptomatic paediatric patients, as spontaneous postnatal involution of urachal remnants has been described (5). Regular monitoring using ultrasound imaging is advised and has a high sensitivity (nearly 80%). Consequently, prophylactic excision during the first year of life is generally not recommended (8,21). A review by Ghattas et al. supports this conservative approach, with surgical intervention reserved for symptomatic cases, particularly in patients presenting with recurrent infections (8). When surgery is required, open excision remains the traditional gold standard, although laparoscopic and robotic approaches have also been reported to be safe and effective alternatives with improved

TABLE 3: Diagnostic workup and differential diagnosis in foetuses with isolated ascites (10–12)

Organ system	Differential diagnosis	Additional diagnostic technique
Cardiac	Heart failure (due to structural cardiac defects)	Structural ultrasound on foetal cardiac echography
	Cardiac Arrhythmias	
Chylous	Lymphatic malformations	
Gastro-intestinal	Meconium peritonitis	Genetics: Prenatal testing cystic fibrosis. Imaging: hyperechogenic bowel, dilated bowel and intraabdominal calcifications
	Small intestinal or colonic atresia	
	Intestinal perforation	
	Cloacal dysgenesis	
	Omphalocele	
	Oesophageal atresia	
	Volvulus	
	Intussusception	
	Biliary atresia	
	Portal venous malformations	
Genetic	Trisomy 18 or trisomy 21	Amniocentesis for karyotyping
	Turner syndrome	Amniocentesis for karyotyping
	Osteogenesis imperfecta type II	
	Others*	
Genital	Ovarian cyst	
	Persistent cloaca/cloacal dysgenesis	
Hematologic	Haemolytic disease of the neonate (Rh or ABO alloimmunization)	Maternal antibody screening and direct antiglobulin test
	Severe congenital anaemia	Kleihauer–Betke test; Doppler flow of the umbilical/cerebral arteries
Infectious	Cytomegalovirus, parvovirus B19, hepatitis A/B/C, herpes simplex 1, 2, varicella, rubella	Serology
	Syphilis, Listeriosis	Bacterial cultures and serology
	Toxoplasmosis	Serology
Metabolic	Niemann-Pick type C	
	Infantile Sialic Acid Storage Disease	
	Sialidosis	
	Mucopolysaccharidosis VII	
	Congenital disorders of glycosylation	
	Wolman disease	
	Lysosomal storage disease	
Obstetric	Severe foetal growth restriction	Abnormal umbilical artery dopplers
	Severe placental dysfunction	
Pulmonary	Congenital cystic adenomatoid malformation of the lung	
	Congenital hernia diaphragmatica	
	Laryngeal stenosis	
Urological-nephrological	Posterior urethral valves	
	Urogenital sinus anomaly	
	Polycystic kidney disease	
	Dysplastic kidneys	
	Lower urinary tract obstruction	
	Ureteropelvic junction obstruction	
	Vesicoureteral reflux	
	Prune belly syndrome	

*Others: cardiosplenic syndrome, Fraser syndrome, chromosome 4p deletion, Sotos syndrome, stomatocytosis, primary lymphangiectasia, skeletal dysplasia, McKusick Kaufman syndrome and 46, XXt(1;4) (q31; q34) (11).

cosmetic outcomes (6). In accordance with the current literature concerning management or urachal cysts (3,6), this patient didn't receive prophylactic surgery yet and currently is treated with prophylactic antibiotics (trimethoprim) due to low grade active vesicoureteral reflux. Currently a cystoscopy is planned at one year of age, and if the cyst persists, an excision will be performed due to the small but potential risk of malignancy.

Strengths and limitations

To our knowledge, no previous cases describing the coexistence of isolated foetal ascites, urachal cyst, and posterior urethral valves have been reported. This case underscores the importance of a thorough diagnostic evaluation in neonates presenting with unexplained ascites in combination with a urachal remnant. Furthermore, the present review provides an overview of the differential diagnosis of foetal abdominal cystic lesions and foetal ascites, which may assist clinicians when confronted with similar clinical presentations. It should be noted that the conditions summarized in the tables are derived from the performed narrative review and are therefore not exhaustive. Given the broad spectrum of clinical entities addressed, a narrative review methodology was considered the most appropriate approach. However, compared with a systematic review, this methodology has inherent limitations, including the absence of a formal quality assessment of the included studies, thereby limiting the ability to formulate specific evidence-based recommendations.

Conclusion

Prenatal detection of an abdominal cyst in combination with isolated ascites requires a thorough diagnostic evaluation. Early recognition of this unique combination, particularly in the presence of bladder wall thickening, may raise suspicion for posterior urethral valves, and thereby facilitate timely diagnosis and appropriate postnatal management. A plausible explanation is that the urachal cyst functioned as a pressure-relieving mechanism, thereby accounting for the absence of hydronephrosis. Clinical follow-up will be necessary to determine whether this presumed pressure-relief mechanism translates into a more favourable long-term renal prognosis.

Statements

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Written informed consent for publication of the medical data and imaging studies was obtained from the patient's parents.

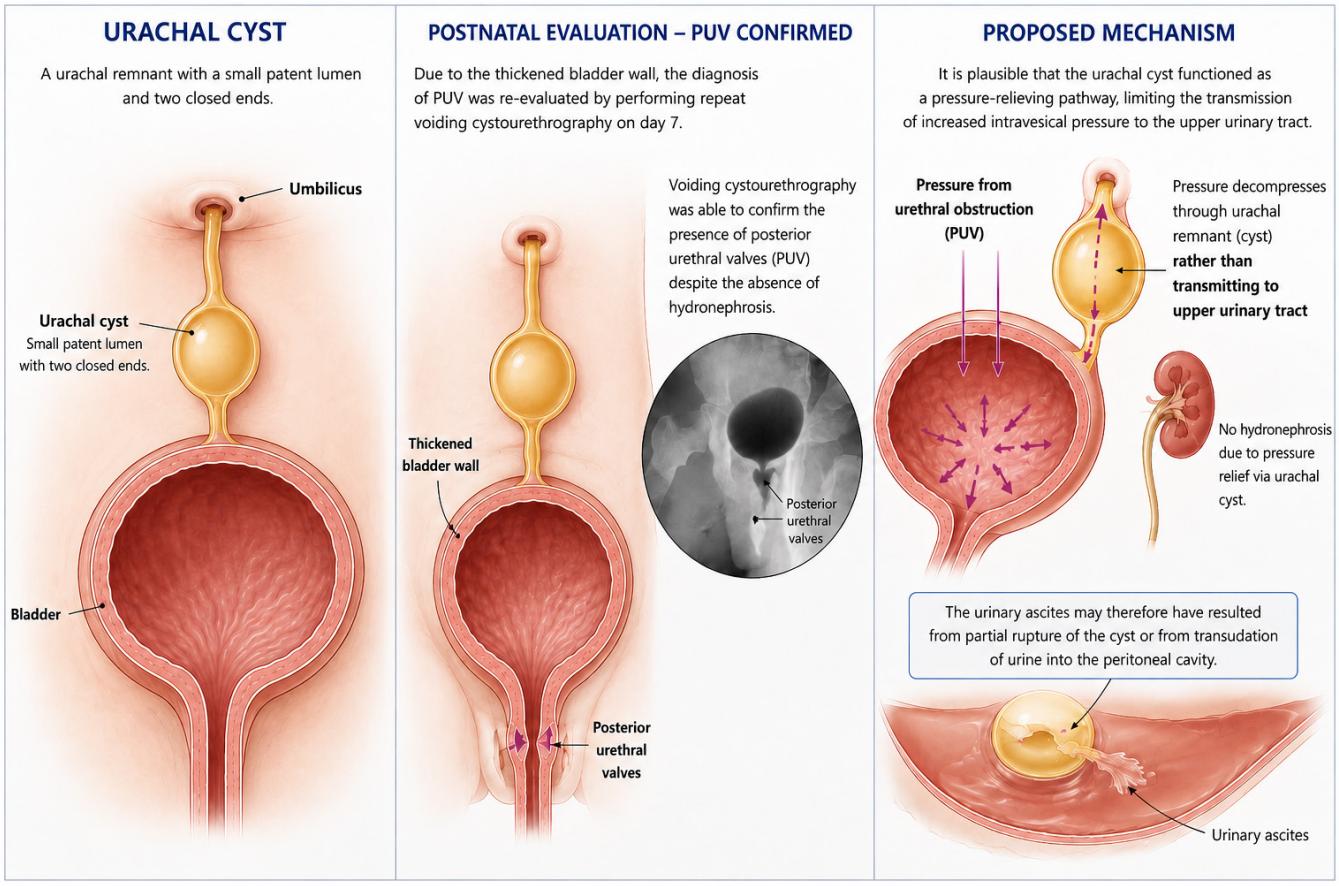


ILLUSTRATION 1: Urachal cyst and proposed mechanism of pressure-relieving pathway.

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Verzorging voor de luierwissel:

een oplossing voor elke situatie

Crème voor de luierwissel 1 2 3

Vanaf de eerste roodheden



Liniment

Belg J Paediatr. 2026;28(3):319-322

Paracetamol Syrups and Propylene Glycol Exposure in Children: A Reflection on the Current Belgian Context

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Keywords

Paracetamol; Propylene glycol; Paediatric pharmacotherapy; Excipients

Abstract

Dafalgan Pédiatrique/Dafalgan Kind recently adapted its syrup. This new formulation contains propylene glycol as excipient, as mentioned in the product information in accordance with the European Commission guideline (> 1 mg/kg/day in neonates). The guideline's thresholds relate to the specific information that should appear in the package leaflet, not similar to safety thresholds. There is a 28-fold difference in propylene glycol exposure between both currently marketed products (Dafalgan versus Perdolan, 7 versus 293.5 mg/kg/day), so that there is an opportunity to limit exposure below clinical relevance, without full avoidance. The current knowledge on propylene glycol in children is summarized

Introduction

Paracetamol (acetaminophen) is the most commonly used medicine in humans, also in children, infants and neonates. Paracetamol is an over the counter (OTC) medicine in Belgium, be it commonly supported by advice of health care providers, like paediatricians or pharmacists (1). Recently, Dafalgan Pédiatrique/ Dafalgan Kind adapted its formulation so that this new formulation contains propylene glycol as an excipient as mentioned in the summary of product characteristics (SmpC) (2,3). Excipients, including alcohols like propylene glycol are commonly added to formulations to ensure stability and quality of a given formulation over a given shelf life ('expiration date'). Alcohols are hereby typically used as solvent for either the active pharmaceutical ingredient, or related to the flavouring, commonly to improve solubility in liquids or water. This means that propylene glycol is not unique to syrups, but can also be present in e.g. intravenous formulations like phenobarbital, digoxin, lorazepam or esmolol vials. This co-solvent has a consistent history of use in various formulations and also food, as has a GRAS (generally regarded as safe) status. For healthcare providers involved in the care of children, there is relevance to consider this switch since - similar to ethanol - the elimination capacity of propylene glycol like any other alcohol is limited, since metabolized by alcohol dehydrogenase (ADH to lactaldehyde, subsequently by aldehyde dehydrogenase to lactate), or (minor route) by primary renal elimination. Although propylene glycol is usually considered innonxious, in larger quantities it can cause metabolic perturbations like lactic acidosis and hyperosmolarity. In the event of overexposure, toxicity may occur, related to accumulation, changes in osmolar gap, kidney or hepatic impairment, with subsequent clinical signs like central nervous system depression (4). Other side effects such as haemolysis, mental status changes or renal toxicity (e.g. renal tubular acidosis, acute tubular necrosis) have been reported as manifestations of propylene glycol toxicity. Case series on intoxication have been described, mainly related to continuous intravenous lorazepam administration in adult and paediatric ICU settings. Specific for infants and neonates, the likelihood of propylene glycol accumulation is proportionally (/kg) higher because of their lower clearance capacity (lower ADH activity and lower renal elimination). Historically, MacDonald et al. reported on the increased incidence of seizures (33 % instead of 11 %), renal failure, increased direct bilirubinaemia following a change in the daily volume

TABLE 1: Overview of the product names with the amount of propylene glycol/ml, indications, registered population, recommended and maximum daily dose and the related propylene glycol exposure (9).

Product name	Indication	Paediatric population	Recommended dose	Maximum dose, and propylene glycol exposure
Perdolan Enfants/kinderen 32 mg/ml 104,8 mg/mL propylene glycol*	Pain Fever	<50 kg	15 mg/kg every 4 h	60 mg/kg/day **196.5 mg/kg/day**
Dafalgan Pédiatrique/Kind 30 mg/ml 3,5 mg/mL propylene glycol*	Pain Fever	Authorized: From 3-16 kg (approx. from birth to 4 years)	15 mg/kg every 6 h	60 mg/kg/day **7 mg/kg/day**
Paracetamol Teva 40 mg/ml no propylene glycol**	Mild to moderate pain Fever	From 3 months	10 mg/kg every 4 h 15 mg/kg every 6 h	60 mg/kg/day **no exposure**
Perdolan 50 mg/ml 1,94 mg/mL propylene glycol **	Pain Fever	From 1 year (>10 kg)	15 mg/kg every 4 h	60 mg/kg/day **2.1 mg/kg/day**

* = commercialized in Belgium at present;
** = not commercialized in Belgium at present.

of intravenous multivitamin administration (with PG as the solvent) from 1 ml/day to 10 ml/day in very low birth weight infants (5). This multivitamin solution for intravenous administration contained 300 mg propylene glycol/ml solution. Therefore, the change in the daily volume administered resulted in an increase of exposure of 300 mg/day to 3 000 mg/day (equal to at least 200 mg/kg versus 2 000 mg/kg/day) and patients were treated with this solution for at least 14 days. The 'Kaletra syrup (lopinavir/ritonavir)' observation serves as the most recent observation on the clinical relevance, be it following co-exposure to ethanol and propylene glycol (42.4% ethanol, 15.3% propylene glycol). Because of case series in neonates, the Food and Drug Agency send out a black box warning and adapted the label so that the drug should not be administrated to any neonate <42 weeks of postmenstrual age and <2 weeks postnatal age) (6). However, there are also data that short term lower propylene glycol exposure (25-50 mg/kg/day) was tolerated well in preterm and term neonates (7). The same situation applies to the EU market. Because of the relevance of excipient toxicity and the potential for clinical adverse events, a European Commission guideline has been developed with warning statements when certain excipients in medicinal products are present above defined thresholds. These thresholds are intended to determine when information or warnings should be included in the product information; they do not represent absolute safety limits, nor do they imply that products exceeding them are inherently unsafe (8). Rather, the acceptability of excipient exposure must be considered in the context of the overall benefit-risk balance of the medicinal product. The assessment report for propylene glycol also states that "it should be kept in mind that higher doses of propylene glycol may be administered, when justified on a case by case basis in order to support the safety of the proposed formulation, and were suggested in the absence of compelling data". "Clinical data showed that in children from the age of 5 years and adult patients, up to 500 mg/kg/day of propylene glycol could generally be considered safe. In the absence of compelling data this safety threshold is decreased to 50 mg/kg/day in children <5 years old, and even to 1 mg/kg/day in (pre) term neonates due to known immaturity of both metabolic and renal clearances of propylene glycol in these populations" (8).

Objectives

Provide an overview on the currently registered and marketed paracetamol syrup formulations for children in Belgium, provide a /kg based calculation of related propylene glycol exposure, applying the registered doses, and bring perspective and provide context related to the existing recommendations of the European Medicines Agency on propylene glycol use in formulations (8).

Methods

The medicinal product database for human use of the Belgian agency was searched for the currently registered and marketed formulations on the Belgian market (9). Based to the specific SmpC on dosing and propylene glycol concentrations, the propylene glycol exposure /kg was calculated.

Results

In Belgium, there are 4 liquid paracetamol formulations registered. However, 2/4 are at present not marketed (Paracetamol Teva 40 mg/ml, Perdolan 50 mg/ml) in Belgium. The product names with the amount of propylene glycol/ml, indications, registered population, recommended and maximum daily dose and the related propylene glycol exposure are listed in Table 1.

Conclusion

'Perfect is the enemy of good'
('le mieux est l'ennemi du bien')

Propylene glycol exposure is for sure a potential relevant issue, with potential severe or serious adverse reactions, as reported in adults, children, infants and neonates (4-8). Consequently, and as a precautionary measure, labelling guidelines with age-based thresholds to report on in the SmpC have rightfully been implemented (9). This provides us with the opportunity to identify, quantify, and prevent or mitigate propylene glycol overexposure. It also results in transparency in the event of polypharmacy with different sources of alcohols as excipient. For paracetamol syrups - and considering the current marketed products – there is a 28-fold difference in propylene glycol exposure between both currently marketed products (Table 1), so that there is an opportunity to limit (7 mg/kg/day) by selecting the best suited formulation, but not to fully avoid exposure above the threshold to report propylene glycol in the product information. Although exposure above the labelling threshold cannot be fully avoided, a resulting exposure level (7 mg/kg/day) is considered acceptable from a clinical safety point of view, as exposure to 25-50 mg/kg/day in neonates was not associated with biochemical signs of accumulation or metabolic disturbances (7).

Conflicts of interest

Karel Allegaert is member of the Paediatric Committee (PDCO) for Belgium at the European Medicines Agency (EMA), is the representative of the European Academy of Paediatrics in the Health Care Providers Working Party of EMA, as well as member of the committee for medicines for human use, Federal Agency for Medicines and Health Products (FAMHP). This short communication reflects his personal opinion, not the opinion of the PDCO, EMA or FAMHP. His conflict of interest is in the public domain. This work has been performed without any funding.

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Impacts of Antenatal Exposure to a Mixture of Endocrine Disruptors on Cognitive and Neuromotor Functions in Preschool Children

PhD Thesis Presented on 19 June 2026 at University of Liège, Liège, Belgium

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Keywords

Endocrine disrupting chemicals; Mixture;
Prenatal exposition; Sex stratified; Cognitive impact

Objective

The effects of prenatal exposure to endocrine-disrupting chemicals (EDCs) on neurodevelopment remain inconsistent, and few studies have specifically examined cognitive processes. Additionally, toxicants are often analysed individually, without considering their combined effects. This study aimed to investigate the impact of prenatal exposure to a mixture of persistent organic pollutants (POPs) on neuromotor and cognitive development in preschool-aged children.

Method

Between 2014 and 2016, 62 children were recruited into a longitudinal cohort study. Cord serum samples were analysed for one organochlorine pesticide, four polychlorinated biphenyls (PCBs), and seven perfluoroalkyl substances (PFASs). At six years of age, children underwent neuropsychological assessments evaluating intelligence, attention, memory, and executive functioning, as well as standardized tests for motor skills, language, and arithmetic abilities. Associations between POP mixtures and these outcomes were analysed using the principal component approach and weighted quantile sum regression, accounting for sex differences.

Result

Higher prenatal exposure to POP mixtures was significantly associated with lower attentional, neuromotor, and language scores when boys and girls were analysed together. In sex-stratified analyses, negative associations with attentional and neuromotor functions remained significant but were observed only in boys. Additionally, boys with higher prenatal exposure to POP mixtures exhibited lower scores in full-scale intelligence quotient (FSIQ), fluid reasoning index, working memory, and planning abilities. In contrast, prenatal exposure to a mixture of EDCs in girls was associated with reduced behavioural regulation, particularly inhibition control. Regarding language development, exposure to POP mixtures was associated with lower receptive language abilities in boys, whereas expressive language was more affected in girls. No significant association was found with arithmetic abilities.

Conclusion

These findings support negative associations between prenatal exposure to a mixture of endocrine disruptors and specific cognitive functions in children. Our study highlights a sex-specific effect, contributing to a better understanding of trends described in the literature.

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Newborn Screening

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Keywords

Neonatal Screening

Newborn screening (NBS) is evolving rapidly with advances in next-generation sequencing (NGS), creating opportunities to complement established biochemical screening and potentially expand the range of disorders detectable in the neonatal period. However, the concept of "genetics-first newborn screening" (gNBS) requires careful definition. Targeted molecular testing for a specific disorder, such as current genetic approaches for spinal muscular atrophy (SMA), should be distinguished from broad panel-based or genome-scale sequencing applied as a primary screening strategy.

Early genomic NBS studies have demonstrated that targeted analysis of sequencing data is technically feasible and can identify additional potentially actionable/treatable findings. However, technical feasibility and an increased screen-positive yield is not equivalent with demonstrated clinical utility or public-health benefit. For many disorders, available studies have not yet established condition-specific screening sensitivity, positive predictive value in unselected newborn populations, long-term clinical outcomes, cost-effectiveness, or the balance between benefits and potential harms associated with uncertain, incompletely penetrant, or late-onset findings.

Importantly, emerging evidence also illustrates the complementary nature of genomic and biochemical information. Studies such as BabyDetect have shown that biochemical data may help prevent inappropriate reporting or interpretation of genomic findings, including those involving *GALT* and complex *CFTR* alleles. These observations support consideration of genomic NBS not as a single uniform strategy, but within different screening options: sequencing as a stand-alone first-tier test; sequencing performed in parallel with conventional biochemical NBS; sequencing used as a second-tier investigation following an abnormal biochemical first-tier result to decrease the number of false positives and increase the positive prediction rate. The latter approach is already incorporated into screening algorithms for selected disorders, including cystic fibrosis and severe combined immunodeficiency (SCID), and may currently provide the most pragmatic framework for integrating genomic technologies into established NBS programmes.

Ultimately, the optimal position of NGS is likely to be condition-dependent and should be determined by its incremental contribution to screening performance, diagnostic certainty, timely treatment, clinical outcomes, cost-effectiveness, and overall public-health benefit. A critical evaluation of genomic NBS should therefore clearly distinguish between technical feasibility, screen-positive rate, diagnostic yield, actionability, clinical utility, and demonstrated benefit at the population level.

The manuscript by Jacquemin et al. can form the base for further discussions involving all stakeholders on the newborn screening strategy of the future.



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Genomic Newborn Screening in Belgium: Opening the Debate of Public Health Evaluation

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Keywords

Genomic Newborn Screening, Next Generation Sequencing, Public Health, Rare Disease

Abstract

Accumulating evidence from international and Belgian pilot studies suggests that genomic newborn screening (gNBS) has reached a level of maturity that now justifies structured evaluation within a public health framework. Recent international pilot studies, including large Belgian data, now provide evidence that first-tier or adjunct genomic screening is technically feasible, clinically informative, and highly acceptable to parents. Belgium has played a leading role in this field. The BabyDetect program has shown that targeted next-generation sequencing can be implemented in a maternity setting with high parental uptake and a meaningful added diagnostic yield beyond conventional screening. At the same time, the rapid development of international programs has exposed major unresolved questions regarding gene selection, variant interpretation, health-economic evaluation, data governance, and equitable access. In this Insight, we argue that the debate should now move beyond whether gNBS is technically possible and instead focus on how it can be evaluated and governed responsibly within the Belgian healthcare system. We review the current evidence, highlight the specific Belgian contribution, and outline the principal challenges that must be addressed before broader public implementation can be responsibly considered.

Introduction

Newborn screening (NBS) is one of the most successful public health interventions of the past 50 years. Since its introduction for phenylketonuria screening in the 1960s, NBS has progressively expanded to include an increasing number of conditions, primarily metabolic and endocrine disorders, and has substantially improved outcomes through presymptomatic diagnosis and early treatment. Today, NBS programs are implemented in all high-income countries, although the number and type of screened diseases vary considerably between jurisdictions. In Belgium, this variability is also observed between the Flemish and French-speaking communities, each operating its own screening program with distinct panels of conditions. Despite these differences, both systems share a common objective: early identification of severe, treatable diseases to enable timely intervention and improve long-term outcomes. However, as in all other countries, conventional NBS in Belgium still relies predominantly on biochemical assays performed on dried blood spots. This model, though highly effective for many metabolic and endocrine disorders, limits the detection of conditions for which no reliable biomarker exists. As a result, many severe, early-onset diseases that would be relevant targets for NBS cannot currently be identified through standard biochemical screening, thereby limiting opportunities for timely diagnosis and early intervention. In this context, genomic newborn screening (gNBS) has emerged as a promising solution to these limitations. By analysing a predefined set of genes causing actionable childhood-onset disorders rather than targeting diseases individually, genomic screening offers a more comprehensive and flexible approach. It enables the inclusion of conditions that cannot be detected using conventional biochemical methods and allows rapid

adaptation of screening panels as new therapies become available. The purpose of this Insight is not to present gNBS as ready for immediate universal implementation, but to examine whether the scientific evidence has become sufficiently mature to justify a structured Belgian public health strategy. We review the current evidence, highlight the specific Belgian contribution, and outline the conditions required for scientifically robust, ethically responsible, and socially acceptable implementation.

What do current pilot studies actually show?

Over the past decade, gNBS has transitioned from conceptual exploration to real-world pilot implementation. Although pilot programs differ substantially in sequencing strategy, target population, gene content, and reporting criteria, the available evidence now allows several conclusions to be drawn regarding feasibility, parental acceptability, diagnostic yield, and the major unresolved challenges for public-health implementation.

Belgian Experience: The BabyDetect Program

Belgium has been at the forefront of genomic NBS implementation with the BabyDetect pilot program, which provides particularly valuable real-world data from our own healthcare context. This study used targeted next-generation sequencing (tNGS) to screen for 165 treatable paediatric conditions across 405 genes. In the initial feasibility and acceptability study conducted in Liège, 90.5% of parents consented to genomic screening, demonstrating remarkably high acceptance; a key prerequisite for any population-based screening program (1). This study also showed that structured pre-test information could be embedded in implementation through dedicated materials and trained consent procedures. The subsequent population-based BabyDetect study further confirmed the feasibility and clinical utility of this approach. Among 3,847 screened newborns, 71 positive cases were identified, corresponding to a screen-positive rate of 1.8% (2). Of these, 41 were G6PD deficiency, a condition also included in conventional biochemical newborn screening in Liège. The remaining 30 positive cases corresponded to conditions not detected by conventional screening, illustrating the added yield that a first-tier genomic strategy may provide. All positive cases were managed through a dedicated clinical pathway for confirmatory assessment, specialist follow-up, counselling, and access to care. Importantly, false-positive and false-negative rates were very low; with one false-negative case related to a previously unreported variant not included in the interpretation pipeline. BabyDetect also illustrates the importance of iterative panel governance, as reporting criteria for selected cardiomyopathy-associated genes were refined during the study in light of variable age of onset and phenotypic heterogeneity. This underscores both the robustness of the approach and the need for continuous refinement of variant databases and interpretation pipelines. Together, these elements illustrate that gNBS implementation requires not only analytical validity, but also clear communication on the scope and limits of screening, predefined reporting rules, and the capacity to ensure rapid and appropriate follow-up for newborns and families.

International Experience: The GUARDIAN and BabyScreen+

Findings from international pilot programs broadly reinforce the signals observed in Belgium. In the United States, the GUARDIAN study evaluated genome sequencing as an adjunct to traditional NBS in a diverse population. Among 4,000 newborns, 72% of families consented to participate, and sequencing was successfully completed in 99.6% of cases (3). The reported screen-positive rate was 3.7%, reflecting the inclusion of a broader set of conditions, including those without established biochemical markers, as well as differences in variant-reporting policy. In particular, the study reported selected variants of uncertain significance (VUS) in specific situations, including autosomal recessive conditions when a VUS co-occurred with a pathogenic or likely pathogenic variant. This broader reporting framework partly explains the higher positivity rate compared with more conservative targeted-panel approaches. This higher rate compared to targeted panels underscores the impact of gene selection and reporting criteria on screening outcomes. In Australia, the BabyScreen+ study evaluated whole-genome sequencing in 1,000 newborns, targeting 605 genes associated with early-onset, treatable conditions. Sixteen infants (1.6%) were identified with actionable findings, most of which were not detected by standard screening (4). Parental acceptability was extremely high, with more than 99% of participants supporting the availability of genomic screening for all parents and their newborns, and psychosocial impact was minimal, with low levels of decisional regret reported.

Cross-study signals: consistency in performance, divergence in panel design

Despite important differences in populations, gene panels, sequencing technologies, and baseline screening programs, a remarkable convergence emerges across studies. In BabyDetect, the overall screen-positive rate was 1.8%. When excluding G6PD deficiency, the screen-positive rate was 0.7%. Similarly, the GUARDIAN authors reported that, when excluding G6PD deficiency, the frequency of positive genomic screening was 0.6%, compared with 0.3% for traditional newborn screening in New York State. This convergence is noteworthy given the differences in panel composition, study design, and reporting policies. It suggests that targeted genomic newborn screening may yield relatively consistent positivity rates across programs when comparable inclusion

criteria are applied. These empirical yields can also be interpreted in light of epidemiological estimates for early-onset rare single-gene disorders. In BabyDetect, the screen-positive rate after exclusion of G6PD deficiency and cardiomyopathy-associated findings subject to refined reporting criteria is approximately 0.5%. This closely aligns with Blencowe et al.'s modelled baseline birth prevalence of early-onset rare single-gene disorders, approximately 4.5 per 1,000 births, or 0.45% (5). Parental acceptance of genomic newborn screening is also consistently high across major pilot studies, including the Belgian BabyDetect study, in which acceptance exceeded 90%. In addition to acceptability, reliability appears robust. Rates of false positives and false negatives remain low when conservative variant filtering strategies are applied. However, this approach may lead to underreporting of uncertain or borderline variants, reflecting a deliberate trade-off between sensitivity and specificity. Together, these data indicate that the central scientific question is no longer feasibility alone, but rather how to define the appropriate scope, governance, and evaluation framework of gNBS. At the same time, one major source of uncertainty remains the marked heterogeneity in condition and gene selection across existing programs. A recent comparative analysis identified more than 25 gNBS initiatives worldwide, highlighting substantial variability in design, sequencing strategy, target population, and genes screened (6). One of the most striking findings from this international comparison is the heterogeneity in gene selection. Across 27 programs, the number of genes analysed ranges from 134 to more than 4,000, with only 1.7% of genes shared by more than 80% of programs. This heterogeneity is informative: it reflects both the momentum of the field and the absence of consensus, underscoring the need for harmonization.

Discussion

Belgium as a Pioneer in Genomic Screening

Belgium is not entering this discussion from the sidelines. The country has already played a pioneering role in the implementation of genetic newborn screening, particularly through spinal muscular atrophy (SMA) screening, and has made major contributions to demonstrating both its clinical and medico-economic value. Early Belgian initiatives, notably the 2018 pilot program in Southern Belgium, were among the first large-scale European efforts to systematically screen newborns for SMA (7). This program rapidly expanded and transitioned into an official screening program, illustrating Belgium's leadership in translating screening innovation from research into public health practice. Importantly, this program has demonstrated huge health economic efficacy. The Belgian experience provided robust real-world evidence supporting the clinical effectiveness of early detection. SMA screening enabled identification of affected infants before symptom onset and to initiate treatment within the first weeks of life, which is a critical determinant of therapeutic success (8). This led to markedly improved outcomes compared with symptomatic diagnosis, including survival, motor development, and reduced need for ventilatory or nutritional support. These findings aligned with broader international evidence that presymptomatic treatment dramatically modifies disease trajectory. Beyond clinical effectiveness, Belgium has also been instrumental in evaluating the economic impact of SMA screening. Studies based on Belgian cohorts demonstrated that early identification through gNBS is associated with improved quality of life and reduced healthcare burden compared with later diagnosis (9). Importantly, cost-effectiveness analyses using real-world Belgian data showed that SMA screening combined with early treatment yields substantial gains in quality-adjusted life years, is cost-effective from a healthcare perspective, and even cost-saving from a societal perspective (10). These analyses incorporate not only medical costs but also caregiver burden, further strengthening the case for screening. This experience is directly relevant to the debate on genomic newborn screening. It shows that moving from pilot implementation to public policy requires more than technical feasibility: it requires demonstration of clinical benefit, operational integration, and long-term economic value. Belgium's early adoption and comprehensive evaluation of SMA gNBS have influenced global implementation. It was among the first countries to screen a significant proportion of newborns before nationwide adoption became more widespread, thereby contributing to international momentum toward broader screening programs. Overall, Belgium has been central in establishing both the clinical benefits and economic justification of SMA newborn screening, supporting its integration into public health systems worldwide. In that respect, the BabyDetect program extends Belgian leadership from single-disease molecular screening to panel-based genomic screening. By generating Belgian data on feasibility, acceptability, workflow integration, and the yield of actionable findings, BabyDetect shows that the value of gNBS lies not only in the sequencing panel itself, but also in demonstrating how screening, confirmation, counselling, and early specialist referral can be integrated within a real healthcare system. This places Belgium in a particularly strong position to contribute to the next phase of this debate.

Key Challenges and Open Questions

The scientific promise of gNBS should not obscure the fact that several important challenges remain before broader public implementation. Technical feasibility alone is not sufficient: condition selection, interpretation policy, economic evaluation, governance, and equity must all be addressed within a coherent public-health framework.

1. Define transparent criteria for condition selection. Condition and gene selection remain insufficiently harmonized. As demonstrated by Minten et al., there is striking variability in the genes included across programs (6). This reflects the lack of an agreed framework for determining which disorders are sufficiently severe, sufficiently actionable, and sufficiently childhood-onset to justify population screening. However, this is not unique to genomic screening as even traditional metabolic screening panels differ between countries or regions. Given that genomic NBS is a relatively recent development (less than 5 years), such variability is expected. Ongoing international collaboration will be essential to support harmonization while acknowledging that some differences will necessarily remain across settings considering treatment availability, health-system capacity and care pathways.

2. Define clinical pathways before implementation. Beyond panel composition itself, genomic newborn screening requires predefined pathways for confirmatory testing, specialist referral, counselling, and access to treatment. This is particularly important when screening identifies conditions requiring rapid intervention or family-based assessment. Without such pathways, genomic screening risks generating results that cannot be translated into timely clinical benefit.

3. Risk of False Positives and False Negatives. Test performance depends not only on sequencing quality but also on interpretation policy. False positives are an inherent risk in any screening program. In genomic screening, this risk is influenced by variant interpretation and reporting thresholds. Conversely, false-negative results may result from technical limitations, incomplete coverage of selected genomic regions, limited detection of specific variant classes, or the exclusion of genes and variants from the reporting framework. Conservative pipelines that report only pathogenic or likely pathogenic variants reduce false-positive findings and downstream anxiety, but they may also miss some affected children. This sensitivity-specificity trade-off should be made explicit and evaluated prospectively rather than handled implicitly within bioinformatic workflows.

4. Medico-Economic Impact. The medico-economic case is not yet established at population level. While traditional NBS has demonstrated clear economic benefits, genomic screening involves higher upfront costs and a much broader range of conditions. The overall value proposition of a broad genomic panel depends on long-term outcomes, downstream investigations, treatment access, healthcare utilization, and family impact. Medico-economic evaluation should also consider the position of gNBS within the broader landscape of genomic testing across the life course. Prenatal carrier screening, diagnostic sequencing in symptomatic children or adults, conventional and genomic newborn screening, and family cascade testing address related but distinct clinical questions and should be considered as complementary components of genomic medicine. However, coordinated pathways, shared infrastructure, and clear rules for data use and reinterpretation may reduce duplication and support efficient use of healthcare resources. In this context, gNBS may also reduce healthcare burden by identifying actionable conditions before symptom onset, shortening diagnostic odysseys, and avoiding sequential investigations after clinical presentation. Future evaluations will therefore require large populations and long-term follow-up to capture not only sequencing costs, but also confirmatory testing, avoided diagnostic investigations, follow-up, family-based assessment, data storage, reinterpretation, and care-pathway organization (11–15).

5. Optimal Sequencing Strategies. The choice of technology remains debated. Targeted next-generation sequencing currently offers advantages in cost control and interpretability, but with limited flexibility regarding potential additional genes/diseases, whereas whole-exome and whole-genome sequencing offer broader coverage and future reusability of data but generate additional challenges related to storage, interpretation, and governance. Though sequencing costs are rapidly decreasing, data storage, security, and long-term governance remain critical concerns.

6. Societal Impact, Education, and Counselling. The implementation of gNBS raises societal questions that extend beyond parental acceptability. Its public-health objective remains aligned with conventional newborn screening: the early identification of serious conditions before clinical presentation. As genomic technologies are integrated into this framework, information and counselling procedures will need to address consent, variant interpretation, residual risk, familial implications, data

governance, and the definition of reportable results (16,17). The BabyDetect feasibility study illustrates that structured information can be embedded in implementation through dedicated materials and trained consent procedures(1). At population level, this will require adequate training of healthcare professionals involved in prenatal, maternity, neonatal, paediatric, genetic, and primary care, and should be evaluated prospectively together with psychosocial impact, equity of access, and clinical utility (16,18).

7. Transition from Pilot Evaluation to Public Health Policy. Transitioning from pilot studies to publicly funded programs will require robust evidence, including clinical effectiveness, cost-effectiveness, ethical and societal acceptability. Given the scale of data required, this transition is likely to take time. At the same time, this transition is no longer purely theoretical: some jurisdictions have already begun to implement publicly supported or region-wide genomic newborn screening initiatives, including Puglia in Italy and Abu Dhabi in the United Arab Emirates, while in the United States, some state-level programs such as Florida have introduced publicly financed genomic sequencing in neonatal or infant care pathways (19–21). In Belgium, genomic screening is also beginning to enter clinical practice through BabyDetect, a prescription-based test costing approximately €650 and partially reimbursed by some insurance organizations. This type of trajectory is not unprecedented, as similar patterns have been observed with non-invasive prenatal testing (NIPT), carrier screening (which remains largely self-funded), and some vaccines such as meningococcal conjugated vaccines, where individual access preceded broader reimbursement. This development nonetheless raises important questions about equity and access, as preventive medicine introduced through individual pathways may increase disparities before broader public implementation becomes possible. These disparities are not only financial: unequal access to information, awareness, and counselling may also restrict genuine freedom of choice, since some families may not even know that such screening exists or may not be equally supported in understanding its benefits and limitations. In that sense, access prior to public funding may represent a transitional phase in the integration of new preventive strategies, but cannot replace the need for an equitable population-based strategy.

Conclusion

Genomic newborn screening represents a major evolution in neonatal healthcare. Emerging evidence from international and Belgian studies suggests that it can complement conventional newborn screening by identifying severe, actionable childhood-onset conditions that are not accessible to biochemical screening alone. The field has therefore reached a stage at which the central question is no longer technical feasibility in isolation, but how genomic screening should be defined, evaluated, and governed within a public health framework. Several uncertainties remain before broad implementation can be justified, including the selection of screened conditions, the balance between sensitivity and specificity in variant interpretation, the long-term clinical and psychosocial consequences of screening, the medico-economic impact at population level, and the preservation of equitable access. Addressing these issues will require large-scale prospective evaluation and sustained follow-up. Belgium is well positioned to contribute to the next phase of gNBS evaluation. Through its experience in neonatal molecular screening, its work in SMA screening and the BabyDetect pilot program, it has already generated important real-world evidence within its own healthcare context. The next phase should focus on consolidating and extending this evidence base, necessary to inform policy decisions. In practical terms, future efforts should focus on two priorities. First, ensuring that healthcare professionals involved in prenatal, maternity, neonatal, paediatric, genetic, and primary care are adequately informed about the benefits, limitations, and clinical pathways of gNBS is essential, so that unequal access to information does not itself become a source of inequity. Second, the establishment of a large-scale, publicly funded pilot program at the federal level based on multidisciplinary collaboration and integrated medico-economic assessment appears essential to generate the evidence needed to guide the future integration of genomic screening into public health systems.

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Paediatric Pharmacotherapy for Common Obesity: Position Statement of a Tertiary Multidisciplinary Paediatric Rehabilitation Centre for Chronic Diseases

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Introduction

Childhood and adolescent obesity has reached epidemic proportions, representing one of the most pressing chronic health challenges worldwide. In our tertiary multidisciplinary paediatric rehabilitation centre, more than 50% of the admitted children present with obesity as part of their complex care needs. These children often belong to a subgroup that responds poorly to ambulatory lifestyle interventions (LI) alone. Indeed, the IMI-SOPHIA study showed that ambulatory LI have a limited effect in older children and adolescents with severe obesity who come from disadvantaged socioeconomic backgrounds and have a history of migration (1).

Our own results, as a tertiary paediatric rehabilitation centre illustrate the effectiveness of intensive LI in a residential setting. In a cohort of 295 adolescents 12-18 years (mean age: 14.9 ± 1.7 years) with obesity treated in 2023-2024, the average weight loss was 17.5 ± 11.6 kg, corresponding to a 15.3 ± 8.7% reduction from baseline weight and a body mass index (BMI) reduction of – 6.5 ± 4.1. Fat mass percentage also decreased significantly: in patients with a stay of less than 10 months, the average body fat percentage decreased from 50% to 43% (–7%), and in patients with a stay of more than 10 months, it decreased from 53% to 41% (–12%).

These results are in sharp contrast to outpatient programmes whose outcomes vary significantly depending on the age of the population. Indeed long-term, multidisciplinary LI can significantly improve BMI and cardio-metabolic health parameters in children with severe obesity, while adolescents show less pronounced benefits—highlighting the importance of early intervention (2-5). A recent longitudinal study confirmed this, showing that children responded significantly better than adolescents to a tailored lifestyle programme, both in terms of BMI reduction and metabolic improvements (6). Systematic review reported that adolescents in intensive outpatient LI programmes (>26 contact hours) achieved an average weight loss of only 1.9 kg over a median period of 6 months (7). Residential LI such as ours therefore offers significantly greater benefits.

However, intensive lifestyle intervention programmes do not always lead to meaningful results or outcomes that patients perceive as significant. Moreover, weight regain is often observed in the longer term—further emphasising the chronic and relapsing nature of obesity. So other strategies should also be considered.

Rather than viewing treatment as a stepwise process, current guidelines recommend the use of obesity management medication (OMM) along with lifestyle intervention, motivational interviewing and psychosocial support to optimize outcomes for children living with obesity aged 12years or older (8,9). In this context, Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as promising therapeutic options, and our centre is preparing to implement them in a structured manner, aligned with national and international guidance.

Other medications such as orlistat, phentermine have already been approved in the US for use in adolescents with obesity over the age of 12, but not in Europe

(10). Setmelanotide is reserved to specific monogenic or syndromic (Bardet-Biedl) obesities and will not be discussed here. For this reason, we will limit ourselves to GLP-1 Ras.
In this paper, we first review the literature, then we describe our own vision.

Efficacy of GLP-1 Receptor Agonists in Adolescents

When combined with lifestyle changes, both liraglutide and semaglutide have been shown to be successful in inducing weight loss in adolescents. The STEP-TEENS study reported an average BMI reduction of 16.1% with semaglutide, compared with a change of 0.6% in BMI in the placebo group after 68 weeks, with 44.9% versus 12.1% of patients achieving normalisation of BMI, respectively (11,12). Liraglutide also showed a significant but more modest 5% reduction in BMI in the SCALE-TEEN study (13). Moreover, greater BMI reduction appears to be achieved when treatment is initiated early in life, as liraglutide induced a −7.4% BMI reduction in children aged 6–12 years compared with a −4.6% reduction in adolescents aged 12–18 years (14).
Furthermore, in the STEP-TEENS study, improvements in cardio-metabolic risk factors (waist circumference, glycated haemoglobin, lipids [except high-density lipoprotein cholesterol] and alanine aminotransferase) were greater with semaglutide than with placebo. These findings are clinically relevant, as BMI, triglycerides and total cholesterol levels have all been identified as childhood risk factors associated with later cardiovascular events in adulthood. In addition, an improvement in weight-related quality of life was observed, mainly due to an improved Impact of Weight on Quality of Life – Kids (IWQOL-Kids) score for physical comfort, which was not observed in the previous study of liraglutide in adolescents with obesity.
It is important to note that the effects of these medications on weight loss and obesity-related comorbidities are observed in combination with lifestyle intervention. There is insufficient evidence to support OMM as monotherapy in adolescents, i.e. without a multidisciplinary treatment strategy, as was demonstrated once again in a recent study (15).
In adults, GLP-1 RAs associated with LI have been shown to enhance weight loss and to maintain weight loss for 2 years, but weight rebound was observed after discontinuation of the medication (16). Therefore, GLP-1 RAs may need to be continued long-term to support a chronic disease management paradigm similar to that of hypertension or diabetes. Encouragingly, real-world data from Qatar, presented at the European Congress on Obesity 2025, show that adolescents treated with liraglutide achieved significant reductions in BMI and maintained weight loss even after discontinuing treatment, with no significant difference in outcomes between those who adhered to therapy (BMI -6.5 ± 17.2) and those who discontinued (-3.9 ± 16.5) (17). In adults as in adolescents with obesity, semaglutide appears to offer a significantly greater chance of greater reduction in actual weight and BMI compared to placebo and liraglutide (18,19). A recent review confirmed semaglutide as being the most effective and safe option of four GLP-1 RAs tested (semaglutide, exenatide, liraglutide and dulaglutide) in children and adolescents with type 2 diabetes or obesity. Such evidence in youth with obesity without diabetes is more limited, though preliminary data also suggest beneficial effects (20).
In addition, the once-weekly administration of sema-glutide offers greater convenience and potentially better adherence compared to the daily administration required for liraglutide. The oral form of semaglutide has been shown to be safe and effective in adults, but unfortunately, there is no information available on its use in adolescents.
Although dual agonists such as tirzepatide (Mounjaro®) have demonstrated even greater weight loss in adults compared to semaglutide, paediatric trials are still ongoing and regulatory approval for this population is still pending. Until more evidence becomes available, semaglutide remains our preferred option for the pharmacological treatment of adolescents with common obesity and liraglutide for 6-12y old children living with obesity.

Changes in food preferences and eating behaviour after GLP-1 Therapy

GLP-1 RAs not only reduce appetite but also influence reward behaviour and food preferences. Functional MRI studies in adults have shown that during the weight loss phase of treatment with GLP-1 RAs neuronal responses to signals from high-calorie foods in the insula, amygdala, putamen and orbitofrontal cortex decrease(21). Adolescents report less craving for dairy and starchy food, smaller meal sizes and a reduced preference for energy-dense foods (22,23).
While these effects in weight loss phase are promising, few data on the persistence of these effects in the weight maintenance phase are available. Reward-based eating—reinforced by an immature prefrontal cortex—remains a challenge in adolescence. This underscores the need for additional and ongoing behavioural and nutritional counselling in addition to pharmacotherapy. Our centre integrates cognitive behavioural therapy as a fundamental pillar of our obesity care which also includes psychosocial support, self-regulation strategies, and motivational interviewing.

Safety, Side Effects, and Long-Term Considerations

The GLP-1 RAs are generally well tolerated. Gastrointestinal symptoms - including nausea, vomiting, constipation, diarrhoea - are the most reported, particularly during the dose escalation phase (11-13). Serious adverse events appear to be rare but there are currently only relatively short-term data available.

However, caution is advised. A higher risk of intestinal obstruction, gastroparesis and pancreatitis was demonstrated in adults living with obesity receiving GLP-1 RAs. Concerns have been raised about an increase in thyroid neoplasia and hyperplasia in adults with diabetes treated with GLP-1 RAs compared with those receiving sodium-glucose cotransporter (SGLT)-2 inhibitors, but more recent data do not confirm an increased risk of thyroid tumours with GLP-1 RAs exposure (24-26). There is a strong need for observational data in children and adolescents to investigate whether these observations in adults may also be relevant for children and adolescents. Therefore, it is crucial that OMM data from practice are documented in registries for children and adolescents with obesity at national and international level.
Little is known about the long-term effects. Starting treatment for OMM at this crucial stage of life can have various effects on healthy growth, such as brain development, and on possible future health risks, such as mental disorders or cancer.

Nutritional and Functional Implications

When combined with the new OMM, the focus of LI may shift from solely promoting weight loss through calorie restriction to encouraging healthier food choices and increased physical activity. This approach supports optimal changes in body composition, enhances overall health and contributes to improved quality of life for patients. For LI in combination with OMM, some evidence and guidance are available for adults but are lacking for adolescents. Nutritional recommendations for healthcare providers supporting adults with obesity who are receiving OMM were recently published (27). According to these guidelines, it is advised to identify any pre-existing nutritional risk factors early on to help prevent adverse outcomes such as malnutrition or the development of eating disorders. During OMM treatment, patients should be closely monitored to address potential deficiencies in fluid or (micro)nutrient intake and to better manage side effects. For instance, it is recommended to avoid high-fat foods, such as fried items, to reduce gastrointestinal discomfort.
Maintaining or even increasing skeletal muscle mass during weight reduction is crucial for overall health, metabolic function, and long-term weight loss maintenance (28). The potential loss of muscle mass during GLP-1 RAs treatment remains a concern. Recent meta-analysis suggests that reductions in fat-free mass (FFM) account for approximately 25–39% of the total weight loss observed with GLP-1 RAs and GLP-1/GIP (Glucose-dependent Insulinotrophic Polypeptide) receptor co-agonists (29,30). This is consistent with the reported percentage of FFM loss with other forms of weight loss (diet-induced or bariatric surgery-induced), indicating that GLP-1 RAs do not exert an additional effect on the proportion of FFM lost (31,32). However, FFM, which is usually measured by dual-energy x-ray absorptiometry (DEXA) in these studies, is only a crude surrogate for skeletal muscle mass. FFM encompasses not only muscle mass but also organs, bone, fluids, and water in fat tissue and it does not capture muscle function or volume. Therefore, the clinical relevance of these changes remains uncertain (33).
At the time of writing, there are no data to establish whether treatment with GLP-1 RAs is associated with physical frailty or sarcopenia (28). No paediatric randomized controlled trials have yet been conducted in which changes in muscle mass, strength or physical performance during GLP-1 RAs therapy have been directly measured. Given the existing research gaps, it is advisable when initiating GLP-1 RAs therapy such as semaglutide in children and adolescents, to monitor body composition (e.g., via DEXA or bioimpedance) and muscle function (e.g. strength testing) in addition to body weight.
Moreover, preservation of muscle mass should be regarded as a key therapeutic objective, parallel to the goals of reducing adiposity and weight-related complications. Beyond appetite regulation, sustainable weight loss requires strategies that support energy expenditure, fat oxidation and lean mass preservation. This underscores the importance of integrating resistance exercise and adequate protein intake alongside pharmacotherapy (34). As demonstrated in older adults, combining protein-rich nutrition with resistance training can help mitigate potential muscle loss (35). Participants randomized to liraglutide 3.0 mg daily plus resistance exercise for one year exhibited a lower percentage FFM loss compared with those receiving drug therapy alone (24.7% vs. 38.6%) (36). Thus, a multidisciplinary approach involving a dietitian and a physical therapist should be integrated into OMM therapy to optimize outcomes, prevent weight cycling and consequently reducing the risk of developing sarcopenic obesity (37). New medications such as selective androgens receptor modulators (SARM) or myostatin-activin pathways inhibitors are currently under development to help preserve skeletal muscle mass (38).
However, the observed loss of FFM may also reflect a reduction in intramuscular fat rather than true loss of contractile muscle tissue, as FFM reductions associated with GLP-1 RAs have not been linked to declines in physical performance (39). In line with these findings, a recent study using MRI to assess muscle volume and composition showed that GLP-1/GIP agonist therapy reduced intramuscular fat infiltration in individuals with type II diabetes after 52 weeks of treatment, without evidence of increased muscle loss (40). Another MRI-based sub-study assessed muscle quality in 128 women living with obesity but without diabetes. They found that, compared with placebo, liraglutide reduced (thigh) muscle fat by 7.8% from baseline, and that the presence of adverse muscle composition (high muscle fat and low muscle mass) decreased compared to controls (41). In fact, excessive deposition of adipose tissue within skeletal muscle (intramuscular adipose tissue, IMAT) also referred as myosteatosis, is a known cardiovascular risk

factor and is associated with insulin resistance, aging, poor muscle quality and reduced mobility. Thus, GLP-1 RAs may improve muscle composition despite concomitant reductions in muscle mass.
Evidence-based recommendations on how to adapt LI to different phases of OMM treatment along the obesity treatment chain are warranted.

Patient Selection and Clinical Integration of GLP-1 RAs Therapy in our Paediatric Rehabilitation Centre

A. For adolescents (≥12 years) who were not taking GLP1-RAs upon admission to our rehabilitation centre, GLP-1 RAs therapy should be considered during hospitalization:

1) After 3 months of intensive LI if:

   a) Persistent obesity, is present, defined as:

      i) BMI ≥IOTF35 (International Obesity Task Force threshold corresponding approximately to adult BMI ≥35) or
      ii) BMI ≥IOTF30 with ongoing obesity-related comorbidities such as (42):

         (1) insulin resistance, defined as HOMA-IR > P90 for age (43).
         (2) metabolic dysfunction-associated steatotic liver disease (MASLD), defined according to the NASPGHAN clinical practice guidelines (44).
         (3) obstructive sleep apnoea (OSA) diagnosed by polysomnography (45,46).
         (4) hypertension defined as blood pressure values above the 95th percentile (47).

   b) Satiety phenotype is identified, characterized by abnormal satiety (i.e., reduced duration of fullness after meals) (48).

2) At any time beyond 3 months during the stay, if:

   a) Weight loss plateaus AND

   b) BMI remains ≥ IOTF 30.

In practice: all patients (≥12 years) admitted to our rehabilitation centre without prior pharmacotherapy begin with an intensive LI program.
After 3 months, weight evolution is evaluated. If predefined criteria are met, semaglutide initiation is considered with dosage titrated guided by clinical response and tolerability, up to a maximum of 2.4 mg/week. Dose escalation to the maximal dose is not mandatory if adequate weight loss and improvement of obesity status are achieved at lower doses. The rate of weight loss, side effects, and achievement of a BMI within the normal range for age and sex are considered during titration. During the maintenance phase, tapering may be considered if increased physical activity and sustained weight loss are achieved (35).
Before starting treatment, realistic goals, expectations, and potential side effects will be discussed with the patient and their family. The patient's motivation and overall wellbeing will be carefully considered in the decision-making process.
Beyond its metabolic benefits, the LI program offers significant psychopedagogical value: it fosters self-awareness, builds coping strategies, and promotes long-term behavioural change. This holistic approach not only supports physical health but also enhances emotional resilience and quality of life (49,50). Importantly, lifestyle intervention will always remain the cornerstone of our treatment strategy, regardless of pharmacological support.
Upon initiation of the medication, patients will be informed of the importance of attending regular follow-up consultations after their stay in our centre. These follow-ups will focus on clinical and behavioural monitoring, including assessments of weight, side effects, and treatment adherence. It will also be clearly communicated that GLP-1 RAs therapy is a long-term treatment strategy, with significant financial implications. Monthly costs may typically range from 145 to 190 euros which may represent a significant long-term financial challenge for most families (51). This information is essential to support informed decision-making and ensure sustained engagement with the treatment plan. Financial feasibility is a key determinant. If the family cannot afford to continue therapy for at least 6–12 months post-discharge, initiation may be postponed to avoid early discontinuation and rebound weight gain.

B. Adolescents (≥12 years) who were already receiving GLP-1 RAs upon admission and had achieved a decrease of ≥4% in BMI or BMI-z-score after 3 months on the medication preceding admission to the Zeepreventorium, will continue the medication during their hospitalisation. For patients who did not achieve a significant reduction in BMI during previous GLP-1 RAs therapy, the care team will evaluate treatment adherence and assess whether the appropriate therapeutic dose was reached, with the aim of considering a potential reinitiation of the treatment.

Our Institutional Commitment

As a tertiary care centre, we support the continuation of GLP-1 RAs therapy initiated by second-line paediatric obesity centres (PMOCs). Conversely, when treatment is initiated within our rehabilitation centre, we ensure a structured transition back to secondary care. This includes the transfer of DEXA scan results, progress metrics, and a comprehensive multidisciplinary follow-up plan. Shared decision-making and transparent communication with families remain essential throughout all stages of care.

We advocate for a cautious, guideline-driven implementation within specialized care settings and highlight the need for longitudinal outcome research, especially in pre-adolescent and adolescent populations.
We recognize our multifaceted role in clinical care, conducting research studies, contributing to national policy committees, and disseminating knowledge.
We commit to:

- Integrating pharmacotherapy in alignment with the latest clinical guidelines.
- Contributing to national registries and advancing real-world outcome research.
- Collaborating with academic institutions to address data gaps in paediatric obesity care.
- Collaborating with second-line PMOCs and first-line providers through joint care pathways.
- Advocating for reimbursement for OMM in paediatric care within specialized centres. Initiation of OMM should always occur under the supervision of an experienced healthcare professional.

Conclusion

When embedded within a patient-centred, comprehensive care model, grounded in behavioural, nutritional, physical, and psychosocial support, GLP-1 pharmacotherapy represents a pivotal advancement in the management of paediatric obesity. In our setting, these medications can play a valuable role in supporting adolescents with severe obesity as they engage in lifestyle interventions.
This pharmaco-therapeutic approach must be individualized and sustained over time to maximize benefit and minimize the risk of rebound. It also reflects our centre's broader commitment to equitable access, long-term continuity of care, and improved health trajectories for children and adolescents with complex obesity.
As a rehabilitation centre, we recognize our responsibility in guiding the safe and equitable use of long-term GLP-1 RAs therapy. These treatments should be initiated only in specialized (second or third line) centres that offer a multidisciplinary LI program. Furthermore, given the high cost and potential financial barriers for families, we are committed to rigorously assessing medical necessity, supporting families in navigating access and reimbursement processes, and advocating for broader systemic solutions to ensure that effective treatment is not restricted by socioeconomic status.

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Beyfortus® (nirsevimab)

Prijs Beyfortus® 2026	
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Prijs terugbetaald (GZ)	12,80€
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BESCHERM

ALLE BABY'S* TEGEN RSV†

†LAGERE-LUCHTWEG AANDOENINGEN VEROORZAAKT DOOR RSV



Patiëntweergave. Dit is een fictief patiëntgeval, uitsluitend bedoeld ter illustratie.

Plan Beyfortus® idealiter vóór aanvang van het RSV-seizoen:

- ✓ Eenmalige injectie voor het hele seizoen (ten minste 5-6 maanden)
- ✓ Dosering op basis van gewicht: 50mg (<5kg) of 100mg (≥5kg)
- ✓ Terugbetaald voor alle baby's in hun eerste RSV-seizoen** en voor kwetsbare kinderen in hun tweede seizoen

SOPHIA

- Geboortedatum: 15 augustus (vóór het RSV-seizoen)
- Geboortestatus: A terme (39 weken), normaal geboortegewicht
- Woont samen met beide ouders en een broer van 3 jaar
- Ging binnen drie maanden na de geboorte naar de crèche
- Was niet beschermd tegen RSV
- Werd in december opgenomen in het ziekenhuis wegens RSV-LRTD

Beyfortus® is het eerste direct langwerkend antilichaam ontwikkeld voor alle baby's[1,*]

Voor al uw vragen scan de QR-code of contacteer: Beyfortus.Belgium@sanofi.com

Sanofi Belgium, MAT-BE-2500985-V3.0-08/2026

†Beyfortus® is geïndiceerd voor de preventie van lagere-luchtwegaandoeningen veroorzaakt door RSV* bij:[1]
i. Pasgeborenen en zuigelingen tijdens hun eerste RSV-seizoen.
ii. Kinderen tot 24 maanden oud die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen.

▾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) (zie rubriek 4.4). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1. **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 <1 kg moeten zorgvuldig worden afgewogen. Er zijn beperkte gegevens beschikbaar over extreem premature zuigelingen (zwangerschapsduur < 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 eertse 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 (zie rubriek 4.4). 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 - Overgevoeligheida a Bijwerkingen uit spontane melding Huid- en onderhuidaandoeningen · Soms – Rashb b Rash is gedefinieerd door de volgende gegroepeerde voorkeurstermen: rash, maculo-papulaire rash, vlekkerige rash Algemene aandoeningen en toedieningsplaatsstoornissen · Soms – Injectieplaatsreactiec ; 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). Kinderen 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 corticosteroiden (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. Voldragen en premature zuigelingen die hun eerste RSV-seizoen beginnen De veiligheid van nirsevimab werd ook beoordeeld in HARMONIE, een gerandomiseerd, multicenter open-labelonderzoek bij 8.034 voldragen en premature zuigelingen (GA ≥29 weken) die hun eerste RSV-seizoen begonnen (en niet geschikt waren voor palivizumab), die nirsevimab (n=4.016) of geen interventie (n=4.018) kregen ter preventie van ziekenhuisopname voor respiratoire syncytiale virusinfectie van de onderste luchtwegen (RSV LRTI). Het veiligheidsprofiel van nirsevimab toegediend in het eerste RSV-seizoen was consistent met het veiligheidsprofiel van nirsevimab in de placebogecontroleerde onderzoeken (D5290C00003 en MELODY). 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: 03/2026. Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau http://www.ema.europa.eu

RSV, Respiratoir Syncytieel Virus; **LRTD,** Lower Respiratory Tract Disease
*tijdens hun eerste RSV-seizoen **Éénmalige terugbetaling voor het eerste RSV-Seizoen en bij jonge kinderen (<2 jaar) die een hartoperatie ondergaan met cardiopulmoniare bypass in hun eerste of tweede RSV-seizoen, of jonge kinderen (<2 jaar) die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen, (zoals beschreven in de aanbevelingen van de HGR (advies 9760)). Toediening voor de start van het RSV-seizoen of vanaf de geboorte voor zuigelingen geboren in het RSV-seizoen.
Referentie: 1. Beyfortus® SKP, 03/2026.

sanofi

Belg J Paediatr. 2026;28(3):341-344

04/07/2026

Prof. Dr. Stéphane Moniotte
President

Dr. Wim Arts -Dr. Pierre Philippet
Vice - Presidents

Minutes of the General Assembly – BAoP

Belgian Academy of Paediatrics
Date: 20 March 2026
Time: 08:30 – 09:30

1. Opening and Welcome

The General Assembly was opened with a welcome to all participants.

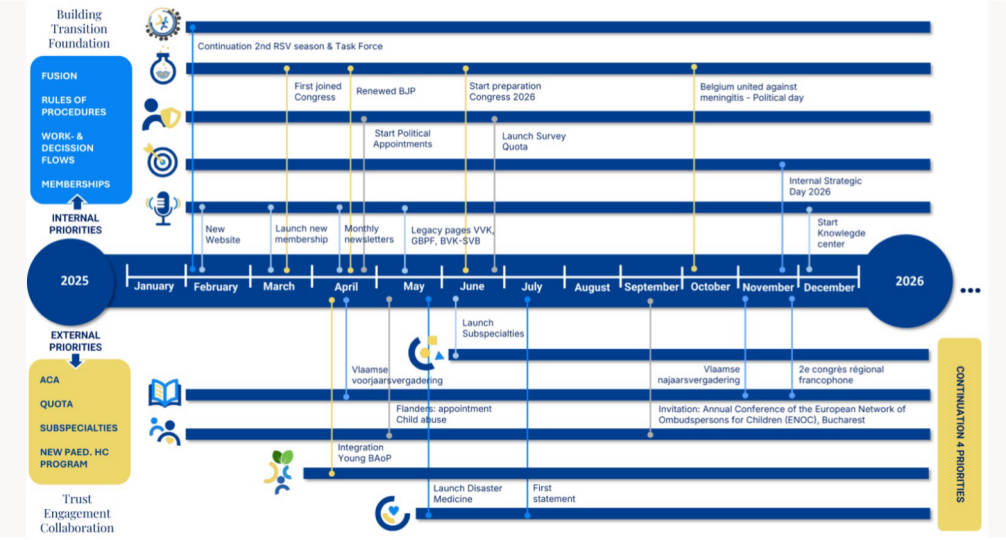
2. Approval of the Agenda

The agenda was presented and approved.

3. President's Annual Report (2025)

The President presented the annual report on behalf of the Board members, covering:

- Current membership status: 821 active members
- Strategic priorities
- Advocacy efforts
- Activities and collaborations
- Key achievements over the past year:



External priorities:

- Nomenclature remuneration (ACA)
- Subspecialty
- Quotas
- Development of new paediatric healthcare programs

4. Approval of the Rules of Procedure

The updated Rules of Procedure were presented and approved.

5. Treasurer's Annual Report (2025)

The Treasurer presented the current financial overview.

The accountant's balance will be delivered end of June → an General Assembly will be planned (Report below)

Proposed remuneration for 2026:

- President: €2,000/month
- Vice-Presidents: €1,000/month
- Treasurer: €500/month

Other financial decisions:

- Adjusted membership fees (e.g. free for first-year trainees, reduced fees for fellows and executive committee members)
- To discuss in the future:
    - Subspecialities affiliated
    - BJP reviewers
- Support allocations:
    - Young BAoP: €3,000 (+ €2,000 regional support)
    - Taskforces: €3,000

7. Taskforces – Updates

Scientific Taskforce

Focus on coordinating and supporting scientific activities nationally and internationally. Active working groups include:

- Guidelines, Choosing Wisely (with YBAoP)
- Nutrition, fluid therapy, climate, vaccination

Young BAoP

Key activities:

- Coordination of training courses (NLS, APLS)
- Organization of graduation symposia
- Development of national guidelines
- Survey on paediatric training differences in Belgium

8. Elections – Board 2026–2030

The General Assembly has elected the following Board members:

Wim Arts,An Bael, Jean-Christophe Beghin, Gunnar Buyse, Stefanie Buyse, Ann De Guchtenaere, Heidi De Vos, Marie-Françoise Dresse, Els Duval, Jonas Dewulf, Jean Evrard, Inge Gies, Levi Hoste, Marie Hoyoux, François Kanen, Stéphane Moniotte, André Mulder, Robert Müller, Luc Pattyn, Pascale Perlot, Pierre Philippet, Michel Pletinckx, Marc Raes, Pierre Smeesters, Sabine Van Daele, Amber Van Baelen, Nathalie Van Hoorebeeck

The Roles (President, Vice-Presidents, Treasurer, Taskforce Chairs, etc.) will be elected by the new board and published on the website.

9. Strategic Discussion

Members were invited to provide input and feedback on future priorities and initiatives.

10. Closing and Acknowledgements

The continued growth of BAoP was highlighted and the session concluded with acknowledgements and appreciation for contributions.

We would like to express our sincere appreciation to the members of the previous board for their dedication over the past years. Their hard work and commitment have played a key role in the development and functioning of our association and have helped pave the way for the future of the BAoP.

Minutes of the General Assembly – BAoP -July

Belgian Academy of Paediatrics
Date: 4 July 2026
Time: 09:30 – 10:00

Annual Report – Treasurer's Report

The Treasurer presented the annual financial report. Following the merger, the bank accounts of the former societies were integrated into the Belgian Academy of Paediatrics (BAoP), resulting in a total of eight bank accounts. Considerable work has been required to regularize and consolidate these accounts.

It was noted that, from next year onwards, the financial responsible for each subaccount will be able to present a separate financial report for their respective account.

An overview of the general account was presented.

Approval of the 2025 Accounts

The consolidated 2025 accounts, including all eight bank accounts, were presented to the General Assembly and approved.

Approval of the 2026 Budget

The proposed budget for 2026 was presented and approved by the General Assembly.

Discharge of the Board of Directors

The General Assembly granted discharge to the members of the Board of Directors for the financial year 2025.

No additional items were raised, and the meeting was closed.

Prof. Dr. Stéphane Moniotte	Dr. Wim Arts	Dr. Pierre Philippet
		
President	Vice-President	Vice-President

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Beyfortus® (nirsevimab)

Prix Beyfortus® 2026	
Prix publique, TVA incluse	613,86€
Prix remboursé (AO)	12,80€
Prix remboursé (AP)	8,50€

PROTÉGEZ

TOUS LES BÉBÉS* CONTRE LE VRS†

†INFECTIONS DES VOIES RESPIRATOIRES INFÉRIEURES (VRS)



Portrait de patient.
Il s'agit d'un cas patient fictif créé à des fins illustratives uniquement.

Planifiez Beyfortus® idéalement avant le début de la saison VRS :

- ✓ Injection unique pour toute la saison (au moins 5-6 mois)
- ✓ Dosage basé sur le poids : 50mg (<5kg) ou 100mg (≥5kg)
- ✓ Remboursé pour tous les bébés lors de leur première** saison VRS et pour les enfants vulnérables lors de leur deuxième saison

SOPHIA

- Date de naissance : 15 août (né avant la saison du VRS)
- Statut à la naissance : À terme (39 semaines), poids de naissance normal
- Vit avec ses deux parents et un frère de 3 ans
- A commencé la crèche avant l'âge de 3 mois
- N'a pas été protégé contre le VRS
- A été hospitalisé en décembre en raison d'une VRS-IVRI

Beyfortus® est le premier anticorps direct à action prolongée conçu pour tous les bébés.[1,*]

Sanofi Belgium, MAT-BE-2500985-V3.0-08/2026

Pour toutes vos questions, scannez le code QR ou contactez: Beyfortus.Belgium@sanofi.com

†Beyfortus® est indiqué pour la prévention des infections des voies respiratoires inférieures dues au virus respiratoire syncytial (VRS) chez[1]:
i. Les nouveau-nés et les nourrissons lors de leur première saison à risque de VRS
ii. Les enfants jusqu'à l'âge de 24 mois qui restent vulnérables à une infection sévère à VRS pendant leur deuxième saison à risque

▾Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de la santé déclarent tout effet indésirable suspecté. Voir rubrique 4.8 pour les modalités de déclaration des effets indésirables. **DÉNOMINATION DU MÉDICAMENT** Beyfortus 50 mg solution injectable en seringue préremplie. Beyfortus 100 mg solution injectable en seringue préremplie. **COMPOSITION QUALITATIVE ET QUANTITATIVE** Beyfortus 50 mg solution injectable en seringue préremplie : Chaque seringue préremplie contient 50 mg de nirsévimab dans 0,5 mL (100 mg/mL). Beyfortus 100 mg solution injectable en seringue préremplie Chaque seringue préremplie contient 100 mg de nirsévimab dans 1 mL (100 mg/mL). Le nirsévimab est un anticorps monoclonal humain de type immunoglobuline G1 kappa (IgG1κ) produit dans des cellules d'ovaires de hamster chinois (CHO) par la technologie de l'ADN recombinant. 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) (voir rubrique 4.4). Pour la liste complète des excipients, voir rubrique 6.1. **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 administré par voie intramusculaire pour les nourrissons dont le poids est <5 kg et une dose unique de 100 mg administré 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 sasion 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 contrôlés 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 1 Effet indésirabe rapporté dans le cadre de notification spontanée Affections de la peau et du tissu sous-cutané · Peu fréquent - Eruptions cutanées2 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, oedème 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). Enfants qui demeurent vulnérables à une infection sévère due au VRS au cours de leur deuxième saison de circulation du VRS La sécurité d'emploi a été évaluée au cours de l'étude MEDLEY chez 220 enfants porteurs de maladie pulmonaire chronique du prématuré ou d'une cardiopathie congénitale hémodynamiquement significative qui ont reçu du nirsévimab ou du palivizumab au cours de leur première saison d'épidémie à VRS et qui ensuite ont reçu du nirsévimab lors de leur deuxième saison d'épidémie à VRS (180 sujets ont reçu du nirsévimab pendant les saisons 1 et 2, 40 ont reçu du palivizumab pendant la saison 1 et du nirsévimab pendant la saison 2). Le profil de sécurité du nirsévimab chez les enfants l'ayant reçu pendant leur deuxième saison d'épidémie à VRS était 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. Nourrissons nés à terme et prématurés entrant dans leur première saison à VRS La sécurité d'emploi du nirsévimab a également été évaluée au cours de l'étude HARMONIE, étude multicentrique randomisée, en ouvert, menée chez 8 034 nourrissons nés à terme et prématurés (AG ≥29 semaines) entrant dans leur première saison de VRS (non éligibles au palivizumab), qui ont reçu soit du nirsévimab (n=4 016) soit aucune intervention (n=4 018) pour la prévention des hospitalisations liées aux infections des voies respiratoires inférieures à VRS (IVRI VRS). Le profil de sécurité du nirsévimab administré lors de la première saison de VRS était cohérent avec le profil de sécurité du nirsévimab observé au cours des études contrôlées contre placebo (études D5290C00003 et MELODY). 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 : 03/2026. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu

VRS, virus respiratoire syncytial; **IVRI,** Infection Virale Respiratoire Inférieure

*pendant leur première saison VRS **Remboursement unique pour la première saison VRS et chez les jeunes enfants (<2 ans) qui subissent une chirurgie cardiaque avec circulation extracorporelle pendant leur première ou deuxième saison VRS, ou les jeunes enfants (<2 ans) qui restent vulnérables à une maladie grave due au VRS pendant leur deuxième saison VRS, (comme décrit dans les recommandations du CSS (avis 9760)). Administration avant le début de la saison VRS ou dès la naissance pour les nourrissons nés pendant la saison VRS.

Reference: 1. Beyfortus®. Résumé des Caractéristiques du Produit (RCP) de l'UE, 03/2026

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