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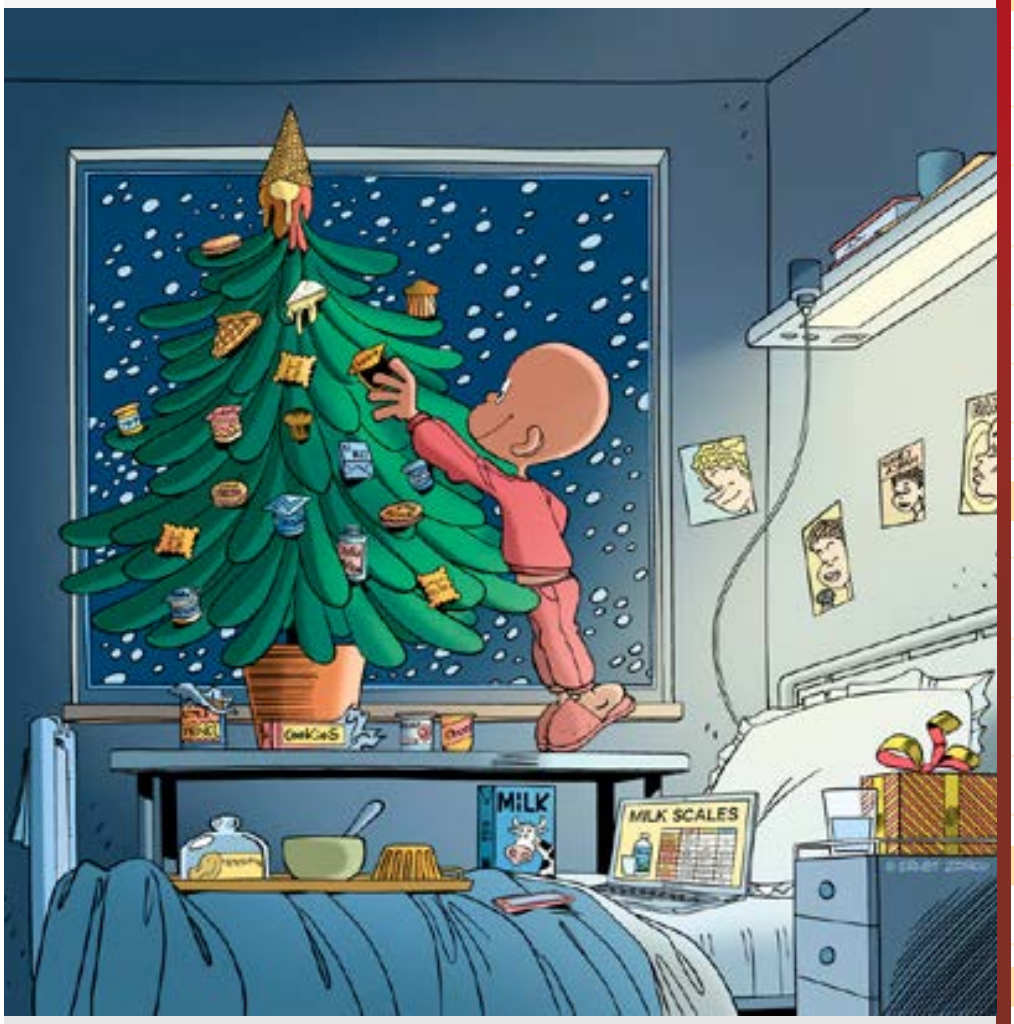


## Articles



## Case Report



## Made In Belgium



## Paediatric Cochrane Corner



Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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# Contents


**DE BVK BEDANKT ZIJN PARTNERS VOOR HUN STEUN**

**LA SBP REMERCIE SES PARTENAIRES POUR LEUR SOUTIEN**

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# Editorial

Happy Holidays !

The year 2021 is slowly giving way to 2022... and with that comes the Holiday season.

Beyond the commercial aspects, this season is a chance to get together, to spend time with family and friends. The SARS-COV-2 virus has disrupted many milestones in our lives. The restrictions it has brought, have made us aware of the importance of social ties for adults and for children. We need relationships, attention and affection. In a modern world advocating independence and freedom, it becomes increasingly clear that family or the belonging to a small supportive group promotes happiness. The progresses we made in our fight against COVID, in particular through the vaccination, should give us some opportunities to celebrate – certainly in an appropriate manner- Christmas and New Year. Some of us may be on duty during these days and may have to postpone their diners or parties. We have a special thought for them. For each of us, and also for all the children we care, we wish to be able to stop for a little while, to leave behind worries and difficulties, to feel surrounded by our loved ones and to be simply together with our families and friends.

This sense of community that we experience in our families is also essential to face the challenges of 2022 and the coming years. Because men and women have been able to collaborate, to pool their strengths, to unite around projects and values, they have been able to build civilizations, to develop and transmit knowledge, to improve living conditions and health. Humans have become leaders of earth and today, we need the same virtues to give a better world for the future generations. In our families, in our work, in our hospital structures, our professional or scientific associations, we observe that trust is essential for for living together. Trust based on information and communication, on listening to others, on competence and commitment. Trust in facts, trust in science and experts, trust in decision-makers and in the directions taken. The events of the last few months have shown us that trust is a dynamic action, a cement that needs to be maintained. Le'ts be aware of this, let's dare to give our trust and be worthy of the trust we receive!

We are confident that you will enjoy this new issue of BJP. It contains several original articles. N. Rodriguez Mier and colleagues compare the clinical evolution and disease burden of children with cystic fibrosis depending on the mode of diagnosis. The impact of the COVID pandemia on early childhood preventive cares (by K. Kastrissianakis and the Collège des conseillers pédiatriques de l'ONE ) and on the parent-child bonding process (by A. Van Loo and MR Van Hoestenberghe) is also analyzed. M. Geeurickx and colleagues described a case series of multisystem inflammatory syndrome in children after SARS-COV-2 infection.

In collaboration with experts, pediatricians in training have also studied and reviewed diagnostic and therapeutic aspects in several disease or conditions: the neuroprotective strategies of neonatal encephalopathy in particular in low-resource countries, the Meckel diverticulum, the differential diagnosis of palmar, plantar and palmoplantar erythema in children, the interest of pulse oximetry to screen for critical congenital cardiopathy in neonates, the current practices and trends on vitamin K prophylaxis in term neonates and, a milk ladder to support progressive reintroduction in children with milk allergy. This inspires Sege Ernst, our cartoonist, for the cover illustration…

Many clinical cases are also published: two cases of neonatal dyshemoglobinemia, a rare cause of congenital enteropathy, a case of severe iron deficiency due to cow's milk consumption, a fatal complication of umbilical veinous catheterization, a flexor tenosynovitis after penetrating trauma, a distal intestinal obstruction syndrome in a child with cystic fibrosis, two cases of subgaleal haemorrhage associated with vacuum-assisted deliveries, a pneumococcal endocarditis in a child with Marfan syndrome, a pituitary stalk interruption syndrome and an acute case of asphyxic asthma.

Our "Made in Belgium" section summarizes the PhD thesis of Jaques van Heerden from UZAntwerp. He studied the management and outcomes of neuroblastoma in South African children.

The paediatric Cochrane Corner section explores the transient tachypnea of the newborn with a specific question: "Are restricted fluid therapy or treatment with salbutamol effective and safe to treat this condition ? "

Once again, on behalf of the entire editorial board, we wish you much reading pleasure and joyful holiday season and a happy New Year !

**Christophe Chantrain and Marc Raes**

**Uw vragen of commentaar**
**Vos questions ou commentaires**

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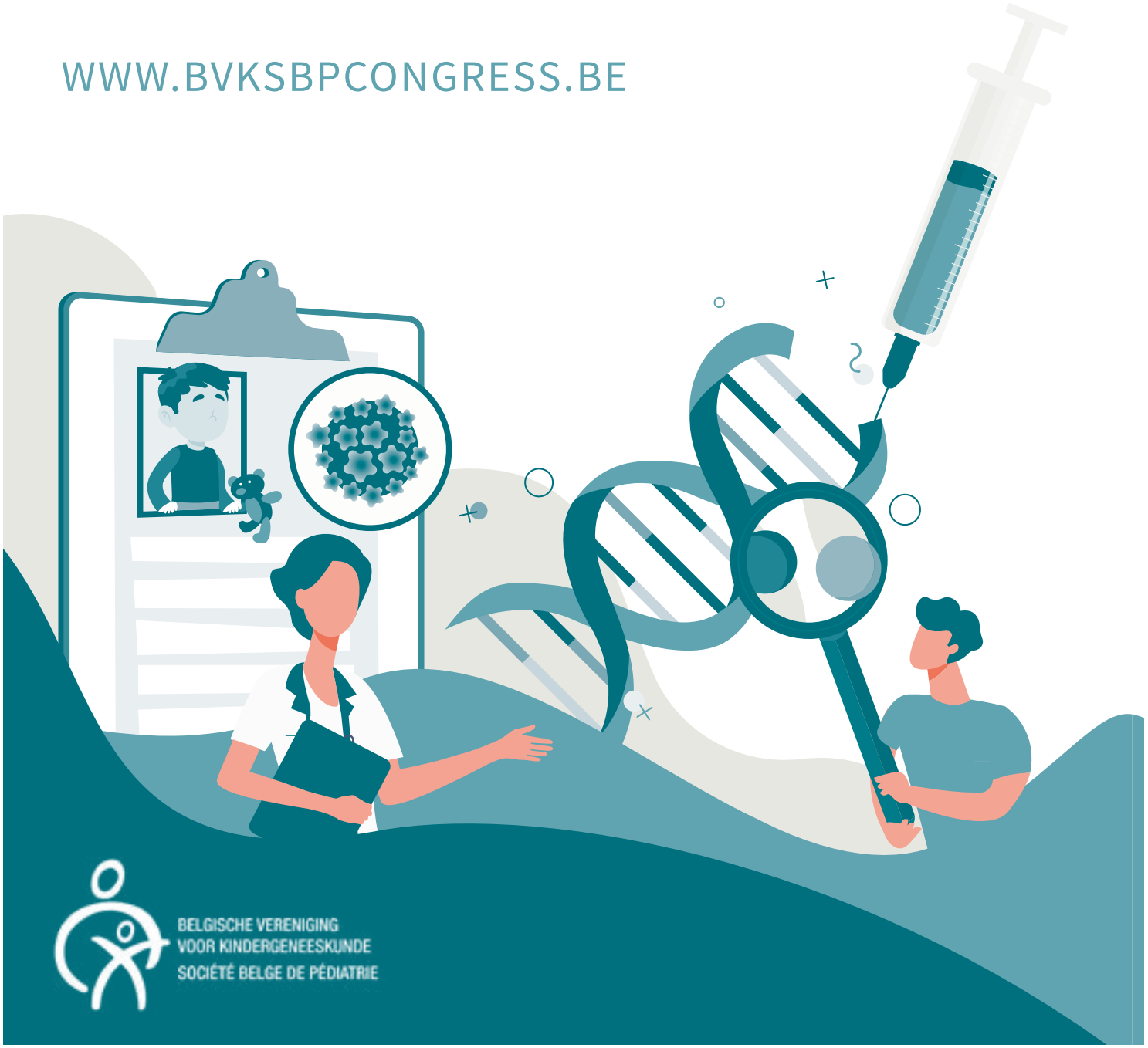

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## In Memoriam

# Dr. Robberecht
# 1948-2021

Emeritus Prof. Dr. Robberecht was born October 19th 1948, he died unexpectedly November 7th 2021.

He was professor in pediatrics at the Ghent University Belgium.

In the early nineteen eighties he started the “Cystic Fibrosis clinic” at the University Hospital Ghent. He was one of the Belgian pioneers taking care for severe gastro-intestinal problems in CF patients, at that time clinically an “orphan disease” because of the multi-disciplinary, demanding and emotional care. Meanwhile he became one of the architects of the “Belgian CF convention” initiating multi-disciplinary care for this complicated disease. He was an active member of the medical comity of the Belgian CF association, respected for his informative lectures for colleagues as well as for parents and patients.

He was internationally well-known as CF gastro-enterologist, many times invited to discuss specific items regarding his clinical research during the yearly European Cystic fibrosis society (ECFS) conferences.

He was one of the first pediatric gastro-enterologists in Belgian pediatric care. He initiated the gastro-enterologic department giving an opportunity for colleagues to be trained and to start pediatric gastro-enterologic care in peripheral hospitals. He was inspiring for the dietary department. Manny colleagues asked specialized advice in challenging clinical problems.

He was author of 119 national and international publications on CF, gastro-enteritis and dietary problems.

He was appreciated by medical students and pediatric residents for his inspiring and ironic classes.

One shall not forget his courage and ironic optimism despite progressive loss of sight leading ultimately to blindness.

We will remember him as an inspiring colleague with a lot of humor and irony but mainly as a dedicated pediatrician.

**PUBLIEKSPRIJS €86.52**

# VACCINEER MET VERTROUWEN TEGEN MenB

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

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

**VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN** Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL** Bexsero suspensie voor injectie in voorgevulde spuit Meningokokken groep B-vaccin (rDNA, component, geadsorbeerd) EU/1/12/812/001, EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004 Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09 **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING** Een dosis (0.5 ml) bevat: Recombinant *Neisseria meningitidis* groep B NHBAfusieeiwit [1,2,3]: **50 microgram** - Recombinant *Neisseria meningitidis* groep B NadAeiwit [1,2,3]: **50 microgram** - Recombinant *Neisseria meningitidis* groep B fHbpfusieeiwit [1,2,3]: **50 microgram** - Buitenmembraanvesikels (BMV) van *Neisseria meningitidis* groep Bstam NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat [2,3]: **25 microgram** [1] Geproduceerd in *E. colicellen* door recombinantDNAtechnologie [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg $Al^{3+}$) [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit) Therapeutische indicaties Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. Dosering en wijze van toediening Dosering Tabel 1. Samenvatting van de dosering: **Leeftijd bij eerste dosis: Zuigelingen van 2 tot en met 5 maanden** [a]**: Primaire immunisatie:** Drie doses, elk van 0,5 ml - **Primaire immunisatie:** Twee doses, elk van 0,5 ml - **Intervallen tussen primaire doses:** Niet minder dan 1 maand - **Intervallen tussen primaire doses:** Niet minder dan 2 maanden - **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de booserdosis [b] [c] **Leeftijd bij eerste dosis: Zuigelingen van 6 tot en met 11 maanden: Primaire immunisatie:** Twee doses, elk van 0,5 ml - **Intervallen tussen primaire doses:** Niet minder dan 2 maanden - **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis [c] **Leeftijd bij eerste dosis: Kinderen van 12 tot en met 23 maanden: Primaire immunisatie:** Twee doses, elk van 0,5 ml - **Intervallen tussen primaire doses:** Niet minder dan 2 maanden - **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis [c] **Leeftijd bij eerste dosis: Kinderen van 2 tot en met 10 jaar - Adolescenten (11 jaar of ouder) en volwassenen*: Primaire immunisatie:** Twee doses, elk van 0,5 ml - **Intervallen tussen primaire doses:** Niet minder dan 1 maand - **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen [d]. [a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld [d] Zie rubriek 5.1 van de volledige SPK. * Gegevens over volwassenen ouder dan 50 jaar ontbreken. **Wijze van toediening** Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. Contraindicaties Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). Bijzondere waarschuwingen en voorzorgen bij gebruik Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen. Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Personen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van personen met complementdeficiëntie, asplenie of miltdisfuncties. Personen met familiale complementdeficiënties (bijvoorbeeld C3- of C5-deficiënties) en personen die behandelingen ondergaan die de terminale complementactivatie remmen (bijvoorbeeld eculizumab) hebben een hoger risico op een invasieve ziekte veroorzaakt door *Neisseria meningitidis* groep B, zelfs als deze personen antilichamen ontwikkelen na vaccinatie met Bexsero. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. **Terugvinden herkomst** Om het terugvinden van de herkomst van biologicals te verbeteren moeten de naam en het batchnummer van het toegediende product goed geregistreerd worden. Bijwerkingen Overzicht van het veiligheidsprofiel De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geinactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥1/10) Vaak: (≥1/100, <1/10) Soms: (≥1/1.000, <1/100) Zelden: (≥1/10.000, <1/1.000) Zeer zelden: (<1/10.000) Niet bekend: (kan met de beschikbare gegevens niet worden bepaald) De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. Zuigelingen en kinderen (tot en met 10 jaar) **Immuunsysteemaandoeningen** Niet bekend: allergische reacties (waaronder anafylactische reacties) **Voedings en stofwisselingsstoornissen** Zeer vaak: eetstoornissen **Zenuwstelselaandoeningen** Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn Soms: insulten (inclusief febriele insulten) Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen Soms: bleekheid (zelden na booster) Zelden: ziekte van Kawasaki **Maagdarmstelselaandoeningen** Zeer vaak: diarree, braken (soms na booster) **Huid en onderhuidaandoeningen** Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster) Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar) Soms: eczeem Zelden: urticaria **Skeletspierstelsel en bindweefselaandoeningen** Zeer vaak: artralgie **Algemene aandoeningen en toedieningsplaatsstoornissen** Zeer vaak: koorts (≥38°C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geinjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid Soms: koorts (≥40°C) Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) **Adolescenten (van 11 jaar en ouder) en volwassenen Immuunsysteemaandoeningen** Niet bekend: allergische reacties (waaronder anafylactische reacties) **Zenuwstelselaandoeningen** Zeer vaak: hoofdpijn Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). **Maagdarmstelselaandoeningen** Zeer vaak: misselijkheid **Huid en onderhuidaandoeningen** Niet bekend: huiduitslag **Skeletspierstelsel en bindweefselaandoeningen** Zeer vaak: myalgie, artralgie **Algemene aandoeningen en toedieningsplaatsstoornissen** Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) **Melding van vermoedelijke bijwerkingen** Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België** Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie Postbus 97 B-1000 Brussel Madou Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **Luxemburg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy - Hôpitaux de Brabois Rue du Morvan 54 511 VANDOEUVRE LES NANCY CEDEX Tél. : (+33) 3 83 65 60 85 / 87 Fax : (+33) 3 83 65 61 33 E-mail : crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments Allée Marconi - Villa Louvigny L-2120 Luxembourg Tél. : (+352) 2478 5592 Fax : (+352) 2479 5615 E-mail : pharmacovigilance@ms.etat.lu Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië DATUM VAN DE GOEDKEURING VAN DE TEKST 07/2020 (V11) AFLEVERINGSWIJZE Op medisch voorschrift. **Referentie:** SmPC Bexsero

VU: GlaxoSmithKline Pharmaceuticals s.a./n.v.
Site Apollo Avenue Pascal, 2-4-6 1300 Wavre Belgium
**PM-BE-BEX-ADVT-210006 - Juli 2021**

# Meckel diverticulum in children

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## Keywords

Meckel's diverticulum, children

## Abstract

Meckel diverticulum represents one of the most common malformations of the digestive tract due to incomplete obliteration of the omphalomesenteric duct. It occurs in 2% of the population, and approximately 4% of all Meckel diverticula cause complications, such as obstruction, haemorrhage, or inflammation. These complications typically occur before the age of five years and frequently require rapid surgical intervention. Diagnosis of a complicated Meckel diverticulum is difficult and often only made during surgery. In this article, the most important diagnostic characteristics and surgical approaches are summarized.

## Introduction

Meckel diverticulum (MD) is a vestigial remnant of the omphalomesenteric duct that connects the yolk sac to the gut of the developing embryo in order to provide nutrition until the placenta is formed. Normally, the duct will obliterate around 7 weeks of gestation. However, failure of closure can result in a wide spectrum of anomalies including intestinal-umbilical fistula, omphalomesenteric duct sinus or cyst, mesodiverticular fibrous bands, umbilical polyp, and most commonly the MD (Figure 1). It is typically located approximately 52 cm (range 7-200 cm) proximal from the ileocecal valve, on the anti-mesenteric border, is 3 cm (range 0,4-11 cm) in length and 1,6 cm (range 0,3-7 cm) in diameter (1).

The prevalence of MD is between 0,3% and 2,9% in the general population (based on both findings during surgery and autopsy) with an estimated lifetime incidence of complicated MD of 4,2% (1,2). MD often becomes symptomatic in the first decade of life. The prevalence of symptomatic disease decreases with age, more than half of all symptomatic patients are younger than 10 years old, some authors even say younger than 5 years old (1,3). In symptomatic patients, there is a male predominance of about 2:1 (range 1,3-7,5:1), especially in patients with a nonobstructive presentation (3-15). Excessive acid secretion in males by ectopic gastric mucosa in the MD could be the reason for predisposition to bleeding or inflammation, as is also seen for peptic ulcer disease in males (3). The occurrence of gastric mucosa is common in symptomatic MD (45-80% of all cases). Other ectopic tissue that is less often seen in MD are pancreatic, duodenal or colonic. All other symptomatic MDs have ileal lining of the mucosa without ectopic tissue.

Even though the majority of MD remains asymptomatic, they have the potential to present with severe complications. The possible complications can be categorized into three groups: bowel obstruction, intestinal haemorrhage, and inflammation with or without perforation. The type of complications will depend on the different characteristics of the MD such as mechanical features (length and position of the MD) and the presence of ectopic gastric tissue located in the diverticulum. Diagnosis of a complicated MD may be challenging, due to its nonspecific symptoms that can mimic various other acute abdominal emergencies. If left untreated, necrosis, perforation, peritonitis or severe anaemia can occur, resulting in life threatening situations. Mortality is rare but has been described in the literature in 2 paediatric cases (4,7). Thus, a quick and accurate diagnosis is essential for a good outcome. The aim of this article is to review the current knowledge on clinical presentation, diagnostic workup, histopathological features, and management in children.

## Clinical presentation

The clinical manifestation of the MD is highly variable. The most common symptom in children is abdominal pain. This is present in half of the paediatric patients (range 32,4-71,4%) (3,4,12-15). The pain is often located in the right fossa or around the umbilicus, mimicking an appendicitis. Other abdominal symptoms are presented in table 1. Since the clinical picture is highly dependent on the underlying mechanism, we will describe the three most important complications more into depth.

**Figure 1:** *Examples of congenital anomalies of omphalomesenteric duct.*
*1. Fibrous connection of the ileum to the umbilicus, 2. Intestinal-umbilical fistula, 3. Omphalomesenteric duct sinus, 4. Omphalomesenteric duct cyst, 5. Meckel diverticulum with Meckel's band, 6. Meckel diverticulum.*
*Adapted from Netterimages: Meckel's Diverticulum: Variants of Vitelline Duct Remnants.*

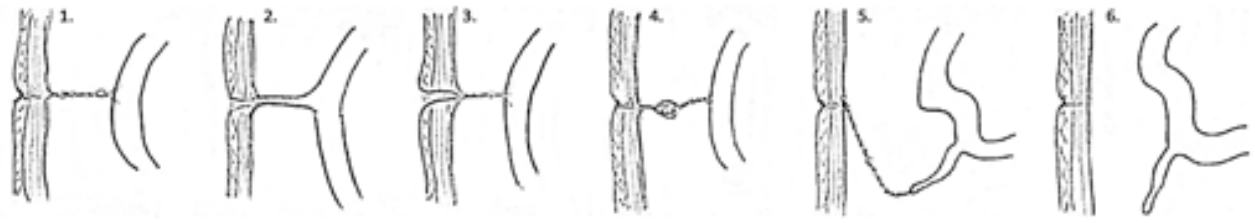


**Table 1.** Main presenting symptoms of Meckel's diverticulum in children

| | Huang[3] (n = 100) | Keese[12] (n = 7) | Chen[4] (n = 233) | Francis[13] (n = 208) | Rho[14] (n = 34) | Tseng[15] (n = 45) |
|---|---|---|---|---|---|---|
| Rectal bleeding | 50 (50%) | 2 (29%) | 116 (50%) | 42 (20%) | 12 (35%) | 25 (56%) |
| Abdominal pain | 57 (57%) | 5 (71%) | 129 (55%) | 119 (57%) | 11 (32%) | 24 (53%) |
| Vomiting/nausea | 53 (53%) | 5 (71%) | 104 (45%) | 106 (51%) | 3 (9%) | 23 (51%) |
| Fever | 25 (25%) | NR | 59 (25%) | 40 (19%) | NR | 12 (27%) |

NR: not reported

### Intestinal obstruction

The most common complication of MD is intestinal obstruction, which is described in 41,5% of all symptomatic cases (range 14,3%-86,2%) (3-12,14,15).

MD can lead to an intestinal obstruction in several ways, intussusception being the principal presentation in the paediatric population (41,9%) (3,4,6-8,10-12,14). Ileo-ileal or ileo-colic intussusception can occur, where the MD will serve as a lead point. In addition, it is suggested that the higher nerve fiber density in the wall of the MD can increase the local peristalsis and induce the onset of intussusception (16). Abdominal pain and nausea or vomiting are the main presenting symptoms in patients with an intussusception. Rectal bleeding or the classic "red currant jelly" stool can be seen as late signs, suggesting bowel ischemia. Although intussusception is commonly idiopathic in children, in 5% of cases a pathologic lead point can be found, characterized by the inability to reduce the intussusception on contrast or air enema. In this group, a MD is the lead point in 37-80% of all cases (17-19).

The second most common cause of obstruction (20%) is volvulus around a Meckel band, which is a mesodiverticular band believed to be a remnant of a vitelline artery (7,10,14). Other types of obstruction can be due to kinking, knotting, strangulation and internal intestinal hernias through openings formed by a Meckel band or abnormal mesentery attached to the MD (Figure 2). A specific type of hernia which is rarely seen, is the Littre hernia, an internal hernia containing only the MD (4).

### Intestinal haemorrhage

Intestinal bleeding from MD is commonly caused by ulceration of the small bowel due to the presence of ectopic gastric mucosa and its acid secretion. Gastric mucosa is present on microscopic histopathology in 45-80% of surgical specimens (4). Intestinal haemorrhage is seen in 37,2% (range 4,6-55,6%) of all complicated MDs (3-12,14,15). The bleeding typically has a dark colour and can be massive in volume, although more chronic forms have also been described with occult bleeding and anaemia (12). In about 50-75% of patients blood transfusion is required (3,4,11,14). Intestinal bleeding in MD patients can also be a presentation of intussusception, or a combination of ectopic gastric tissue and intussusception, in which cases the bleeding will be accompanied by abdominal pain.

### Inflammation

The diverticulum can become inflamed due to bacterial overgrowth in the obstructed lumen, resulting in peritonitis due to diverticulitis with or without perforation. Peritonitis represents 20,8% (range 13-27,6%) of all symptomatic MD cases and is manifested by abdominal pain, nausea/vomiting and fever, mimicking the diagnosis of an appendicitis (3,5-11,14,15). Diverticulitis can lead to perforation which can be life threatening. This evolution is mentioned in four paediatric cohort series and it is probably seen in up to 15% of all symptomatic MDs (6,7,9,11). Finally, some case reports describe that the inflamed MD can present as a chronic form of ileitis that is misdiagnosed as isolated small bowel Crohn's disease (20).

## Diagnostic approach

When there is clinical suspicion, radiological and nuclear imaging can be helpful in diagnosing complications from MD, and seldomly demonstrate MD as the cause. According to Daneman et al., the inflamed, haemorrhagic and the inverted, intussuscepted MD have a spectrum of features recognizable on ultrasound, CT and air enema in a significant number of children (44%) (21). Preoperative diagnostic rate in the study by Chen et al., with 233 symptomatic MD patients, was 24,89% (4). In the review by Rho et al., 57,6% of symptomatic MDs (20/34) were diagnosed by imaging techniques (14). The diagnosis of MD is in many cases made during exploratory surgery. Table 2 shows an overview of the most typical presentation forms and investigations likely to be helpful during diagnosis. In table 3, recommendations for practical use are suggested.

### Diagnosing intestinal obstruction due to MD

As described earlier, there are different types of obstruction due to MD, intussusception being the most prevalent. Intussusception can be diagnosed on ultrasound in most cases, or, if necessary, on computed tomography (CT) scan (3). These investigations will not often reveal the MD as the lead point, as demonstrated by Huang et al., where the MD as the cause of intussusception was only confirmed during surgery in all of their 17 cases of intussusception. Furthermore, attempts for barium reduction failed or there was subsequent recurrence of intussusception (3). This should always raise concern for an obstruction related to a MD (22).

Other types of obstruction include volvulus, kinking, knotting, strangulation due to fibrous bands or herniation. Findings such as distended small bowel loops on plain radiograph or CT scan are helpful but not specific for MD. Lin et al. studied 102 paediatric patients with symptomatic MD, 48 patients underwent a CT scan, but only 3 patients revealed a suspected MD (8). In a smaller study by Olsen et al., MD was only mentioned in the CT report in five out of the 16 patients (31%) (23).

### Diagnosing the bleeding MD

A pertechnate scintigraphy (Meckel scan) can identify ectopic gastric mucosa from a (bleeding) MD. Intravenous Technetium-99m pertechnate is taken up by the mucoid cells of gastric mucosa and subsequently excreted into the bowel lumen. Normal uptake is seen in the stomach, and to a lesser extent in the proximal small bowel. Subsequently, activity is seen in the bladder due to accumulation of radioactive urine after renal excretion (Figure 3).

A Meckel scan is the best noninvasive method for preoperative diagnosis of bleeding MD with high sensitivity (86-100%) and a variable specificity (22-100%). False negative results could be attributed to the "washout" phenomenon. Excessive bleeding or rapid intestinal transit with intestinal hypersecretion can dilute the pertechnate and wash it out faster than it can be caught on image. In addition, active bleeding can result in reactive vasoconstriction in the diverticulum that can limit the delivery of the tracer. Swaniker et al. described 50% false negative results in patients with haemoglobin levels lower than 11 g/dl (24). On the other hand, Suh et al. reported that both sensitivity and specificity rise up to 100% once rectal bleeding in association with anaemia is considered, indicating that the bleeding should be abundant enough (25). Furthermore, false negative results have also been described due to an area of gastric mucosa smaller than 2 cm2, which may be too small to be visualised on the scan (11). However, other authors claim that the quality of nuclear medicine has improved over the last years and this should currently not be an issue (26). Finally, mucosal ischemia or necrosis may also result in a false negative scan. False positive results have been described due to intestinal duplications, obstructions, intussusception, ectopic kidney, vascular tumours, arteriovenous malformations and inflammatory foci (11). In cases of obstruction or inflammation caused by MD, the presence of gastric mucosa is less common, therefore test results for a Meckel scan will rarely be positive and its use in this context is not recommended (3).

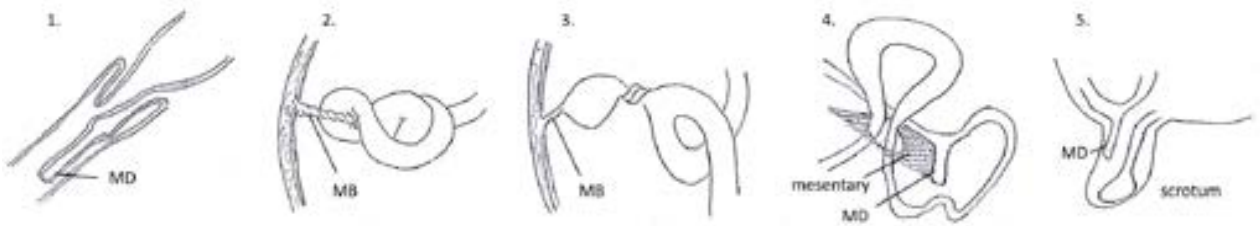
In order to increase the diagnostic value of the Meckel scan, premedication with certain drugs has been introduced. Histamine-2 (H2)-receptor

**Table 2.** Overview of clinical presentation forms and proposals for diagnostic investigations.

| | Obstruction | | Intestinal hemorrhage | Inflammation | |
|---|---|---|---|---|---|
| | Non intussusception | Intussusception | | Diverticulitis | Perforation |
| **Symptoms** | | | | | |
| Abdominal pain | + | Intermittent | No pain | Appendicitis-like | + |
| Nausea/vomiting | + | + | | + | + |
| Rectal bleeding | | + | Massive, dark coloured | | |
| Anaemia | | | + | | |
| Fever | | | | + | |
| | | | | | |
| **Diagnostic investigations** | | | | | |
| Radiography | + | Unable to reduce on contrast enema | | | + |
| Ultrasound | | + | | Actively rule out appendicitis | |
| CT scan | + | | | + | + |
| Meckel scan | | | + | | |
| Laparoscopy | + | + | + | + | + |

Non intussusception forms of obstruction: volvulus, strangulation due to torsion of fibrous bands, kinking, knotting and internal intestinal hernias

**Figure 2 :** *Types of obstruction caused by MD.*
*1. Intussusception, 2. Volvulus around Meckel's band, 3. Strangulation by torsion of Meckel's band, 4. Internal hernia through the mesentery of MD, 5. Littre hernia. MD = Meckel's diverticulum, MB = Meckel's band.*
*Adapted from Netterimages: Meckel's Diverticulum: Complications of Meckel Diverticulum and Vitelline Duct Remnants.*



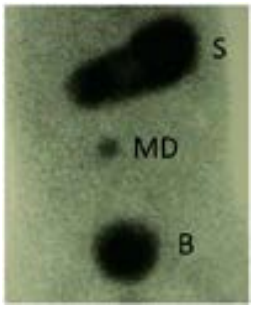

antagonists (e.g. ranitidine) inhibit the release of pertechnate into the bowel, concentrating the signal in the MD. Tseng et al. saw a 11% higher yield of positive Meckel scans in children with 3-day oral H2-blocker use prior to examination than those without (75% vs 64%) (15). Irvine et al. could increase the sensitivity and specificity to 100% using ranitidine for 24 hours prior to the examination (26). No studies with proton pump inhibitors in this context have been found. Other forms of premedication include pentagastrin that enhances mucosal uptake of pertechnate into the gastric mucosa, and glucagon that slows down small bowel motility (27). A repeated Meckel scan is recommended if the initial scan is negative or equivocal, but clinical suspicion for MD is still high or patient preparation was inappropriate.

There are other examinations less commonly used for diagnosing a bleeding MD. Tseng et al. was able to detect the bleeding source thanks to a red blood cell scan in four out of five patients with a negative Meckel scan (15). Magnetic resonance enterography has been successful in diagnosing a bleeding MD in 4/25 children with obscure intestinal bleeding (28). Double balloon enteroscopy can be a reliable diagnostic tool for a bleeding MD in children with a negative Meckel scan, as described in a small case series in China (29). Access to this technique, however, remains an important limitation. Finally, video capsule endoscopy (VCE) has been shown to be useful in the diagnosis of a bleeding MD. In a recent study by Wu et al., 15/37 children with intestinal bleeding from MD were positive on VCE, of which only 12 by Meckel scan (30). Despite limited evidence, VCE can potentially be of added value in the diagnosis of a bleeding MD. Shortcomings of VCE are the limitation of the patient's age range, potential risks of delayed passage and obstruction requiring surgical removal of the device (31). In Belgium, VCE is only reimbursed when there is a need for blood transfusion.

**Table 3.** Proposed recommendations for practical use.

| **Recommendation** |
|---|
| In case of acute abdominal pain,<br>· offer radiography to rule out obstruction or perforation,<br>· offer ultrasound to rule out appendicitis,<br>· consider CT scan if former investigations are insufficient or consider laparoscopic exploration. |
| When intussusception is suspected, offer barium reduction for resolution and be aware of relapse. |
| In case of failed reduction with barium enema or relapse of intussusception, offer laparoscopic exploration. |
| In case of rectal bleeding,<br>· consider upper and/or lower endoscopy.<br>· offer a Meckel scan with premedication.<br>· offer a second Meckel scan when the scan is negative and clinical suspicion remains. |

**Figure 3 :** *Meckel scan. The Meckel scan shows physiological enhancement in the stomach (S) and bladder (B). In the right upper quadrant the Meckel's diverticulum (MD) appears. S = stomach, MD = Meckel's diverticulum, B = bladder.*



Rectal bleeding is not specific for a bleeding MD. Obviously, upper and/or lower endoscopy should be considered during diagnostic workup for intestinal haemorrhage to investigate intestinal polyps, inflammatory bowel disease or other pathology.

### Diagnosing the inflamed MD

Meckel diverticulitis can be seen on a CT scan as a cystic mass with surrounding inflammation. On ultrasound, a thick wall mass with a "gut signature" is visible, but can easily be mistaken for an appendicitis (22). The appendix should be actively sought on imaging to rule out appendicitis. In case of perforation, free intraperitoneal air can be seen on plain radiograph or CT scan. Radiation exposure remains an important concern in children, so limited use should be promoted.

## Management

Once MD is suspected or diagnosed in a symptomatic patient, surgical excision is necessary. This can be performed by diverticulectomy, wedge-shaped excision or segmental bowel resection followed by end-to-end anastomosis. It is key to make sure there is no remaining ectopic mucosa left that can further harm the intestine, and sites of ulceration or gangrene tissue should be excised completely. Commonly, a long MD with a length-width ratio of more than 2 cm will have ectopic tissue at the tip or body and not at the base. In this case a simple diverticulectomy is proposed. In contrast, when the diverticulum is short or broad-based, gastric mucosa is likely to be located at the base of the MD and a broader approach is necessary (11,14). Other authors have proven that a diverticulectomy-only approach is sufficient and safe regardless of the size of the diverticulum (32,33). In cases of a bleeding MD, the bleeding site is typically adjacent to the ileal wall, and a wedge-shaped excision is often preferred (3). However, some studies showed that by performing a simple diverticulectomy, gastric heterotopia is completely resected and there is no increased risk of postoperative bleeding, a lower overall complication rate, and shorter operative times and hospital stays (34). Wedge or segmental resection is the preferred treatment of choice in children presenting with obstruction or diverticulitis with inflamed or perforated base.

The procedure can be done laparoscopically when diagnosis is certain or following exploratory diagnostic evaluation. This minimally invasive surgical technique is safe and associated with short hospital stays with minimal complication rates (8). In order to avoid laparotomy, Menezes et al. promotes an alternative method: the authors performed resection of MD in five patients laparoscopically but brought the diverticulum out of the abdomen via the umbilical port to perform resection-anastomosis without doing a laparotomy (11).

It remains controversial whether all incidentally diagnosed MDs should be resected. Some authors suggest resection of all MDs because of potential life-long risk for complication and low risk associated with laparoscopic resection. Although postresection complications are rare, intestinal adhesion obstruction and wound infections can occur. The main argument not to resect is the low risk of MD becoming symptomatic. Based on a systematic review, 758 resections are required to prevent one death from MD (2). Other authors recommend resection only when there is suspected ectopic gastric mucosa or adhesive bands. Slivova et al. showed that the presence of gastric heterotopia was associated with the width of the diverticulum. They recommend to resect an asymptomatic MD when the width of the diverticulum is more than 1,5 cm (34).

## Pathological findings

MD is called a true diverticulum since it comprises all four layers of the intestinal wall: mucosa, submucosa, muscle and peritoneal serosa as the surface. In about half of the cases (28-84%), it contains ectopic or heterotopic tissue that can lead to complications (3-6,8-15). Gastric mucosa is the most common type of ectopic tissue (in 75% of cases) followed by pancreatic mucosa or a combination of gastric and pancreatic mucosa. Only 1 paediatric patient with colonic tissue has been reported (5).

MDs with ectopic tissue are more likely to become symptomatic, 50-60% in comparison to 4,6% in the overall MD population (4). Acid secretion from gastric mucosa or pancreatic enzymes from pancreatic tissue can cause bleeding and ulceration (35). In contrast, MDs complicated by obstruction or inflammation less frequently contain ectopic tissue. Ectopic pancreas tissue, however, has been shown to be a lead point for intussusception (3).

In very rare occasions, tumours can arise in children with MD, such as adenocarcinoma, carcinoid tumors, desmoplastic small round cell tumors, and benign mesenchymal tumors (lipoma, hemangioma, and hamartoma) (36).

## Conclusion

MD is an infrequent congenital anomaly that generally remains asymptomatic during lifetime. However, it can lead to serious life-threatening complications, such as intestinal obstruction (mainly caused by intussusception), haemorrhage, and inflammation. Although complications from MD are possible at any age, they occur more often in children. Several diagnostic imaging studies are available but will only indirectly indicate the presence of MD by detecting its complications, and generally have a low accuracy to reveal the MD itself. During diagnostic workup for abdominal symptoms, MD should be considered for prompt diagnosis and treatment. Important characteristics specific for MD are 1) dark, massive rectal bleeding causing anaemia and often the need for transfusion, 2) the inability to reduce an intussusception on contrast enema or subsequent relapse, 3) clinical suspicion for appendicitis which is ruled out on ultrasound. In case of rectal bleeding and/or anaemia, a Meckel scan can support the diagnosis of a bleeding MD with a high sensitivity and specificity, and should be repeated when the result is negative and suspicion remains. Finally, laparoscopy can be a diagnostic modality of choice in children suspected to have MD. As for the treatment, a laparoscopic diverticulectomy-only approach has been found to be sufficient and safe in most cases.

### Conflict of interest

The authors have no conflict of interest to declare.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# Variants in DGAT1 causing enteropathy: a case report and review of the literature

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## Keywords

Diacylglycerolacyltransferase 1, DGAT1, Enteropathy, Congenital diarrhea

## Abstract

**Background:** Diacylglycerolacyltransferase 1 (DGAT1) is an enzyme that catalyzes the final step of triglyceride synthesis and genetic variants have been described in association with congenital diarrhea.

Methods: We present a patient with a novel variant in the DGAT1 gene and a review of previously published cases. A search was conducted in PubMed, Cochrane Library and Embase until December 2020 and 22 cases of children diagnosed with variants in DGAT1 and gastrointestinal disease were identified from 8 articles. Data on patient characteristics, clinical presentation, diagnostic findings and treatment were extracted and analyzed.

**Case description:** Our patient presented with failure to thrive, vomiting and diarrhea and was diagnosed with protein-losing enteropathy. The novel homozygous variant c.469-2A>G in DGAT1 was found and after starting with parenteral nutrition and a fat-free diet, she showed a favourable evolution with dramatic improvement of growth.

Results: A vast majority of patients presented with symptoms of failure to thrive, vomiting and diarrhea within the first three months of life but not necessarily at birth. Parenteral nutrition was required in 78.2% of cases and 61.1% of them weaned off. At follow-up, 73.7% were receiving a fat-restricted diet. Mortality was 17.4%.

Discussion: DGAT1 deficiency is a rare but severe disorder, that will likely be encountered more often in the future as DGAT1 is added to screening panels for congenital diarrhea. Key to the treatment is restriction of enteral fat with appropriate parenteral supplementation, but more detailed information on nutritional management strategies and their effects on clinical outcome is needed.

## Background

Chronic diarrhea in infants can be either aqcuired, for example after infection or surgery, or congenital. Inherited causes, termed congenital diarrheas and enteropathies (CODEs), are less common but can be extremely severe. Most CODEs are monogenic, autosomal recessive disorders with onset typically early in life. In the majority of CODEs, the genetic variant directly affects the intestinal epithelium, whereas in others epithelial function is impaired secondarily by dysregulation of the immune system (1, 2).

Congenital protein-losing enteropathy (PLE) is a subtype of CODE that is characterized by increased protein loss from the gastrointestinal system. Monogenic causes of congenital PLE include variants in CCBE1, CD55 and PLVAP (3-5). Also, several loss-of-function variants in the gene encoding for diacylglycerolacyltransferase type 1 (DGAT1) have been described in patients with congenital PLE. DGAT1 is an enzyme that plays a central role in the final step of triglyceride synthesis, catalyzing the reaction of diacylglycerol and fatty acyl-CoA to triacylglycerol. Diacylglycerolacyltransferase type 2 (DGAT2) catalyzes the same reaction but is expressed in the liver, whereas DGAT1 is mainly expressed in the small intestine (6). The mechanism causing PLE in DGAT1 deficient patients is not yet fully understood, but experimental studies show impaired lipid droplet formation in DGAT1 deficient cells compared to healthy controls (7). Lipid droplets are cytosolic organelles that play an important role in dietary fat absorption and protect enterocytes from lipotoxic effects caused by excessive postprandial concentrations of fatty acids and sterols (8). This was confirmed in vitro, with cell death occurring at significantly lower doses of oleic acid in DGAT1 deficient cells compared to healthy cells, suggesting that lipotoxicity-induced enterocyte apoptosis might be the underlying mechanism of PLE in DGAT1 deficiency (Figure 1A) (7). Previously, a reversible loss of apical transporters leading to altered polarity with impaired integrity of tight junctions between enterocytes was observed in duodenal tissue of a patient with DGAT1 deficiency, which might be another possible explanation for the resulting PLE (Figure 1B) (9).

Here, we describe a patient with a DGAT1 variant and failure to thrive. We performed a literature review of all previously reported cases of this rare but severe disorder and analyze patient characteristics, clinical presentation, laboratory and histologic features, treatment and outcome. We then discuss optimal nutritional management of patients with DGAT1 variants. This overview will support clinicians in diagnosis and management of these children.

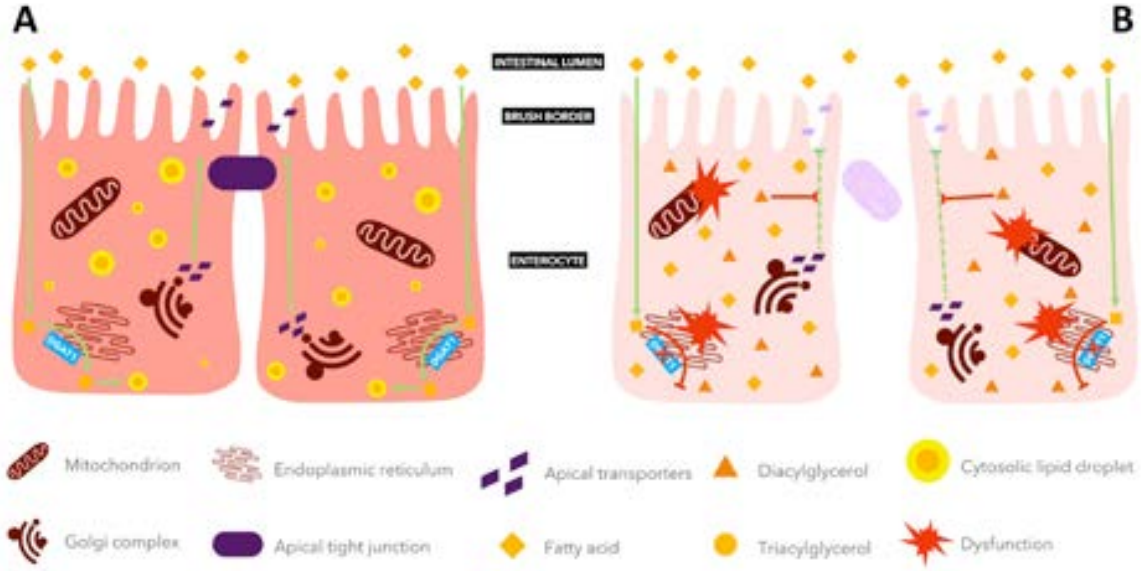
## Methods

A search conducted in PubMed, Cochrane Library and Embase using 'DGAT1 deficiency', 'DGAT1 mutation', 'DGAT1 diarrhea', 'DGAT1 enteropathy', 'DGAT patients' and the Emtree term 'diacylglycerol acyltransferase 1' singly combined with Emtree terms 'enzyme deficiency', 'gene mutation', 'diarrhea' and 'protein losing enteropathy' until December 2020 provided 306 results. All relevant articles were in English and full text versions were available. Additional search on 'DGAT1 hypogammaglobulinemia' and 'DGAT1 hypoalbuminemia' and review of the references of these articles did not yield any extra publications. We identified 22 cases of children diagnosed with variants in DGAT1 and gastrointestinal disease from 8 articles. Data on patient characteristics, clinical presentation, diagnostic findings and treatment were extracted and analyzed. Continuous data are presented as median and categorical variables are reported as counts and percentages. If a variable was not determined, it is not included in the denominator.

## Case description

A 2.5-month-old previously healthy girl presented with diarrhea and feeding difficulties. She was born in Belgium, to consanguineous parents of Turkish origin, after an uncomplicated full-term pregnancy. At first presentation, she had an acute episode of vomiting and diarrhea, complicated by Klebsiella sepsis and hip arthritis, severe metabolic derangement and hypoalbuminemia. She stabilized after treatment with antibiotics and intravenous fluids. She was

**Figure 1 :** *Schematic overview of proposed hypotheses regarding the underlying mechanisms causing protein-losing enteropathy in DGAT1 deficiency. A: In healthy enterocytes, fatty acids are absorbed from the intestinal lumen, and then directed from the apical membrane to the endoplasmic reticulum for triacylglycerol synthesis. This process is catalyzed by DGAT1 and results in the formation of neutral lipid storage organelles called cytosolic lipid droplets, thereby protecting the epithelium from lipotoxicity. Trafficking and insertion of apical transporters and junctional proteins result in polarization of the epithelial cells, which is necessary for effective absorption of nutrients and junctional integrity. B: If enterocytes lack DGAT1, triacylglycerol synthesis is impaired, leading to fewer cytosolic lipid droplets and excess of fatty acid and diacylglycerol (upstream products in the pathway of triacylglycerol synthesis). These high amounts of intracellular lipids lead to endoplasmic reticulum stress and mitochondrial dysfunction, resulting in cell death. In addition to this lipotoxicity, deficits in apical transporter trafficking caused by intracellular diacylglycerol and alterations in intercellular junctions of enterocytes that have been observed in DGAT1 deficient cells might contribute to malabsorption and protein loss.*




initially assumed to have cow's milk protein allergy because of elevated IgE levels specific for casein and because she improved slightly when started on elemental formula. However, this was insufficient to explain the clinical course: she persistently failed to thrive and she had recurrent episodes of diarrhea and vomiting whenever enteral feeding was restarted or increased despite the use of different formula feeds, including extensive hydrolyzed whey protein and amino acid based-formula. Gastroduodenal and colonic endoscopy showed no macroscopic or microscopic abnormalities. She developed hypoalbuminemia and hypogammaglobulinemia and technetium 99m-labeled human serum albumin scintigraphy confirmed the diagnosis of PLE. She received several albumin infusions and parenteral nutrition every time she relapsed. The clinical course was complicated by recurrent catheter-related thrombosis for which she received low molecular weight heparin. She also suffered from iron deficiency anemia, for which she received packed cell transfusion and iron supplementation, and from an episode of acute gastro-enteritis due to rotavirus for which she was rehydrated with oral rehydration salts.

A congenital diarrhea gene panel analysis containing 64 genes (DIA00v17.1) was performed, using next generation sequencing (NGS) by the Illumina NGS sequencing system (10). A novel homozygous variant c.469-2A>G in DGAT1 was found, explaining the clinical presentation through aberrant gut epithelial lipid metabolism (7). Both parents and the older brother were identified as heterozygous carriers. No other pathogenic or likely pathogenic variants were found.

After establishment of this diagnosis at the age of 9 months, she was started on a fat-restricted diet and parenteral lipid administration, after which we observed a favorable evolution with normalization of stool pattern and a very good weight gain from far below -2 standard deviation (SD) to more than 0 SD in three months time (Figure 2B). Her height and head circumference increased from approximately -2 SD and -1.5 SD to +1 SD and +1.5 SD respectively at the age of eighteen months (Figures 2A and 2C). Also, weight for height increased from below -2 SD to more than +1 SD before stabilizing around 0 SD (Figure 2D). Until the age of eighteen months, a fat-free diet was continued in the form of extensively hydrolyzed whey protein maltodextrin mixture via nasogastric tube, fruit and vegetables. She was then weaned off parenteral feeding, but as she developed deficiencies of linoleic and arachidonic acid, monthly infusions of SMOFlipid were administered. At the age of 26 months she started vomiting and developed edema, severe lactic acidosis and a combined cardiogenic and distributive shock caused by a thiamine deficiency. She is now 31 months old, completely weaned off parenteral nutrition since one month and thriving with a fat-free formula via nasogastric tube and oral intake of solid food with a maximum of six grams fat per day.

## Results

### Patient characteristics

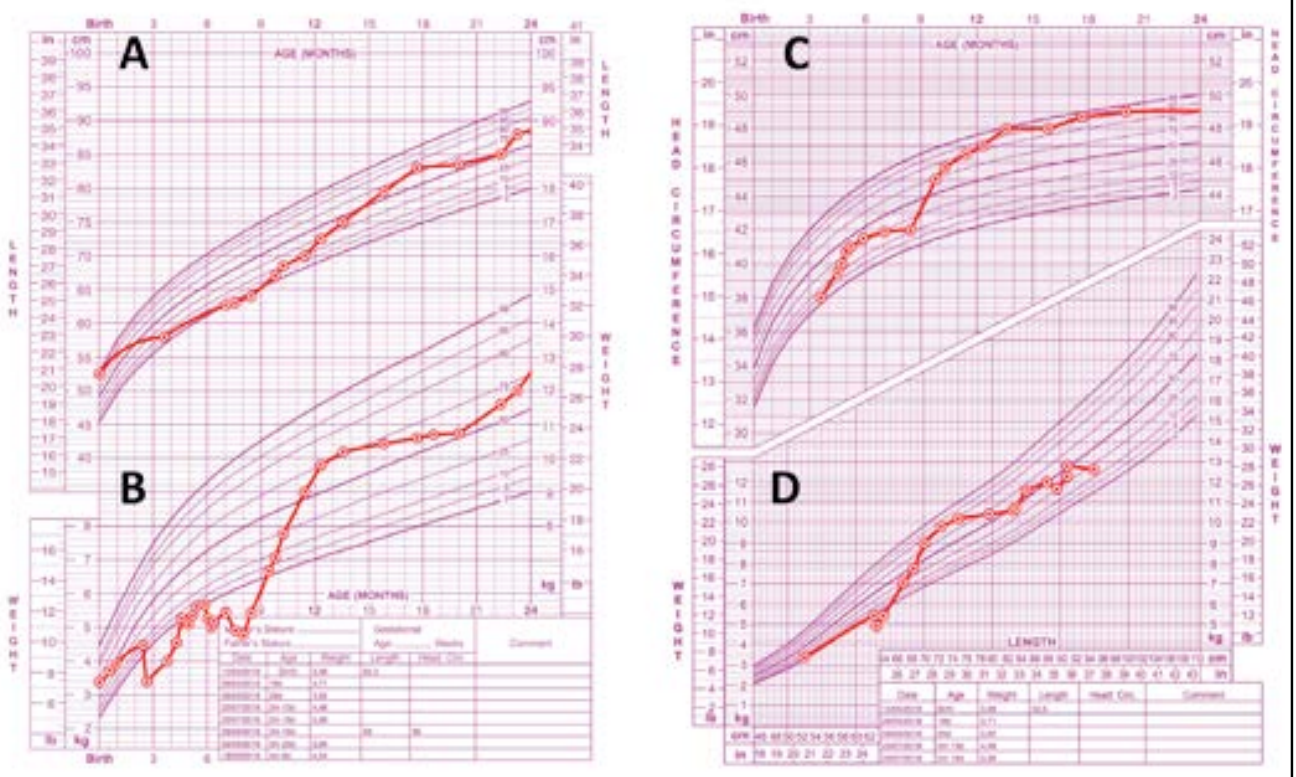
Children with DGAT1 variants present at a very young age: the age of onset was less than one month in 65.2%, and less than three months for 95.7% of all patients. Of all cases, 39.1% were female. Ten affected children (43.5%) were born to consanguineous parents. Thirteen genetic variants of DGAT1 were reported in sixteen families. Two patients had a compound heterozygous variant, the others were homozygous (Table 1).

### Clinical presentation

Clinical presentation and laboratory findings are summarized in Table 1. Most patients presented with failure to thrive (18/20 = 90%). Two patients did not fail to thrive: one because he underwent surgery for an incarcerated inguinal hernia and received parenteral nutrition from birth, the other because he was started on a fat-restricted diet very shortly after birth to treat vomiting because he had an older sibling who was thriving on a similar diet. For three patients, no information on thriving was available. Vomiting was present in sixteen patients and diarrhea in twenty patients.

Laboratory findings showed hypoalbuminemia in eighteen patients (18/21 = 85.7%), but in only seven of them edema was present. Although hypertriglyceridemia appears to be a feature of human DGAT1 deficiency (6, 11), it was assessed in only fourteen cases and elevated in eight of them (57.1%, range 112-739 mg/dL). Derangement of electrolytes was described in four patients, mainly low serum bicarbonate, magnesium, phosphorus, sodium and potassium levels. In four cases low vitamin D, low calcium, secondary hyperparathyroidism and/or osteopenia were described. Our case also had decreased levels of vitamin A and zinc. Metabolic acidosis was mentioned in four patients. Newborn screening and/or additional metabolic

**Figure 2 :** *Growth of reported index case in World Health Organization growth standards. A: Length for age; B: Weight for age; C: Head circumference for age; D: Weight for length.*




screening was performed in six patients, showing no evidence of inborn errors of metabolism. Alpha-1-antitrypsin was elevated in stool of nine patients (9/11 = 81.8%). Stool elastase levels were low in two cases (2/7 = 28.6%).

In nineteen patients endoscopy was performed, but macroscopic abnormalities were not seen in any of them. Histologic findings were abnormal in nine patients (9/19 = 47.4%). The abnormalities found in these patients consisted of duodenal enterocytic lipid accumulation, shortening and rarefaction of microvilli, focal vacuolization and partially blunted villi, CD10 positive globules, laterally located microvilli, blunting of duodenal mucosa and patchy gastric metaplasia, focal acute colitis with cryptitis, mild chronic inflammation, focal foveolar metaplasia and dystrophic microvilli.

Extra-intestinal manifestations and comorbidities were present in seventeen children. Recurrent infections or sepsis were described in ten of them (10/17 = 58.8%), probably at least partially related to hypogammaglobulinemia, which was present in fifteen patients (15/18 = 83.3%). Malabsorption led to iron deficiency anemia in three patients. Venous thrombotic disease was seen in three patients. Two affected siblings were diagnosed with Gilles de la Tourette syndrome and treated with dexamphetamine. Other comorbidities were corneal cystine crystal accumulation, nephrolithiasis, hepatomegaly with jaundice due to fibrosis and cholestasis and crossed fused renal ectopia with hydronephrosis. Developmental delay was seen in two patients and hypotonia in one.

### Treatment and outcome

Eighteen patients required parenteral nutrition (18/23 = 78.2%). Eleven patients were weaned off parenteral nutrition but insufficient details were available to determine a median age of weaning. At follow-up, fourteen children received a diet with some degree of fat restriction (14/19 = 73.7%), varying from a regular diet without dairy products to a completely fat free diet with parenteral lipid administration. Nutritional management was not described in detail for every case, but most children were started on an elemental formula feed.

The two patients with low fecal elastase received supplementation of pancreatic enzymes, after which stool frequency improved. Although the youngest of these children is still below the third percentile for height and weight, symptoms resolved after two years in the older one.

Two children were treated with cholestyramine; one started at the age of 27 months because of combined hyperlipidemia and was thriving on an unrestricted diet at the age of 46 months, the other child did not need any adaptation of enteral diet. Only one other child received a normal diet, but she was still not thriving and depended on parenteral nutrition due to a complicated course after small bowel transplantation because of a misdiagnosis of microvillus inclusion disease.

Supportive treatment with albumin and/or red blood cell transfusion was given in eleven cases and six children received intravenous immunoglobulines during the course of the disease.

Four patients passed away (4/23 = 17.4%). Two of them died of sepsis at the age of 6 and 17 months. Age and cause of death of the other two patients were not specified.

## Discussion

In this review, we provide an overview of the clinical presentation of 23 patients with DGAT1 variants. DGAT1 deficiency is a rare disorder that can result in severely impaired growth and dependence on parenteral nutrition. Moreover, delayed diagnosis and complications of treatment impede clinical progress in these children. Mortality was demonstrated to be 17.4% in published cases. Supportive and nutritional management with a focus on fat restriction leads to resolution of symptoms and improved growth in the majority of patients, and sometimes even appears to be needed only temporarily. As DGAT1 is included in gene panels for congenital diarrhea it is likely that the diagnosis of DGAT1 deficiency will be encountered more often by clinicians. Therefore, practical guidelines for nutritional management of these patients will become increasingly important.

**Table 1 :** *Patient characteristics, presentation and laboratory findngs * = index patient; † = died; M = male; F = female; U = unknown; ND = not determined or not described; N = normal; H = high; L = low. References: patients 2-11 (7), patients 12 and 13 (12), patient 14 (9), patient 15 (17), patients 16-18 (11), patients 19 and 20 (6), patient 21 and 22 (18), patient 23 (19)*

| Patient | Sex | Origin | Consan-guinity | Variant | Age of onset | Failure to thrive | Vomiting | Diarrhea | Edema | Serum triglycerides | Hypoalbu-minemia | Hypogamma-globulinemia | Alpha-1-antitrypsin in stool | Elastase in stool |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1* | F | Belgium, Turkish | + | c.469-2A>G | 2.5 months | + | + | + | + | H | + | + | ND | ND |
| 2 | M | Turkey, Turkish | + | c.1202G>A, p.W401X | Birth | + | + | + | + | H | + | + | ND | ND |
| 3† | F | Turkey, Turkish | + | c.1202G>A, p.W401X | Birth | + | + | + | + | N | + | + | ND | ND |
| 4 | F | Turkey, Turkish | + | c.573_574delAGinsCCCATC-CCACCCTGCCCATCT | 3 weeks | + | + | + | + | H | + | + | N | N |
| 5 | M | Turkey, Turkish | + | c.937-1G>A | 2 months | + | + | + | - | N | + | + | ND | ND |
| 6 | M | Turkey, Turkish | + | c.953insG, p.I319Hfs*31 | 40 days | + | + | + | - | ND | + | + | ND | L |
| 7 | M | Turkey, Turkish | + | c.953insG, p.I319Hfs*31 | 2.5 months | + | + | + | - | N | + | + | ND | L |
| 8 | M | The Netherlands, Caucasian | + | c.629_631delCCT, p.S210_Y211delinsY | First month | - | + | - | - | ND | - | ND | ND | ND |
| 9 | M | The Netherlands, Caucasian | + | c.629_631delCCT, p.S210_Y211delinsY | First month | + | + | - | - | ND | - | ND | ND | ND |
| 10 | M | The Netherlands, Caucasian | ND | c.629_631delCCT, p.S210_Y211delinsY | Birth | + | + | + | - | ND | + | + | H | ND |
| 11 | F | The Netherlands, Caucasian | ND | c.629_631delCCT, p.S210_Y211delinsY | Birth | + | + | + | - | ND | + | + | ND | ND |
| 12 | M | South-Asian descent | ND | c.314C>T, p.L105P | Shortly after birth | + | ND | + | ND | H | - | + | H | N |
| 13 | M | South-Asian descent | ND | c.314C>T, p.L105P | Shortly after birth | + | ND | + | ND | ND | ND | ND | H | ND |
| 14 | M | Hispanic | ND | g.13827T>C, p.Ala226_Arg250del | 7 weeks | + | + | + | ND | ND | + | + | N | N |
| 15 | F | Caucasian | ND | maternally c.1013_1015delTCT, p.Phe338del and paternally c.1260C>G, p.Ser420Arg | 1 month | + | + | + | ND | N | + | + | H | ND |
| 16 | M | Arab-Muslim | + | c.884T>C, p.Leu295Pro | 2 months | + | ND | + | + | H | + | + | H | N |
| 17 | M | Ashkenazi Jewish | - | g.13827T>C, p.Ala226_Arg250del | 8 days | + | ND | + | + | N | + | - | H | N |
| 18 | M | Ashkenazi Jewish | - | g.13827T>C, p.Ala226_Arg250del | 17 days | - | ND | + | ND | H | + | - | H | ND |
| 19† | F | Ashkenazi Jewish | - | g.13827T>C, p.Ala226_Arg250del | 3 days | + | + | + | ND | H | + | + | H | ND |
| 20 | M | Ashkenazi Jewish | - | g.13827T>C, p.Ala226_Arg250del | 3 days | ND | ND | + | ND | H | ND | - | H | ND |
| 21† | F | Chinese, Han or Uyghur | - | c.895-1G>A | 0 months | ND | + | + | ND | ND | + | ND | ND | ND |
| 22† | F | Chinese, Han or Uyghur | - | c.249-6T>G | 30 months | ND | ND | ND | + | ND | + | ND | ND | ND |
| 23 | F | Chinese | - | maternally c.895-1G>A and paternally c.751+1G>C | Shortly after birth | + | + | + | ND | H | + | + | ND | ND |

Our review shows that a majority of patients presented with failure to thrive, vomiting and diarrhea, and only a minority was described to have edema. Lack of improvement on elemental formula feeds should therefore prompt to think of PLE, even in the absence of edema. Early laboratory testing for signs of malabsorption in these children, including alpha-1-antitrypsin in stool and serum albumin level, is indicated as advised in the diagnostic algorithm proposed by Thiagarajah et al (1). Serum triglycerides are elevated in 57.1% of patients with DGAT1 deficiency, and should be measured as well. Because histologic findings are often nonspecific, endoscopy is not very useful for detecting abnormalities related to DGAT1 deficiency, although it maintains its place in the diagnostic process to rule out other conditions. Early diagnosis and adequate nutritional management might decrease the need for symptomatic treatment like albumin or red blood cell transfusions, administration of intravenous immunoglobulines or parenteral nutrition.

Infants presenting with persistent diarrhea or vomiting and failure to thrive are often started on an elemental formula because of suspected cow's milk protein allergy. However, as elemental formula feeds developed for treating cow's milk protein allergy generally contain around 30% of total calories from fat – comparable in composition to breast milk and standard infant formula – they are not expected to lead to improvement in patients with DGAT1 deficiency.

Nutritional management in DGAT1 deficiency poses a great challenge, but recent findings about possible underlying mechanisms causing PLE in these patients have provided leads (7-9). Key to the treatment seems to be a restriction of enteral administration of fat with appropriate parenteral supplementation of fat and fat-soluble vitamins to bypass the impaired process of triglyceride synthesis and protection against lipotoxicity. More detailed descriptions of treatment strategies could provide clarity on which

enteral formula feeds are best given and what the maximum or tolerated range of calories from enteral fat is in patients with DGAT1 deficiency. Enteral fat tolerance might differ between genetic variants and might be determined more precisely if it would be possible to establish the degree of enzyme activity (12). From clinical practice perspective, enteral fat tolerance can be established for patients individually by starting with complete enteral fat restriction, meeting essential fatty acid needs from parenteral nutrition, followed by a progressive increase of the quantity of fat in the diet with close monitoring of symptoms. Some patients appeared to show some improvement when enteral fat was provided in the form of MCT, but the effect on symptoms, growth and need for parenteral nutrition is still largely unknown. Studies addressing the effect of MCT on lipid droplet formation by DGAT1 deficient cells might shed light on the role of MCT in the prevention of lipotoxicity and its place in the treatment of DGAT1 deficiency.

Parenteral nutrition has a prominent role in the management of DGAT1 deficiency and this leaves clinicians with a lot of choices to make about type of intravenous lipid emulsion and fat-soluble vitamin preparations, frequency, dose and way of administration and follow-up of clinical and biochemical parameters (13). Parenteral nutrition is indicated whenever enteral nutrition leads to ongoing symptoms or nutrient deficiencies including essential fatty acids deficiency. Clinicians should be aware of risks like catheter-related thrombosis and sepsis or parenteral nutrition associated liver disease. Mixed lipid emulsions appear to be associated with less liver injury in hospitalized children than soybean-based lipid emulsions (14, 15). Hypertriglyceridemia and electrolyte derangements due to the disorder could be complicating factors in the follow-up. DGAT1 deficiency was associated with higher serum levels of triglycerides in 57,1% of the patients, possibly due to overcompensation of hepatic DGAT2 (6).

Pharmacological treatments like pancreatic enzyme supplementation or cholestyramine were sporadically used in DGAT1 deficiency and had a beneficial effect on stool frequency, but the low number of patients treated and the information provided was insufficient to draw meaningful conclusions. Since pancreatic enzymes mainly affect fat digestion and cholestyramine the absorption of cholesterol, it is theoretically not very likely that DGAT1 deficient patients would benefit from these interventions.

One hypothesis about the underlying pathophysiology is that DGAT1 deficiency causes a defect in the formation of intracellular lipid droplets. Previous studies showed that DGAT1 mutant fibroblasts contained fewer cellular lipid droplets when exposed to oleate, the conjugate base of oleic acid, compared to wild-type cells. This effect on lipid droplet formation was confirmed in patient-derived cells and organoids (7, 11). While in murine intestine both DGAT1 and DGAT2 are expressed, in human intestine only DGAT1 is highly expressed (6). However, recent findings showed functional DGAT2 expression in human epithelial stem cells and the capacity of DGAT2 to compensate for lipid droplet formation when DGAT1 function was inhibited in these stem cells (16). So far, no therapies have been described to increase intestinal DGAT activity in patients with DGAT1 deficiency, but upregulation of DGAT2 expression in human mature enterocytes could be a promising target for future therapeutic interventions (16). In vivo overexpression of DGAT2 in enterocytes of patients with DGAT1 deficiency has not been described, but could theoretically explain the favorable prognosis with restored enteral fat tolerance in some patients.

A limitation of this review is that no conclusions can be drawn about the effect of different management strategies on clinical outcome, because only observational case series are available. As they differ in the level of detail provided considering treatment choices, comparisons are difficult to make. Furthermore, the rarity of the disorder impedes the implementation of prospective comparative studies.

Since an increase of cases diagnosed with DGAT1 deficiency can be expected, as the gene is added to screening panels for congenital diarrhea, sharing of detailed nutritional management strategies and their effects on clinical outcome is needed to improve and accelerate treatment of these patients and decrease morbidity, mortality and complications in the future.

**Disclosure**

No potential conflicts of interest were reported by any of the authors.

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# De Harmonie familie breidt zich uit

Pampers Harmonie


**NIEUW**


babydoekjes met **99% water**

0% plastic

Article

# Impact of the COVID-19 pandemic on early childhood preventive care activities of Office de la Naissance et de l'Enfance (ONE)

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## Keywords

COVID-19, preventive child care, day care, community health services, social support

## Abstract

The Office de la Naissance et de l'Enfance (ONE) is a public organisation overseeing preventive care activities for children within the Wallonia-Brussels Federation. One of the main missions of ONE is to offer free preventive care consultations from birth to the age of 6 years. ONE also issues health recommendations for early childhood day care facilities.

The COVID-19 pandemic had a considerable impact on these ONE activities.

As events and political decisions unfolded between March and December 2020, actions were taken first to limit children's consultations to the most essential services like vaccination, and later to facilitate a cautious return to regular activities.

After initial difficulties to ensure sufficient doctor presence were addressed, vaccination was successfully pursued. Although many families were supported, delays in follow-up and screening inevitably occurred and constitute a challenge for the future.

With regards to day care facilities, protocols were put in place to limit at-risk contacts. Conditions for authorising access to day care were regularly reviewed, and measures to take after a SARS-CoV-2 infection occurrence were regularly adapted in line with national recommendations.

Day care facilities were provided with key contact persons within ONE for advice, who were themselves supported by regular updates of recommendations. Broader communication and closer collaboration with doctors working outside ONE were highlighted as critical.

This pandemic crisis raised many challenges, yet the commitment and adaptability of professionals within and outside ONE allowed for continuity of preventive care for young children, and contributed to ensuring quality day care.

## Introduction

The *Office de la Naissance et de l'Enfance* (ONE) is well known to Belgian French-speaking paediatricians. This public organisation, placed under the authority of the Government of the French Community, is the reference body of the Wallonia-Brussels Federation for all matters relating to preventive care in childhood (1).

One major mission of ONE is to support children within, and in relation to, their family and social environment. This mission is carried out primarily through the following services:

- Prenatal consultations
- Children's consultations and home visits
- Child protection teams (*équipes SOS enfants*)
- School medicine services (*services de promotion de la santé à l'école*)

The other major mission of ONE is to authorise, support and evaluate services that provide childcare to children outside the family environment. These include:

- Early childhood day care facilities
- After school activities (*accueil extrascolaire*) and homework schools (*écoles de devoirs*)
- Holiday centres (*centres de vacances*)

Alongside these two main missions, ONE has developed expertise in the following domains: parenting support, health promotion and health education, and the promotion of continuing education amongst childcare professionals. ONE also conducts evaluations of the needs of the population and research into emerging public health issues in order to make necessary adjustments to its services.

The arrival of the COVID-19 pandemic significantly disrupted social activities and the organisation of healthcare in general. In private medical practice and hospitals, non-essential services were suspended and only emergency consultations were maintained. The services provided or supported by ONE were also inevitably impacted.

This article will review how ONE early childhood preventive activities adapted to the circumstances of the pandemic crisis between March and December 2020. The first part will focus on preventive care follow-up for children aged 0 to 6 years in the context of ONE consultations. The second part will focus on early childhood day care facilities for children aged 0 to 3 years.

## Part one: Preventive care follow-up for children aged 0-6 years in the context of ONE consultations

### Outline of the service in usual times

Preventive care follow-up from the antenatal period up until a child's 7th birthday is offered by ONE to all families within the Wallonia-Brussels Federation. The purpose of this service is to promote the healthy development of children through regular health checks, vaccinations, advice and parenting support. The service is free of charge and taken up on a voluntary basis. Children are seen at regular intervals according to a predefined schedule (fig. 1). Some children requiring closer follow-up due to physical or psychosocial vulnerability are offered additional appointments in what is referred to as "enhanced follow-up" (*suivi renforcé*).

At a local level, ONE preventive care services are provided through a network of 846 professionals called *Partenaire Enfants-Parents* (PEP's) who are di-

i Translation: Office of Birth and Childhood

rectly employed by ONE. These are professionals with a background in nursing, social care, or midwifery, who receive specific training upon joining ONE. They visit parents on maternity wards (*service de liaison*) and offer home visits. Together with doctors and volunteers, they run the preventive care children's consultations in one of 584 locations across the Wallonia-Brussels Federation. In 2019, 70-75% of children younger than 2 years living in Wallonia or Brussels were registered with ONE and attended a consultation at least once within the year. This percentage drops in higher age groups, giving an average attendance rate of 42% across the age range 0-6 years (3).

About a thousand doctors work within ONE consultations, mostly general practitioners (85%) and paediatricians (13%). They assess children in pairs with a PEP's, paying particular attention to priority areas and guidance set by ONE (2). About 4500 volunteers (often senior people) welcome families to the consultations and take anthropometric measurements. They may also take on additional duties, such as looking after the premises and completing various administrative tasks.

As part of parenting support activities, parents and children also have access to group sessions organised within the consultation (*activités collectives*). These are free of charge and aim to promote learning, play and socialisation. Examples of activities include reading, psychomotricity, baby massage and play sessions.

In addition, ONE organises a visual screening programme for children aged between 18 and 36 months. At this age, visual screening aims primarily to detect amblyogenic risk factors (4). It takes place within ONE consultations or day care facilities, and is performed by an orthoptist, or a specifically trained doctor or nurse. The screening programme organised by ONE reaches about two thirds of children born in the Wallonia-Brussels Federation (1).

**Actions taken during the pandemic**

In March 2020, a crisis unit was set up within ONE, which included the ONE general administrator, a crisis coordinator, and managers from key directorates (health, human resources, logistics, communication, protection at work). The crisis unit was responsible for the identification and analysis of information about the new coronavirus, and for making strategic decisions for ONE and interacting with the relevant ministries. A representative of the ONE crisis unit was present at the Risk Management Group (RMG) which monitored the overall situation at the federal level.

On 13 March, following the magnitude of the COVID-19 epidemic, the Belgian National Security Council announced lockdown restrictions for the population. This included the closure of schools for all children. On 19 March, the RMG recommended maintaining only essential services.

With the support of the vaccination programme of the Wallonia-Brussels Federation and the *groupe interuniversitaire d'experts en vaccination* (GIEV), ONE deemed that the vaccination of infants is an essential service. The concern was that stopping this vaccination could have serious consequences for the health of infants in the short term (adding workload to curative health services, already under pressure because of COVID-19), and in the long term, as a drop in vaccination coverage could lead to the resurgence of other epidemics. This view was echoed in recommendations issued on 20 March by the Regional Office for Europe of the World Health Organisation (5).

Consequently, ONE gave the following instructions regarding its consultations:

- Consultations are maintained to ensure vaccinations for children between 2 and 15 months, and to allow the follow-up of children considered to be particularly at risk. For the latter, the PEP's are asked to prioritise the most vulnerable children amongst children receiving a suivi renforcé.

- Volunteers are no longer allowed to participate in consultations, whether or not they belong to a high-risk group for COVID-19.

- Doctors or PEP's belonging to high-risk groups are exempted.

- Appointments for consultations are spaced out to avoid crossing of families.

- Each child is accompanied by only one adult (symptom-free).

- Hygiene measures are enhanced and include disinfection of equipment and surfaces between visits.

- Home visits are no longer allowed; PEP's are asked to contact families by telephone.

- Visual screening examinations and group sessions are suspended.

Some maternity wards organised follow-up of new-borns up to 2 months of age within the hospital, but this practice was not generalised. In order to guarantee adequate care for new-borns, as of 7 April all PEP's were asked to make sure by telephone call that new-borns were seen in a paediatric consultation during the first month of life, and if that was not the case, to book them into a ONE consultation.

On 4 May, the country entered a phase of gradual easing of lockdown restrictions.

Schools reopened with specific timetables and protocols (phase 2 – 18 May).

ONE maintained a cautious attitude with regard to the organisation of its services:

- Hygiene measures and the spacing of appointments still apply. Surgical masks are now available and used by the doctor and the PEP's.
- Systematic appointments for children in the first month of life and all *suivis renforcés* are resumed.
- Consultations which include a vaccination are now also allowed for older children (5-6 years), although priority is still given to vaccinations administered between 2 and 15 months, as per international guidance advising to prioritise primary series vaccinations (5).
- Medical examinations are gradually extended to the following key ages: 1, 2, 3, 4, 8-9, 15, 18 months.
- PEP's are encouraged to make telephone contact with the families of children registered with the consultation.

Between June and October 2020, as the gradual easing of lockdown restrictions continued, instructions were again adapted:

- Medical examinations are further extended and anthropometric measurements are resumed.
- Home visits are allowed for the *suivis renforcés*.
- Visual screening examinations restart as of 8 June.

From mid-October 2020, as the second wave of the COVID-19 epidemic hit Belgium, new lockdown measures came into place.

ONE re-considered certain decisions taken at the beginning of the summer:

- Home visits are limited to exceptional situations.
- Visual screening examinations are again suspended.

**Successes**

In this unprecedented situation, there emerged a number of positive points:

At the beginning of the first lockdown period, many ONE consultations were being cancelled due to absence of doctors. In order to help ONE pursue its vaccination activities, the *Groupement Belge des Pédiatres de Langue Française* (GBPF) made an announcement inviting paediatricians to join ONE consultations. Thanks to this doctor mobilisation effort, twenty-five doctors came forward, including some general practitioners. A number of doctors already working within ONE consultations also offered to work additional hours. Over the following weeks, more than three-quarters of planned consultation sessions were held.

Consultation staff showed flexibility and creativity. Opening hours for consultation sessions were extended to compensate for the effect of having to space appointments and allow for a greater number of children to be seen. Communication channels with parents were diversified (telephone, WhatsApp, Messenger, Teams).

Parents were given the opportunity to share their concerns about their child through contacts with ONE, when many other preventive and parenting support services were not available. This was particularly important for new mothers, as reduced support during this period has been shown to have detrimental effects on maternal mental health. Moreover, during the COVID-19

ii Translation: Child-parent partner. Formerly known as *Travailleur médico-social* (TMS)
iii Translation: inter-university group of experts in vaccination
iv Translation: Belgian association of French-speaking paediatricians.

pandemic, mothers in the perinatal period were prone to heightened distress, and generally had reduced social and emotional support (6).

In the absence of a digital ONE record and vaccination registry (these are currently being developed), it is not possible to assess the impact of the pandemic on vaccinations taking place within ONE consultations accurately. Some indications on the magnitude of this impact can be provided by the number of vaccine orders made by ONE consultations. Compared to 2019, orders decreased by 5-6% in 2020 for the DTPa-Hib-VHB-IPV (Hexyon®), PCV13 (Prevenar13®) and Measles-Mumps-Rubella vaccines (M-M-R-vax-pro®). The decrease was larger (18%) for the DTPa-IPV vaccine (Tetravac®) given at 5-6 years, which can be explained by the priority given to primary series vaccinations. Notwithstanding the limitations of indirect data based on vaccine orders, these figures tend to suggest that the impact of the pandemic on the vaccination of children attending ONE consultations is not as preoccupying as it has been is certain other countries (7). Nevertheless, it is important to stay vigilant to the vaccine status of children and to use every opportunity for catch-up vaccinations where necessary.

### Challenges

Many challenges were identified during the crisis, some of which have implications also for the post-pandemic period:

ONE and the *Collège de Médecine Générale de Belgique Francophone* (CMG) had, at one point in time, different positions regarding the continuation of preventive care consultations. This temporarily led to confusion among general practitioners working within ONE consultations. The CMG reviewed its position on 19 March following discussion with ONE.

The number of visits to ONE consultations decreased by about 30% in 2020 compared to the previous year, which could lead to delay in the detection of some medical problems. The largest decrease was observed in the second trimester of 2020 (41%).

With the interruption of home visits and the decrease of contacts with families within consultations, it is feared that situations of vulnerability may have not been recognised as readily, resulting in adverse consequences for the future.

PEP's making contact by telephone were not able to adequately reach parents with whom there is a language barrier and with whom consultations are normally conducted through an interpreter. In Brussels, about one fifth of ONE consultation time is normally carried out in the presence of a formal interpreter.

Due to the interruption of visual screening examinations, delays have occurred in the visual screening programme. This may result in lower coverage rates for the current cohort of children aged 18 to 36 months.

### Conclusion

In times of pandemic crisis, it is important to maintain preventive care activities in order to avoid delays in vaccination and the possible resurgence of vaccine-preventable diseases. It is also essential to maintain close contact with families in order to detect or prevent situations of vulnerability, which are accentuated by the social isolation imposed by lockdown restrictions. Thanks to the remarkable mobilisation of PEP's and doctors, ONE was able to pursue vaccination activities and to support many families through this challenging period.

## Part two: Early childhood day care facilities for children 0-3 years

### Outline of the service in usual times

In 2019, early childhood day care capacity in the Wallonia-Brussels Federation reached 47000 places (3). Day care is either based in a dedicated facility for a large number of children (*accueil collectif*) or in the home of a childcare professional (*accueil familial*).

ONE has a role in promoting quality day care by authorising, supporting and evaluating early childhood day care facilities. A network of ONE professionals spread across the different provinces of the Wallonia-Brussels Federation provide information and support to day care managers and childcare professionals, and ensure that day care facilities fulfil legal norms.

Support on health issues is provided more specifically through the day care facility doctor, who visits the day care facility on a regular basis to perform health checks on the children. For day care facilities without a doctor, support on health issues is provided by one of nine health advisors (*Référent Santé*). These are nurses with a master of public health employed by ONE.

The day care facility doctor and the *Référent Santé* must pay particular attention to health areas and guidance set by ONE (8). Health priorities in the day care setting include vaccination, management of infectious diseases and epidemic risks, hygiene and disinfection, the health of children with special needs, and health information for childcare professionals.

### Actions taken during the pandemic

On 13 March, the National Security Council announced that early childhood day care facilities were to remain open.

In response to this decision, ONE elaborated hygiene and social distancing protocols aimed at limiting at-risk contacts within day care facilities:

- Only one person can drop off or pick up the child, and movement of parents and staff within the day care facility is restricted.
- Children with chronic conditions that weaken their immune system should be cared for at home .
- PEP's are no longer deployed in the day care facilities where they normally work in pairs with doctors performing health visits. This practically results in the discontinuation of preventive care follow-up in many day care facilities. Families are directed to ONE consultations for vaccinations.

Between 16 March and 4 May, child attendance at day care facilities fell as a result of lockdown restrictions. The government of the Wallonia-Brussels Federation decided, on the one hand, to suspend the financial contribution of parents and, on the other hand, to grant allowances to day care facilities. Support measures amounted to a total of EUR 18 million (10).

From 4 May onwards, attendance rates began to rise gradually. To support decision making, an algorithm was created by the *Collège des Conseillers Pédiatres de l'ONE* specifying the symptoms which justify a child's exclusion from day care, and incorporating the measures to be taken when a child or his/her cohabitant, or a childcare professional, is infected with SARS-CoV-2 (fig. 2). This algorithm has since been regularly adapted, in line with Sciensano's evolving recommendations.

Many day care facilities had to close because of COVID-19 cases or quarantine amongst childcare professionals and they could benefit from financial assistance from ONE (10).

### Successes

Despite the many difficulties, some positive points can be highlighted:

Day care facilities having to deal with situations related to COVID-19 were provided with a key contact in the person of the *Référent Santé*. This person played a crucial role in disseminating accurate up-to-date information, and in supporting day care facilities with COVID-19 tracing and the application of recommendations.

Recommendations were regularly updated and communicated by e-mail to managers of day care facilities, and via an online platform to doctors of day care facilities. The COVID-19 crisis additionally emphasised the importance of broader communication of ONE recommendations. In particular, paediatricians and general practitioners working outside ONE needed to be informed of criteria justifying exclusion from and return to the day care facility. This was aimed by including a link to the ONE website in the Newsletter of the COVID-19 Belgian Paediatric Task Force .

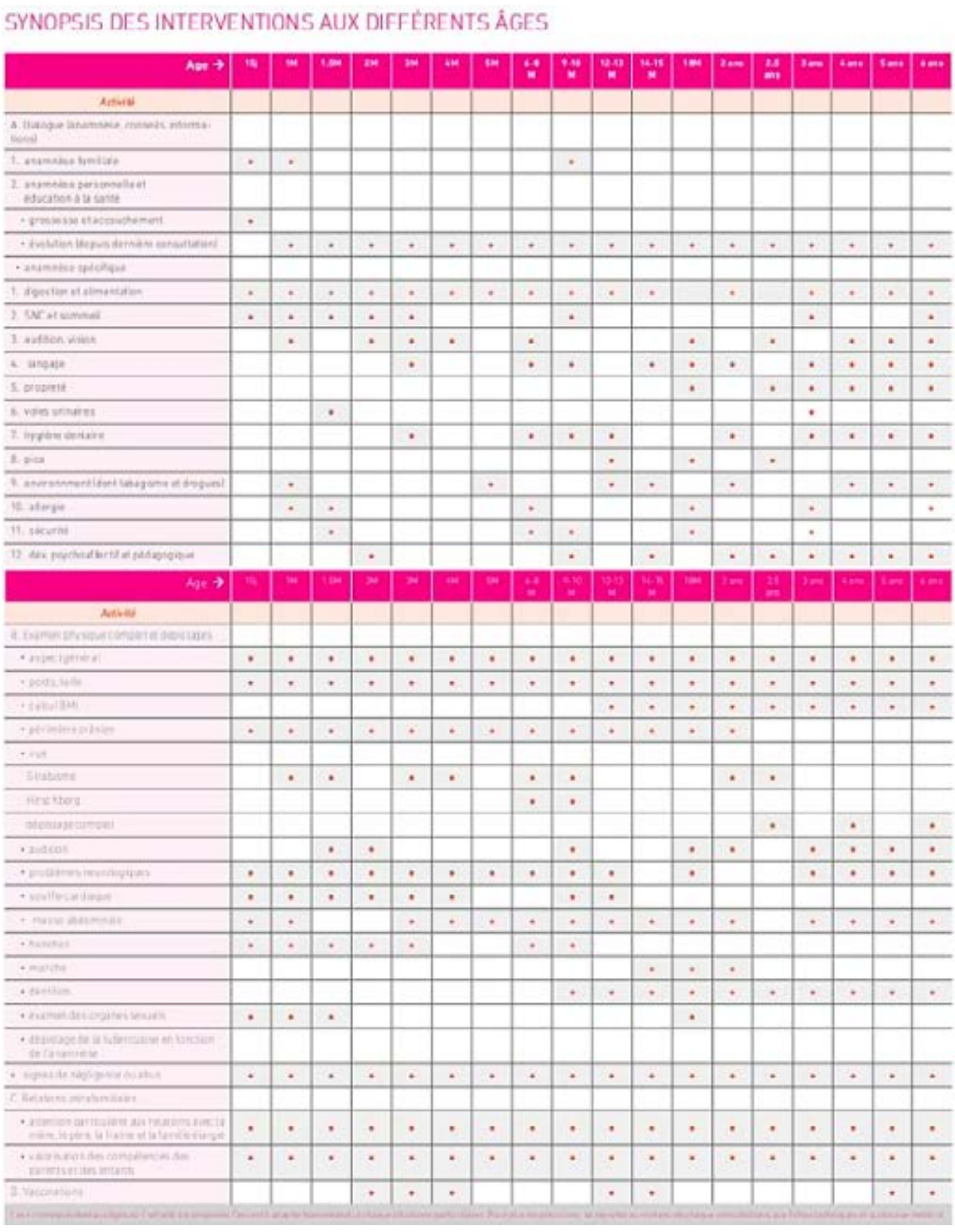
### Challenges

The challenges were multiple, and constitute points of attention for the future:

With, on the one hand, the rapidly evolving knowledge about SARS-CoV-2 and, on the other hand, rapidly changing decisions at a political level, ONE recommendations needed to be reviewed at short intervals. Frequent changes have at times undermined understanding and acceptance of the recommendations by childcare professionals and parents.

vi A list of specific conditions to be taken into consideration when deciding whether a child should attend school (or daycare) was subsequently elaborated by the Belgian COVID-19 Paediatric Scientific Committee and published in August 2020 (9).
vii Translation: College of Paediatric Advisors of ONE. This College advises ONE on health matters and is composed of paediatricians (Conseillers Pédiatres) overseeing early childhood ONE activities within each province.
viii Sciensano: national public health institute of Belgium

**Figure 1 :** *ONE consultation schedule: summary of interventions (2)*

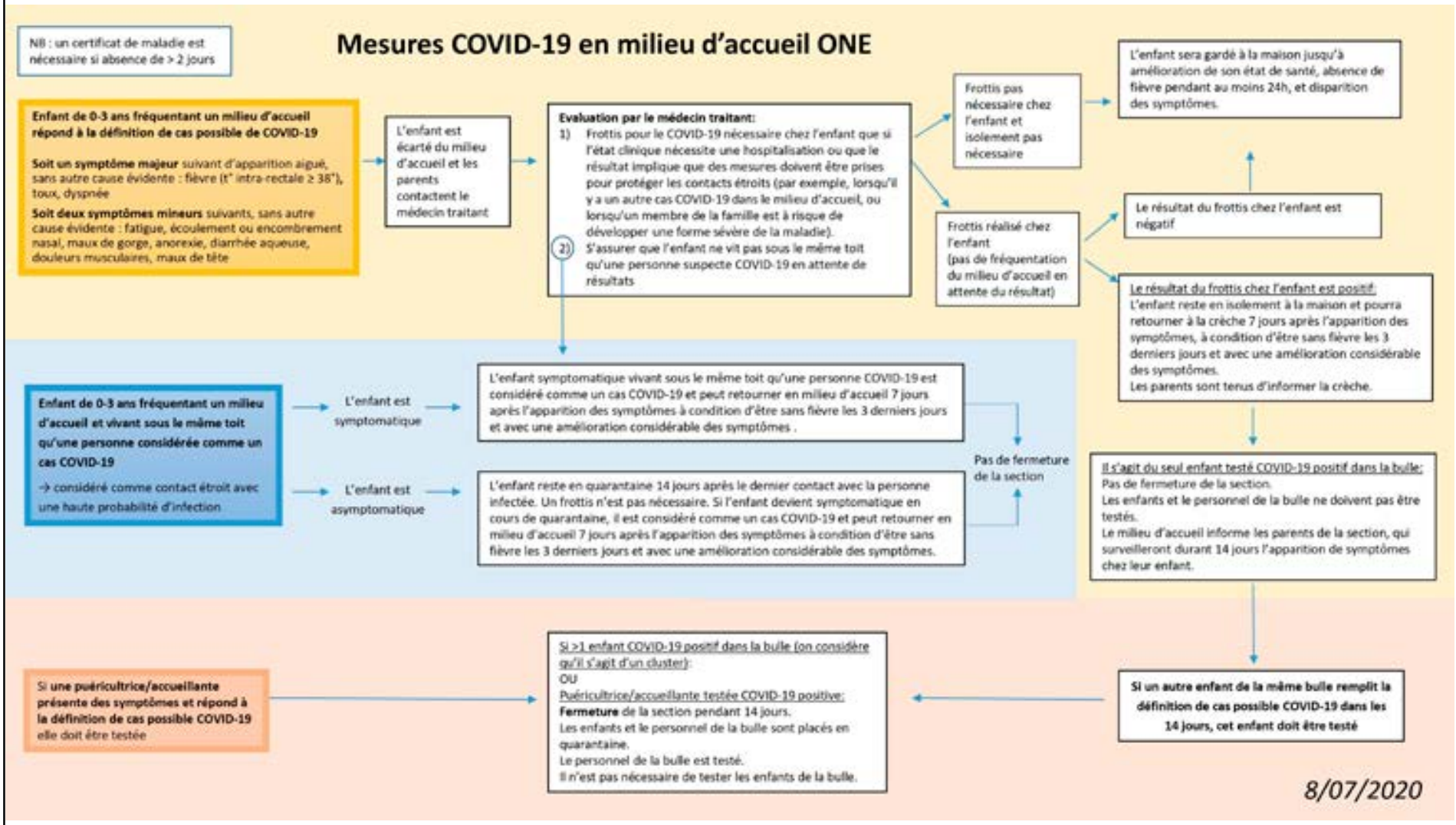



To ensure coordinated action and communication, every update in recommendations and associated communications needed to be validated by the ONE crisis unit. This sometimes caused a time-lag in implementation in the field.

Paediatricians and general practitioners are important actors in the application of criteria for exclusion from and return to the day care facility after an illness. Yet, ONE does not currently have a direct channel to communicate with all these professionals.

The COVID-19 pandemic highlighted the need for closer collaboration with occupational health to ensure that day care facilities receive concurring messages which take into account both the protection of childcare professionals and the well-being of children.

**Figure 2 :** *Algorithm to support decision making in day care facilities*



At peaks of the COVID-19 epidemic, the number of requests for advice relating to confirmed or suspected cases of SARS-CoV-2 generated substantial workload for day care doctors and the *Référent Santé*, which regularly exceeded normal working hours. Moreover, involvement of infectious disease control experts from partner organisations (AVIQ  & COCOM ) was possible only for a very limited number of situations, as these experts' attention was largely drawn towards adult care settings, including nursing homes.

### Conclusion

This pandemic has highlighted the complexity of supporting day care facilities during an epidemic crisis. It is essential to be able to adapt to the evolving epidemiological situation and to review recommendations continually. This includes reviewing conditions for authorising access to day care facilities. Recommendations must be coordinated with those of other official organisations, and must be communicated widely. This can help to ensure safe and quality day care for children, while supporting childcare professionals and society.

## General Conclusion

This article has reviewed how ONE early childhood preventive activities adapted to the circumstances of the pandemic crisis between March and December 2020.

The sudden outbreak of the pandemic caused considerable initial disruption to ONE operations. Nevertheless, and in a context of rapidly shifting public health recommendations and political decisions, the organisation managed to adapt and deliver preventive care services, and to support day care facilities, thereby fulfilling essential missions.

This pandemic crisis raised many challenges, yet the commitment and adaptability of health professionals within and outside ONE allowed for continuity of preventive care for young children, and contributed to maintaining quality day care.

This unprecedented crisis also highlighted new opportunities for collaboration between actors within the early childhood field. Such collaboration should be pursued and strengthened during the remainder of the pandemic and beyond.

### Acknowledgments

The ideas presented in this article are the result of discussions held during the bi-monthly meetings of the *Collège des Conseillers Pédiatres de l'ONE*. This College advises ONE on health matters and is composed of paediatricians (*Conseillers Pédiatres*) overseeing early childhood ONE activities within each province.

### Conflicts of Interests

The authors have no financial disclosures relevant to this article. The authors declare that they have no competing interests. This article has been written without financial support.

ix COVID-19 Belgian Paediatric Task Force: scientific group advising authorities, professionals and the public on matters pertaining to COVID-19 and children.

x Agence pour une Vie de Qualité (AVIQ): public agency with health responsibilities at the level of Wallonia.

xi Commission Communautaire Commune (COCOM): public agency with health responsibilities at the level of Brussels.

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Article

# Does a restrictive visitor arrangement on the NICU, due to the COVID-pandemic, have a negative impact on the parent-child bonding process?

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## Keywords

COVID-19, Parent-child bonding, Premature baby.

## Abstract

**Background and objectives**

Due to the COVID-19 pandemic and the associated safety measures, visitor arrangements on the neonatal intensive care unit had to be drastically restricted. This single-centre prospective study investigated the influence of this restrictive visitor arrangement on parent-child bonding.

**Methods**

Thirty parental couples were recruited. Their preterm children were born at a gestation age between 25+4 and 37+3 weeks.

During restricted visitor policy only one parent at a time was allowed to visit and kangaroo the baby with a time restriction of 3 hours per day per parent. During non-restrictive policy there were no time restrictions for parental visits and parents were allowed to visit their baby simultaneously.

Fourteen couples were recruited during restricted visitors policy in April 2020. Sixteen couples were recruited in the following period with non-restrictive policy. The couples filled in two questionnaires, the Dutch Postpartum Bonding Questionnaire and the Dutch Edinburgh Parental Depression Scale, at one week postpartum (T1) and at the child's age of four months (T2).

**Result**

At T1 there was a significant (p= 0.019) lower Postpartum Bonding Questionnaire-score in the non-restrictive group, representing better parent-child bonding. This difference between these groups was not found at 4 months postnatally.

**Conclusion**

We suggest that restrictive visitor policy on the neonatal intensive care unit had a negative effect on early parent-child bonding. This shows the importance of an unlimited visitor policy. Little is known about long-term effects of parent-child bonding at specific ages, although some reports emphasize the importance of very early parent-child bonding. Further investigations are needed.

## Introduction

Parent-child bonding is a very important, well-known, but hard to define concept.

It is an innate system in mammals that consists of biological reactions that make a parent and child seek reciprocal proximity, and stimulates the parent to keep the child safe. The evolutionary purpose is to ensure survival to a reproductive age. But there is more. Early attachment will also shape future behaviour of the child and recent brain research with Diffusion Tensor Imaging tractography has shown that the quality of parent-child interaction influences development of connectivity in certain areas of the brain(1-3).

To achieve secure attachment the caregiver needs to be present and available, responsive and sensitive to the emotional and physical needs of their infant. Personal factors like parental stress and depression can influence the responsivity and sensitivity of the parent and thus jeopardise the parent child bonding, but also external factors such as separation from the child and low responsiveness of the infant have impact on the bonding process (4). Earlier studies found that physical closeness on the neonatal intensive care unit (NICU) facilitates emotional closeness and benefits the parents' psychological well-being and their relationship with their baby (5). Research in the field of neonatology has identified different other external factors that have impact on the parent-child bonding. It is known that prematurity and the associated compromised health expectation play a negative role in the quality of parental engagement with the baby (6-8). On the other hand, having a vulnerable child can also intensify the parental care and bonding. When parents have access to abundant resources (material resources such as food and financial income, but even more important non-material resources such as support in how to find relevant information and how to use problem-solving tactics), they are more likely to invest in their high risk child. This non-material support is offered to parents by a highly engaged NICU-staff during the hospitalisation of their child. The more parents are present, the more this kind of support reaches them (9). Long hospitalisation also has a negative effect on bonding. Breastfeeding on the other hand is a positive contributing factor (10, 11). Parent-child bonding can also be fostered by skin-to-skin contact (SSC) (12). Earlier studies indicated that immediate SSC in the delivery room has a positive effect on the early bonding process (13). In addition, support of the partner during this neonatal period is shown to be an important factor for the mothers' wellbeing and will enhance her interaction with the baby (14).

In this COVID-19 pandemic protecting the most fragile individuals in our society is top priority. This applies strongly to the infants on a neonatal intensive care unit. In April 2020, the peak of the first wave of the COVID-pandemic in Belgium, the hospital visitor arrangements were drastically cut down. At this point, there were no national or international guidelines available with advise on NICU visitor arrangements. Our local hospital protocol did not allow any visitors for patients at that time. Parents of paediatric and neonatal patients were excepted in this protocol, but their visits were restricted. The restricted

visitor policy was based on the national protocols for social distancing (1,5 metre distance and surgical masks). Due to infrastructural limitations in the NICU ward we had to limit the amount of people present at the same time on the ward. The visitors restriction meant that only one parent at a time was allowed to visit and kangaroo the baby with a time restriction of 3 hours per day for each parent. Parents were not allowed to visit their baby together. As a consequence the present parent was also deprived of support of their partner during their visits. In July and August a lower national infection rate permitted diminished restriction measures. Larger groups were allowed to have outdoor contact, and smaller groups indoor. In our NICU-unit all parents were allowed to visit their baby together, at any time and with no time restriction.

Since restrictive visiting arrangements limited time for interaction with the baby, skin-to-skin contact and breastfeeding and also made simultaneous visit of both parents impossible, we hypothesized that the restrictive visitor arrangement could negatively influence parent-child bonding.

## Methods

Approval was granted by the Research Ethics Committee Ziekenhuis Oost-Limburg (ZOL) (ctu2020029).

In this single centre prospective study conducted at the NICU ZOL parents were asked to fill-out 2 questionnaires on 2 different points in time: at 1 week postnatal age ( T1) and at 4 months post-natal age (T2). Both parents or either father, or either mother filled in both questionnaires at T1 and T2 (see table 1 for the distribution). Thus for each parent couple one set of questionnaires was completed at both of the different points in time by the same person(s). The questionnaires were anonymised and completed online. The gestational age, days of hospitalisation and the self-reported daily time both of the parents spent with their child, regardless whether they were just holding the baby or whether they practiced SSC, were noted. Crib scores were calculated for each neonate, indicating the severity of disease (15).

**Table 1:** Baseline characteristics

| | Restrictive group | Non-restrictive group | Total |
|---|---|---|---|
| **Female gender baby, n (%)** | 8 (53%) | 9 (53%) | 17 (53%) |
| **Mean gestational age** | 32+5 | 32+5 | - |
| **Mean duration of stay (d)** | 36 | 39 | - |
| **Respondent mother, n (%)** | 9 (64%) | 10 (63%) | 19 (63%) |
| **Respondent father, n (%)** | 1 (7%) | 1 (6%) | 2 (7%) |
| **Respondent both parents, n (%)** | 4 (29%) | 5 (31%) | 9 (30%) |
| **Crib score, mean** | 1.07 | 1.69 | - |

Abbreviations: n, number

All infants admitted to our NICU in April 2020 and for the non-restrictive period in July and August 2020, were screened for eligibility. Additional inclusion criteria were: at least 1 week NICU-admission, good understanding of Dutch language and parental informed consent.

Perceived parent-child bonding during the covid-restricted visitor arrangement, in which only one parent at a time was allowed to visit and kangaroo the baby with a time restriction of 3 hours per day for each parent, was compared to a visitor arrangement where both parents were allowed at the same time without time restrictions.

Dutch validated self-report questionnaires were used, one on parental-child bonding, the Postpar-tum Bonding Questionnaire (PBQ) (16) and one on mental well-being of the parents, the Edin-burgh postnatal depression scale (EPDS) (17).

The PBQ consists of 25 statements, each followed by six alternative responses ranging from 'al-ways' to 'never'. Positive responses, such as "I enjoy playing with my baby", are scored from zero ('always') to 5 ('never'). Negative responses, such as "I am afraid of my baby", are scored from 5 ('always') to zero ('never'). The PBQ categorizes these 25 statements into 4 factors, from which we only used factor 1: general bonding. This factor is based upon 12 of the statements with a maxi-mum total score of 60, all scores up to 11 are categorised as normal (18). The other factors of this questionnaire are for detecting severe bonding problems and fears in parents with pre-existing psychological problems, which is not applicable for our group.

The EPDS consists of 10 items, developed to detect postnatal parental depression. Parents have to indicate how often they experience certain symptoms or feelings during the past week. The answers of the EPDS range from 'yes, always', 'yes, most of the time', "no, not very often' to 'no, never' and score respectively from 0 to 3. The total score is between 0 and 30. Evins et al. set the threshold value at a score of 11 or higher, indicating parental depression with a high sensitivity (19, 20). This threshold was also used in this study.

### Statistical tests

For comparison of the PBQ data we used paired and unpaired T-tests where appropriate. The EPDS data was compared with the Mann-Whitney U test and the Wilcoxon signed-rank test.

We conducted a power analysis to calculate the desired sample size. With a power of 0.8 and a alpha of 0.05 we found a sample size of 32 included parent couples.

## Results

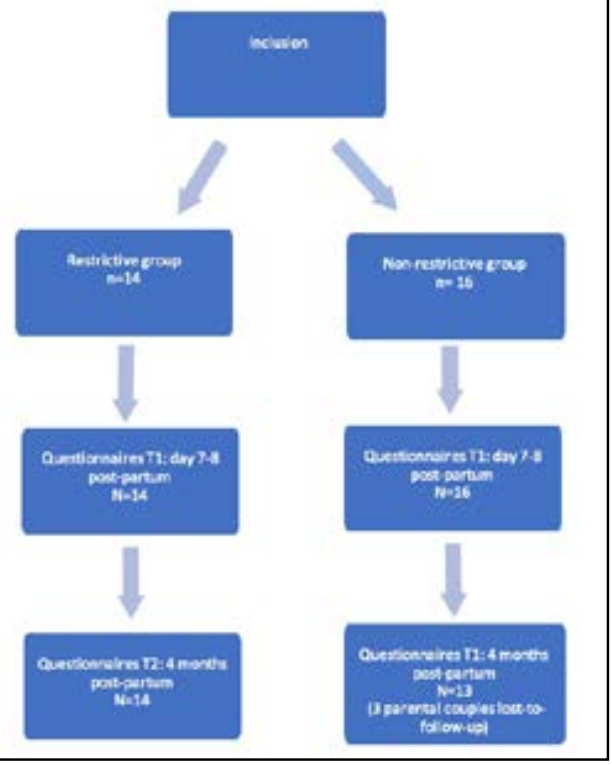
### Recruitment

Thirty couples of preterm children born between a gestational age of 25+4 and 37+3 weeks were recruited. Fourteen couples were recruited during the restricted visitors policy of 8 weeks. Sixteen couples were recruited in the following period with non-restrictive policy for parents (figure 1). There were no differences in baseline characteristics between the two groups (Table 1).

There was a loss to follow up of 3 couples in the non-restrictive group on T2, therefore the T2 data of these 3 couples was excluded for the T2 analyses and for the T1 versus T2 analyses.

On T2 all of our included patients were discharged.

**Figure 1 :** *Flowdiagram timeline*



**Results T1 (restrictive versus non-restrictive group)**

The total PBQ score on factor 1 (general bonding) was compared between the two groups and initially no significant difference was found. However reviewing the separate data of the non-restrictive group one extra-ordinary high result stood out (Figure 2), it differed greatly from the main trend of result in this group. When this single score was considered an outlier and excluded from the non-restrictive group, there was a significant difference (p=0.019) between the restrictive (mean score 5.41) and non-restrictive group (mean score 2.50) at T1 with lower PBQ scores in the non-restrictive group. This indicates a better perceived parent-child bonding in a non-restrictive visitor arrangement.

No significant difference in EPD scores was found for both groups at T1.

**Results T2 (restrictive versus non-restrictive group)**

The total PBQ score on factor 1 (general bonding) and the EPD scores was compared between the two groups (restrictive group mean score 4.64, non-restrictive group mean score 5.54) and no significant differences was found at the age of 4 months postnatally.

Results T1 versus T2

The total PBQ score on factor 1 (general bonding) for both the restrictive (mean difference 0.50, p= 0.75) and non-restrictive group (mean difference -2.58, p= 0.07) was compared at T1 and T2 and no significant difference was found.

However, a significant difference for the EPDS between T1 and T2 for both the restrictive (T1 median 11.50, T2 median 5.50, p=0.011) and the non-restrictive group (T1 median 10.00, T2 median 8.00, p=0.011) with lower EPD scores on T2 was found, indicating fewer depressive feelings at the child's age of 4 months.

**Daily time spent with child**

Table 2 shows the different indications of time spent with the child filled in by the parents on T1 and T2. There is an evident difference between the groups consistent with the restrictive measures on T1. At T1 65% of the parents in the restrictive group spent 2-4 hours per day with their child, while in the non-restrictive group at T1 only 19% of the parents spent 2-4 hours per day with their child, while 50% spent 4-6 hours per day and 31% even more than 6 hours per day. At T2 equalization of time parents spent with their child in both groups is seen.

**Table 2:** Self-reported daily time spent with child

| | T1: restrictive | T1: non-restrictive | T2: restrictive | T2: non-restrictive |
|---|---|---|---|---|
| **<2 hours/day contact** | 0% | 0% | 0% | 0% |
| **2-4 hours/day contact** | 65% (N= 9) | 19% (N=3) | 7% (N=1) | 0% |
| **4-6 hours/day contact** | 21% (N=3) | 50% (N=8) | 7% (N=1) | 23% (N=3) |
| **>6 hours/day contact** | 14% (N=2) | 31% (N=5) | 86% (N=12) | 77% (N=10) |

## Discussion

The forced restricted visitor policy for parents due to the COVID-19 pandemic provided a unique opportunity to look at the importance of physical closeness in the NICU on the parent-child bonding.

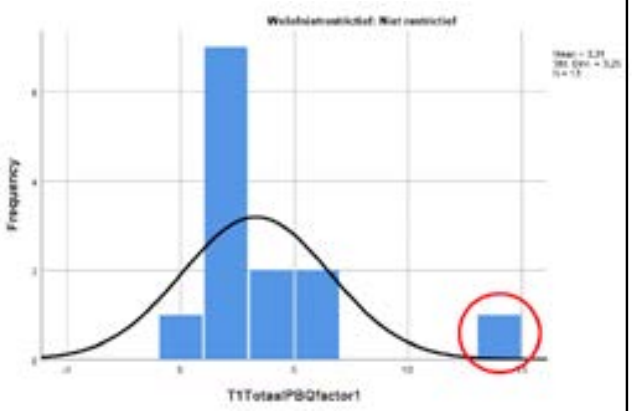
In this study we found a strong indication that restricted visitors' arrangements on the NICU had a negative impact on the early parent-child bonding.

Factors that might explain this impact are differences in SSC, a lower rate of really breastfeeding, a lesser extent of parental presence and skin to skin contact, interaction and the lack of the partners' support.

**1. Skin to skin contact and parental presence**

Previous studies have shown beneficial effects of physical contact between parent and infant with Kangaroo care and baby massage in the NICU (21, 22). The restricted visitor arrangement was implemented during the first COVID-19 lockdown in Belgium. With the national lockdown measures everybody had

**Figure 2 :** *Data histogram of total PBQ factor 1 with a single outlying result*




drastically less social obligations and more time at home. Many fathers were temporarily unemployed or working from home at their own rhythm during the whole period of the study. Since each parent had only 3 visiting hours a day, they both made great efforts to kangaroo as long as possible during these hours. When parents visit the baby together, we see that it is more likely the mother that will kangaroo during the visit. Together they could achieve a daily SSC-time of 6 h and sometimes even a little more: they were allowed to stay a bit longer when there were few parents present and distance could be guaranteed. Previous (2019) observations on the daily time of SSC on our NICU showed an average SSC time of 4 hours per day. A total time of SSC that to our experience was not less during the restricted visitors policy, but we did not measure the SSC-time exactly. On the other hand we saw that total time spent with the baby was less in the restricted group, compared to the non-restricted group.

On the other hand SSC is not always obvious for first-time fathers. Fathers tend to grow slower into parenthood. Their first concern is to protect the mother and their child. Their primary stress on the NICU is caused by loss of control. Involving them early in care for their premature baby frequently is, at first, an extra source of stress for them (23, 24). Since fathers in the restricted group were very quickly engaged in SSC, it could be that they experienced more stress at that time. This could have had a negative effect on the bonding with their child. In our study there were only 2 fathers that filled in the PBQ alone. This small sample size makes it impossible to make conclusions. Further research on the fathers of premature born children could give more insight in the importance of paternal skin-to-skin care.

**2. Breastfeeding:**

Breastfeeding has a positive effect on the mother-child binding process (11). Since mothers had maximal 2 options per day to breastfeed: at the beginning and at the end of their visit, this could have contributed to the negative impact on the parent-child bonding in this group. We did not collect data on the daily number of breastfeeding moments.

**3. Presence of the partner**

Another factor that might explain the negative effect of visit restrictions on parent-child bonding is the lack of presence of the parents' partner during the visit. There is little, but nevertheless increasing, literature on the role and importance of the father of a NICU patient (14). The support and presence of the partner can keep NICU-parents in emotional balance. Although all parents experience a lot of stress on the NICU, this does not need to be deleterious. The stress they undergo on the NICU can also be an opportunity to grow stronger as a couple and as a parent. From this point of view not allowing parents to be together near their baby could make them more insecure and might hinder bonding and interaction with their child.

Finally we can ask ourselves whether the more difficult bonding in the first week after birth is of importance for the further development of the baby,

when we see that this difference is levelled out at 4 months of age? Only few research is done on the effects of the quality of early parent-child bonding on later behaviour. In a literature review Thompson mentioned quite a few clinical studies that proved a strong relation between early attachment and specific personality features and anxiety disorders later on. But other studies in his review failed to confirm this (16). Nevertheless recent neuroscience research has demonstrated that early parent-child interaction defines the quality of connectivity between pallidum and temporal cortex, a trajectory for emotions and social behaviour. In depressed parents with lower parent-child interaction and lower bonding, less connectivity in this area was found (1). Other brain research indicates the importance of early (adverse) environment in the way the prefrontal cortex develops. The frontal circuits that originate from this prefrontal cortex have an important role in complex cognitive skills like decision-making and regulation of behaviour and emotions later on in life (25). Another clinical study investigated the effect of parental presence and infant holding on the neuro-development of the preterm infant and confirmed a positive effect of early parenting in the NICU on the neurobehavior of the child at term age (3).

A limitation in this study is the lack of exact data on SSC ratio and direct breastfeeding ratio in both groups. Secondly, only 6 to 7% of fathers filled in the questionnaire. Having parents fill in the questionnaires separately might have given more insight in the underlying mechanisms that hindered parent-child bonding in case of visit restrictions. The biggest limitation of this study however was the small sample-size. This sample-size was determined by the limited time frame with the restricted visitor arrangement during the first lockdown. There was a lower admission-rate at our NICU in these months, which is now confirmed in different studies (26). This unfortunately also caused a lower inclusion for this study then initially expected. However, even with this smaller sample-size the importance of a non-time restricted visitor arrangement for both parents and their babies was demonstrated.

## Conclusion

This study strongly suggests that a restrictive visitor policy on the NICU has a negative effect on early parent child-bonding.

The findings of this study emphasize the need to develop a visitor arrangement that facilitates parent-child bonding, and also could help to encourage parents to spend more time together with their babies in the NICU. Especially, since early parent-child bonding can have implications for the child later on. Further long-term studies for a better understanding of the relationship between early bonding and the effects later in life are needed. The results of this study should also encourage hospital management to provide sufficient space and facilities for each preterm infant and their family, so they can really “be together”, physically and emotionally.

### Conflict of interest statement

The authors have no conflict of interest to declare.

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Article

# Clinical Evolution and Disease Burden in Belgian Cystic Fibrosis Patients: effect of Newborn Screening?

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## Keywords

Hereditary spherocytosis; diagnosis; red blood cells; hemolysis; membrane protein defect

## Abstract

**Objectives:** We compared the clinical evolution and disease burden of 3 groups of Belgian children with cystic fibrosis (CF) depending on the mode of diagnosis: meconium ileus (MI), newborn screening (NBS) and clinical diagnosis (non-NBS) at 1-, 2- and 6 years of age.Methods: We conducted a retrospective observational cohort study based on data collected from the Belgian CF Registry report of 2016 including patients diagnosed between January 2006 and December 2016.

**Results:** 306 CF patients were enrolled. Age at diagnosis was the lowest in MI patients (median 0.12 months, IQR 0.00-0.36 months) but lower in NBS patients (median 1.38 months, IQR 0.82-1.74 months) compared to non-NBS patients (8.01 months, IQR 2.47-37.58 months, p-value < 0.001). Height z-scores at 1 year of age were better in NBS patients (median = -0.13, IQR -0.99 – 0.50) compared to non-NBS patients (MI median = -0.56, IQR = -01.53 – 0.02, non-NBS median = -0.54, IQR = -1.02 – 0.12, p = 0.03377). Annual prevalence of bacterial infections was not different between the 3 patient groups at the predefined time points. Burden of therapy was lower for NBS during the first 2 years of life. Lung function at 6 years of age did not show significant differences between the 3 groups.

**Conclusion:** This study suggests a beneficial trend for NBS as primary method of CF detection when comparing age at diagnosis, clinical evolution and burden of therapy between NBS and clinically diagnosed CF patients. A standardized care program after CF-NBS is needed to further improve the benefits of NBS.

## Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder primarily affecting the respiratory and the digestive system. It is caused by the presence of mutations on both copies of the cystic fibrosis transmembrane conductor regulator (CFTR) gene ( ). Absence of functional CFTR results in increased viscosity of exocrine secretions and primarily causing chronic lung infections and exocrine pancreatic insufficiency ( ). Until recently, the majority of diagnoses of CF in Belgium were made based on clinical suspicion.

Several studies have shown that starting therapy very early improves clinical outcome and prognosis, 'early' being specified as before 2 months of age ( , ). Therefore, it is important to diagnose CF as early as possible. Timely diagnosis can be achieved through a newborn screening program ( ). This program provides the opportunity to improve outcomes by initiating monitoring and treatment in the pre-symptomatic period ( ). It has been shown that compared with non-NBS CF patients, NBS patients are indeed diagnosed earlier and have their first clinic visit at a younger age ( ). Moreover, early diagnosis after newborn screening improves survival in cystic fibrosis patients ( , ).

At the time of this study, Belgium had no official program for newborn CF screening However, for many years, there have been local screening initiatives where patients were detected using cystic fibrosis newborn screening algorithms (10). The median age at diagnosis for the newly diagnosed CF patients in 2013 was 8.2 months but progressively decreased to 3.8 months in 2016 ( ,11). In 2016, about 18.0% were diagnosed by newborn screening (10). An official neonatal screening for CF (CF-NBS) by means of blood spot screening at the age of 3 to 5 days was introduced in January 2019 in Flanders (12,13). Wallonia and Brussels followed in January 2020 (14).

The aim of this registry study is to compare the demographics and clinical evolution of 3 groups of Belgian children with CF depending on the mode of diagnosis: meconium ileus (MI), newborn screening (NBS) and clinical diagnosis other than MI (non-NBS). We expect that CF patients with a NBS diagnosis will have a lower age at diagnosis. This could possibly lead to a better weight evolution, less burden of therapy and a better respiratory outcome.

## Materials and methods

### Study population

We conducted a retrospective observational cohort study based on data collected from the Belgian CF Registry (BCFR) report of 2016. Inclusion criteria for analysis were patients diagnosed with CF (typical and atypical) between January 2006 and December 2016. Typical CF was defined as having a positive sweat test and/or two CF disease - causing mutations. Atypical CF was defined as having a normal (Cl< 30 mmol/l) or intermediate (30mmol/l ≤ Cl ≤ 60 mmol/l) sweat test result or absence of 2 disease-causing mutations. Patients diagnosed after ten years of age were excluded. Within the selected patients, three cohorts are defined: patients presenting with meconium ileus at birth (MI), patients with a clinical diagnosis based on CF symptoms other than MI (non-NBS) and patients diagnosed based on newborn screening (NBS). The newborn screening cohort consists of patients with CF diagnosis after NBS during non-official temporal NBS initiative programs using a two-step algorithm of IRT/DNA (immunoreactive trypsinogen/DNA), IRT/IRT or IRT/PAP (pancreatitis-associated perotein).

### Data collection

The Belgian CF Registry collects clinical and demographic data of patients followed at all seven accredited CF Referral Centers in Belgium. The data in this registry consists of an annual point summary of clinical data. Clinical data include anthropometry (height, weight and BMI), lung function (percentage predicted FEV1 and FVC), microbiology i.e., annual prevalence of recorded

pathogens, prevalence of chronic infections, days of hospitalization and of IV antibiotics and other CF treatments. Microbiological annual prevalence is defined as pathogens found at least once during the whole year (11). Chronic bacterial infections were defined according to modified Leeds criteria (15). Method of CF diagnosis, sweat test result, genotype (CFTR mutations) and pancreatic status are registered at diagnosis.

We studied the following variables for the three defined groups: age at diagnosis (in years), height z-scores, weight z-scores, BMI z-scores, FEV1% predicted (Global Lung Initiative reference equations) and point prevalence of Methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa and Burkholderia cepacia infections (16-18),. The following treatment parameters were studied: days of hospitalization (per year), days IV antibiotics (per year), use of hypertonic saline, oral azithromycin and acid suppression therapy (proton pump inhibitor (PPI) or histamine 2 (H2) receptor blocker. We also specifically looked at number of hospitalization and IV antibiotic treatment for more than 14 days per year. All parameters were studied at three different points in time: at 1- (T01), 2- (T02) and 6 (T06) years of age. Anthropometric measures (height z-scores, weight z-scores and BMI z-scores) were compared yearly from 1 year of age until 6 years of age (16,17). Lung functions (percentage predicted FEV1 and FVC) were compared at 6 years of age (T06).

### Statistical analysis

We compared the three predefined cohorts at three time points: T01, T02 and T06. We also conducted a post-hoc analysis discarding the MI cohort to solely compare the non-NBS cohort with the NBS cohort. All data after a transplant is set to missing. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Means (SD), medians (Interquartile range - IQR), counts (n) and proportions (%) were used to describe the demographic and clinical characteristics of each group in the study sample. Bar charts and/or line graphs were obtained to depict outcome measures. Continuous outcomes were tested for normality. Differences were tested using Wilcoxon Rank Sum or Kruskal Wallis tests. Pearson Chi-square or Fisher Exact ($n \leq 5$) analyses were used to compare proportions between groups. An $\alpha$ value of 0.05 was set and all tests were two-tailed.

## Results

### Description of the cohort

In the BCFR, 1275 alive patients were registered by January 2016 with a median (IQR or range) patient age of 22.5 years (10). Since January 2006, 25 to 50 new CF diagnosis were made per year (10). A total of 306 patients were eligible for this study: MI (n = 47), NBS (n = 74) and non-NBS (n = 185). Both typical (n = 289) and atypical CF (n = 17) cases were included. Patients with an incomplete genotype (n = 28) all had a sweat chloride > 60 mmol/L and were thus categorized as typical CF. Patients with missing sweat test (n = 32) all had two disease-causing mutations identified and were thus classified as typical CF. Patients with an intermediate sweat test result i.e., 30 mmol/l ≤ CI ≤ 60 mmol/l (n=17) all had two identified mutations but only one mutation was clearly disease-causing and were therefore categorized as atypical CF.

Within the typical CF cases (n = 289), 47 patients were MI, 175 non-NBS and 67 NBS.

Within the atypical CF cases (n = 17), 10 patients were non-NBS and 7 NBS. As expected, MI did not occur in this group.

There were 132 typical CF patients F508del homozygous with a different distribution between the 3 cohorts (72/185 (39%) non-NBS patients, 32/74 (43%) NBS patients and 28/47 (60%) MI patients, p = 0.0384) and 80 patients heterozygous for F508del mutation (49/185 (26%) non-NBS patients, 22/74 (30%) NBS patients and 9/47 (19%) MI patients, p = 0.0907). Twelve atypical CF patients were heterozygous for F508del mutation (6 non-NBS patients and 6 NBS patients).

The majority of typical CF patients were pancreas insufficient (n=255/289 (88%), 149 non-NBS patients, 59 NBS patients and 47 MI patients) and all the atypical CF cases were pancreas sufficient (n =17)).

## Diagnosis

Median age at diagnosis was lower in NBS patients compared to non-NBS but was lowest in MI patients (Table 1). Excluding MI patients, NBS detected CF significantly earlier compared to non-NBS. Median sweat chloride increased from patients with a clinical diagnosis to NBS patients and finally to MI patients (Table 1). Post hoc analysis revealed that mean sweat chloride did not differ significantly between the NBS (median = 103.3 mmol/l, IQR = 83.0 – 110.0) and the non-NBS patients (median = 98.0mmol/l, IQR = 83.1 – 107.5, p = 0.3884).

### Anthropometric measures

At one year of age, weight z – scores were not statistically different between the 3 groups (Fig. 1). Height z-scores however were higher in NBS patients compared to MI and clinically diagnosed patients (Fig 1). At two years of age, neither height, weight nor BMI z-scores were significantly different between the 3 groups (Fig. 2).

At six years of age, newborn screened patients had lower weight and BMI z-scores compared to non-NBS patients (Fig 3). Height z-scores were not significantly different between the 3 groups (Fig 3). The proportion of patients with height greater than or equal to the 25th percentile increased from NBS patients (51.5%) to MI patients (57.1%.) and finally to clinically diagnosed patients (77.7%, p = 0.0092). The proportion of patients with BMI greater than or equal to the 25th percentile was higher in NBS patients (69.7%) compared to MI patients (42.9%) but was highest in clinically diagnosed patients (75.5%, p = 0.0132). Weight above the 25th percentile was not statistically different between the 3 groups (p = 0.0812).

### Prevalence of bacterial infections

At one year of age, the prevalence of the bacterial infections with P. aeruginosa, MRSA and B. cepacia was low and not statistically different between the 3 groups (Fig. 4), neither was the prevalence of chronic with P. aeruginosa or chronic MRSA infections.

Similarly, the prevalence of these bacterial infections and of their chronic infections at two and six years of age (at T06 also chronic Achromobacter xylosoxidans and Stenotrophomonas maltophilia infections) were not statistically different.

### Burden of therapy

During their first year of life (T01), NBS patients had the lowest number of hospitalized days, followed by clinically diagnosed patients and MI patients (Table 2). The proportion of patients hospitalized for more than 2 weeks was also lower in NBS patients (13.4%) compared to clinically diagnosed (18.5%) and MI patients (34.2%, p = 0.0332). The total days of IV antibiotic treatment was lower in NBS patients compared to MI and clinically diagnosed patients (Table 2). The proportion of patients using antibiotics for more than 2 weeks was not statistically different between the 3 groups. The proportion of patients using acid suppression therapy was significantly lower in the NBS cohort (38.8 %) compared to the MI (73.7%) and non-NBS cohort (50.9%, p = 0.0027). The use hypertonic saline or oral azithromycin were not statistically different between NBS, MI and clinically diagnosed patients.

At T02, the total number of hospitalized days and days of IV antibiotics did not differ significantly between our 3 groups (Table 3). The proportion of patients using acid suppression therapy was lower in NBS patients (35.0 %) compared to clinically diagnosed (50.0 %) and MI patients (69.4 %, p = 0.0046). The use of hypertonic saline was lower in NBS patients (33.3%) compared to clinically diagnosed (54.4%) and MI patients (55.6%, p = 0.0200). Other treatments (hospitalization or IV antibiotics for more than 2 weeks or oral azithromycin) were not statistically different between the 3 cohorts.

At 6 years of age, the total number of hospitalized days and days of IV antibiotic treatment was not significantly different between the 3 groups (Table 4). The proportion of patients using acid suppression therapy was lower in NBS patients (48.5 %) compared to MI patients (61.9 %) but was lowest in clinically diagnosed patients (34.0 %, p = 0.0402). Other treatments at T06 (hospitalization or IV antibiotics for more than 2 weeks, hypertonic saline or oral azithromycin) were not statistically different between our 3 groups.

Finally, the spirometry measures (FEV1 and FVC percentages of predicted and z-scores) at T06 were not significantly different between the 3 cohorts.

## Discussion

As expected, and based on registry data, age at diagnosis was lower in NBS patients compared to patients with a clinical diagnosis based on other symptoms than MI. However, advantages in outcome were less pronounced than expected. Only at 1 year of age, NBS patients had better height z-scores compared to non-NBS patients. Bacterial infections showed no differences between the 3 patient groups at the predefined time points. At 6 years of age, there was no significant difference between the 3 groups in lung function.

Burden of therapy was however lower for the NBS group mainly during the first 2 years of life. During their first year of life, NBS patients were less hospitalized and needed less antibiotics and antacids compared to MI and non-NBS patients. During their second year of life, NBS patients needed less antacids and hypertonic saline compared to MI and non-NBS patients.

The results of the current registry study regarding the age at diagnosis are similar with a national registration study in The Netherlands where the median age at diagnosis for NBS patients was 3.6 weeks compared to 31.5 weeks for clinically diagnosed patients (19). A retrospective study in Poland using a similar screening algorithm to detect CF further supports this finding with a median age at diagnosis being 1 month in NBS patients compared to 7 months in non-NBS patients (20).

Some of the earliest evidence for newborn screening regarding clinical evolution of CF patients depending on the mode of diagnosis is the Wisconsin trial (21). They concluded that early diagnosis of CF through neonatal screening improves long-term growth. The screened group had a much lower proportion of patients with weight and height data below the 10th percentile throughout childhood. A follow-up study showed that this growth benefit is sustained through puberty leading to a taller adult height in the screened versus the control group with differences in adult height being primary attributable to NBS and better prepubertal growth (22).

The evaluation of CF patients (up to 2 years old) after nationwide implementation of CF NBS in the USA showed that NBS is associated with a significant improvement in growth outcomes and reduction in P. aeruginosa infections (23). In an American CF cohort described by Collins et al. patients diagnosed after NBS have improved growth (height for age and BMI) until 15 years of age and preservation of normal pulmonary function (FEV1 and FVC) from 6 to 15 years of age (24). Acquisition or colonization of P. aeruginosa was similar between NBS and non-NBS patients in this study (24).

Comparison of the USA and Australian CF data registries to assess the impact of NBS showed that children (≤ 18 years of age) diagnosed with CF after newborn screening benefited from better BMI and lung function (FEV1) than those diagnosed clinically (25). Moreover, a retrospective study in New South Wales (Australia) concluded that height, weight, BMI and lung function (FEV1) were better in the screened group compared to non-screened patients on transfer to adult care (9). Non-screened CF patients had a higher rate of infection with P. aeruginosa before 18 years of age and lower age of P. aeruginosa acquisition when compared with NBS patients in this study (9).

Specifically, for lung function, a retrospective study in the UK found equivalent pulmonary outcomes in genetically similar patients with a screening diagnosis and clinical diagnosis although receiving fewer therapies suggesting that therapy burden is lower in newborn screened CF patients (4).

All together, these studies showed a sustained growth benefit for NBS patients, some but not all document a better lung function in NBS patients while results on P. aeruginosa infections were divided.

These differences in findings with our study could be attributed to small sample size of our study, the lack of an official NBS program in Belgium (and thus no standardized care after NBS) at the broad time period studied, reflecting not all patients included received the same treatment. Furthermore, CF patients with a clinical diagnosis already have good outcome in Belgium. This implies that hospitalized days and days of IV antibiotic treatments in this group are already low making it more difficult to detect differences with the NBS group. However, there is still room for further improvement.

**Table 1.** Baseline values at diagnosis by cohort.

| Variable | Category | n | Mean (SD) | Median (IQR) | Pr > \|Z\| |
|---|---|---|---|---|---|
| Age diagnosis (years) | MeconIleus | 36 | 0.03 (0.05) | 0.01 (0.00 - 0.03) | < 0.0001 |
| | NBS | 70 | 0.12 (0.10) | 0.11 (0.07 - 0.15) | |
| | Non-NBS | 162 | 1.75 (2.15) | 0.67 (0.21 - 3.13) | |
| | | | | | |
| Age diagnosis (months) | MeconIleus | 36 | 0.32 (0.63) | 0.12 (0.00 - 0.36) | < 0.0001 |
| | NBS | 70 | 1.38 (1.23) | 1.27 (0.82 - 1.74) | |
| | Non-NBS | 162 | 21.04 (25.85) | 8.01 (2.47 - 37.58) | |
| | | | | | |
| Sweat test chloride | MeconIleus | 26 | 108.14 (19.4) | 107.7 (97.1 - 118.0) | 0.0138 |
| | NBS | 65 | 96.1 (26.7) | 103.3 (83.0 - 110.0) | |
| | Non-NBS | 155 | 94.78 (19.6) | 98.0 (83.1 - 107.5) | |

**Table 2.** Hospitalized and IV antibiotics treatment days at T01 by cohort.

| Variable | Category | n | Mean (SD) | Median IQR | Pr > \|Z\| |
|---|---|---|---|---|---|
| Days hospitalized | MeconIleus | 38 | 18.6 (26.9) | 10.5 (0.0 - 21.0) | < 0.0001 |
| | NBS | 67 | 7.1 (18.3) | 0.0 (0.0 - 7.0) | |
| | Non-NBS | 108 | 10.3 (19.3) | 3.0 (0.0 - 12.0) | |
| | | | | | |
| Total Days IV antibiotics | MeconIleus | 38 | 7.4 (10.7) | 0.0 (0.0 - 16.0) | 0.0225 |
| | NBS | 67 | 3.7 (9.6) | 0.0 (0.0 - 0.0) | |
| | Non-NBS | 108 | 5.7 (11.3) | 0.0 (0.0 - 10.0) | |

At 1 year of age (T01) it is even more difficult to prove differences in burden of treatment between NBS patients and clinical diagnosis patients because the latter have a higher median age at diagnosis making the time lapse until their first birthday much shorter. Also, some treatments may be started from diagnosis irrespective of symptoms (for example hypertonic saline). Moreover, there were slightly more atypical cases in the clinical diagnosis group. These patients usually have milder CF symptoms resulting in better mean outcomes in this group.

The main strength of the current study is that we included burden of therapy in our outcome parameters which is absent in a number of other reports on outcome after NBS. The study also included a post-hoc analysis excluding patients presenting with meconium ileus, a group of which the outcome will not change with NBS.

However, some limitations should be noted. First, we conducted a retrospective observational cohort study based on data collected from the BCFR. Data collection depended on the completeness and verification of screening and diagnostic data which cannot be guaranteed by the registry. Second, during the study period there was no official newborn screening program in Belgium, so we relied on local screening initiatives that did not all use the same screening algorithm and may not always foresee immediate referral to a CF center and start treatment. Therefore, patients may not have fully benefited from the advantages of newborn screening. This also implies that screened patients all come from some regions with screening and are thus not equally spread over Belgium. Socio-economic differences between Belgian regions and CF centers may induce significant bias. Third, this study had potentially an insufficient sample size for statistical measurement of differences between cohorts. Finally, we did not apply the Bonferroni adjustment for multiple testing correction: $p < \alpha/n$ to time points T01, T02 and T06.

This study was a first attempt to report on newborn screening for CF in Belgium and its potential benefits on clinical evolution and burden of therapy compared to clinically diagnosed children. The obtained results may suggest that NBS babies are currently not being followed up and treated intensively enough in Belgium.

Future research can focus on the evaluation of national NBS in Belgium and longitudinal outcome parameters after the implementation of an official newborn screening program in Flanders from 2019 and Brussels and Wallonia since January 2020 using the same screening algorithm (13,14). Further development of targeted and potentially disease modifying therapies will continue to change the course of the CF scene in Belgium.

## Conclusion

Several studies have stressed the importance of implementing CF newborn screening programs. Altogether, our study showed some beneficial effects of NBS as primary method of CF detection when comparing age at diagnosis, clinical evolution and burden of therapy between NBS and clinically diagnosed CF patients. Further research is needed after implementation of NBS in Flanders in January 2019 and after national implementation of NBS in Belgium in January 2020. Standardized follow-up and therapy according to international guidelines should be offered (26).

### Conflict of interest

There is no conflict of interest with other people or organizations that could inappropriately influence or bias the content of this paper.

### Financial disclosure

The authors declare that there are no financial conflicts

**Figure 1:** *Weight and height z-scores at T01. Boxplots describing weight and height-for-age z-scores by cohort at T01.*

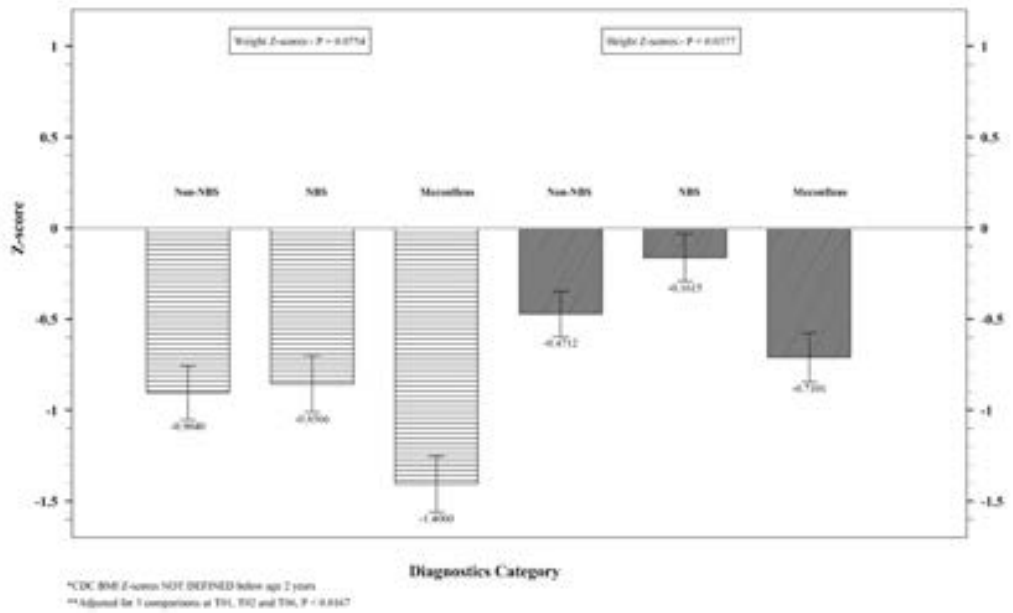



**Figure 1:** *BMI, weight and height z-scores at T02. Boxplots describing BMI, weight and height-for-age z-scores at T02 by cohort.*

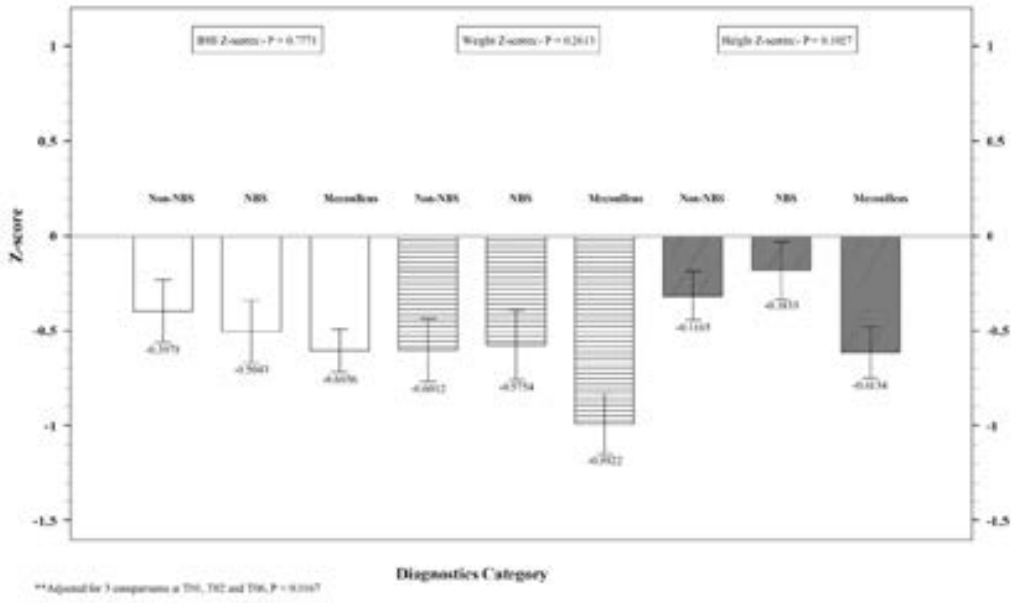


**Figure 3:** *BMI, weight and height z-scores at T06. Boxplots describing BMI, weight and height-for-age z-scores at T06 by cohort.*

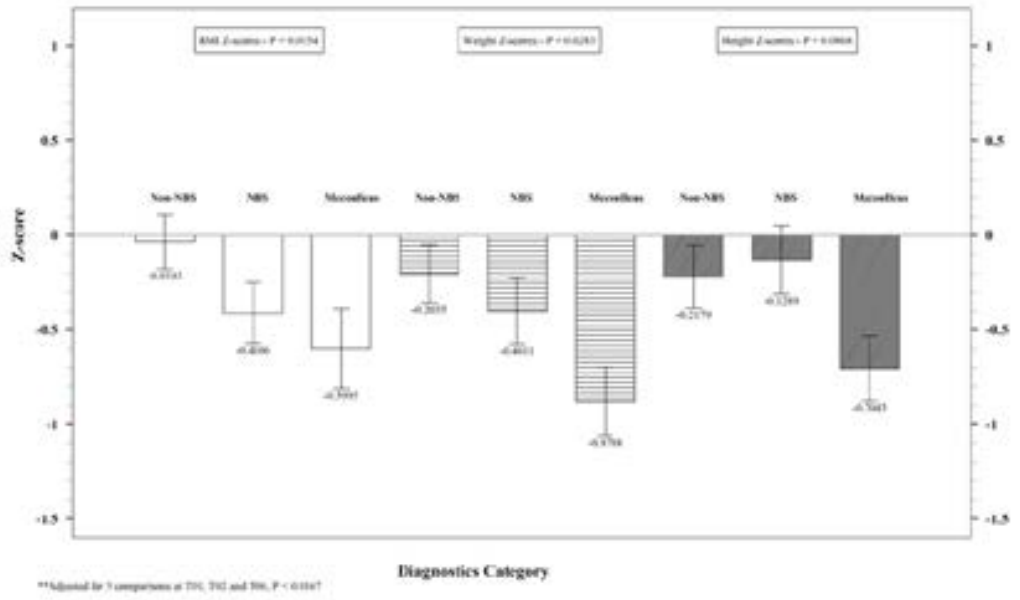
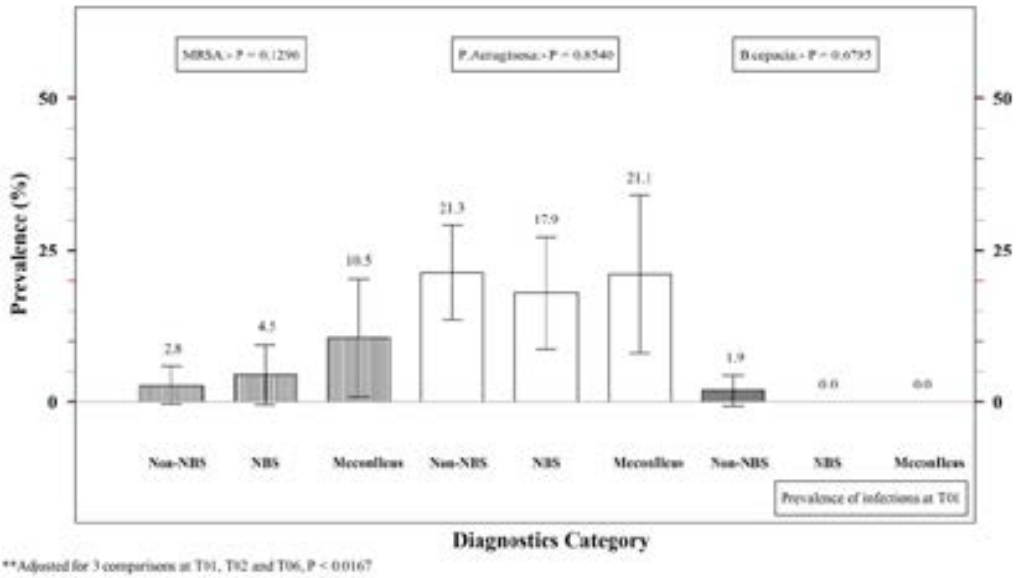



**Figure 4:** *Prevalence of bacterial infections at T01. Boxplots describing prevalence of MRSA, P. aeruginosa and B. cepacia infections at T01 by cohort.*



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Article

# Unexplained neonatal cyanosis: don't forget the dyshemoglobinemias

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## Keywords

Methemoglobinemia, sulfhemoglobinemia, infant, saturation gap, cyanosis

## Abstract

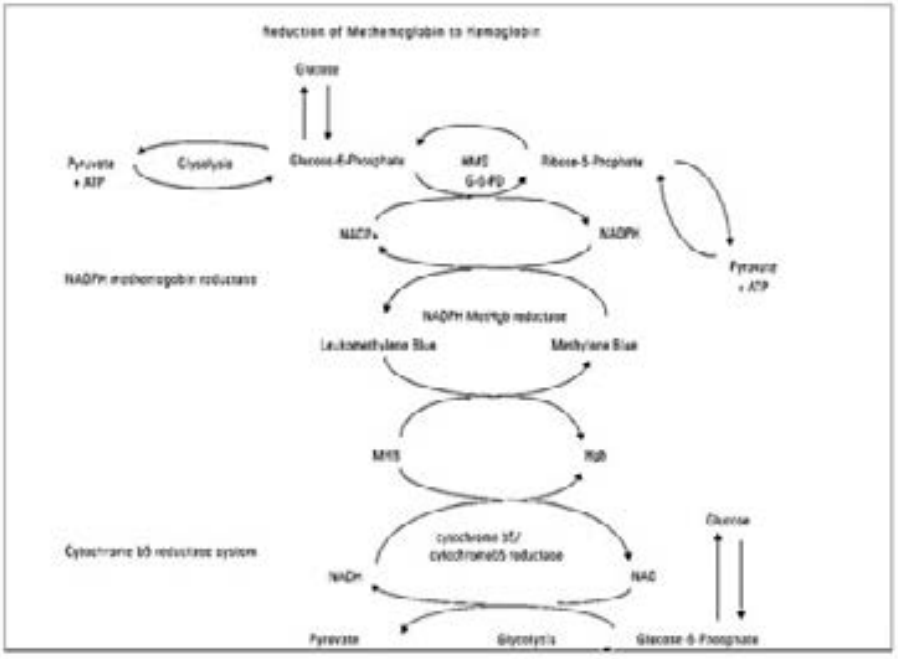
The diagnosis of dyshemoglobinemias is a challenge. A high index of suspicion is required in neonates with central cyanosis out of proportion to the oxygen saturation, not responding to supplemental oxygen and an oxygen saturation gap exceeding 5%. Gold standard for the diagnosis is co-oximetry. We report two neonates with rare forms of dyshemoglobinemias. The first neonate has a, probably congenital, methemoglobinemia and was treated with methylene blue (rescue treatment) and vitamin B2 (maintenance therapy). The second neonate had a sulfhemoglobinemia due to Escherichia coli and was treated with blood transfusions. Early recognition of dyshemoglobinemias is vital because early therapy is life-saving.

## Introduction

The differential diagnosis of central cyanosis in a newborn infant not only includes respiratory, cardiac, pulmonary and neurological causes, but also dyshemoglobinemias or hemoglobinopathies have to be considered. Dyshemoglobinemias are disorders in which the oxygen-carrying capacity of hemoglobin is impaired due to alterations in its structure (1).

In methemoglobin, hemoglobin is oxidized from the ferrous (Fe2+) to the ferric state (Fe3+) in response to oxidative stress (1). Normally protective counteracting mechanisms keep the methemoglobin level below 1% of the total hemoglobin level (3). The most important pathway is the cytochrome b5-methemoglobin reductase (CYB5R) pathway which converts methemoglobin to hemoglobin (1, 3, 4). The second pathway is the nicotinamide adenine dinucleotide phosphate (NADPH)-methemoglobin reductase pathway (4-5) (see Figure 1). Other pathways, which need an exogenous medium, are the flavine reductases (6). Furthermore, intracellular glutathione and ascorbic acid reduce oxidant compounds (4). Whenever these counteracting mechanisms fail to keep the methemoglobin below 1%, methemoglobinemia occurs (7). The pathophysiology of sulfhemoglobinemia is not completely understood. Sulfhemoglobin is formed when there is a second reaction in methemoglobin which irreversibly incorporates sulfur into heme (3). The diagnosis of dyshemoglobinemias is a challenge as neonates can present with various vague or life-threatening symptoms.

**Figure 1:** *Pathways for the reduction of methemoglobin to hemoglobin. Figure from Wright RO et al. (3)*
*(ATP: Adenosine triphosphate; HMS: hexose monophosphate shunt; MHB: methemoglobin; Hgb: hemoglobin. NAD: nicotinamide adenine dinucleotide; NADP: nicotinamide adenine dinucleotide phosphate; NADPH: nicotinamide adenine dinucleotide phosphate hydrogenase.)*



## Materials and methods

This narrative review, illustrated with case descriptions, gives an update on the pathophysiology, diagnosis and treatment of two rare dyshemoglobinemias.

## Cases

The first case is a girl born at 35 weeks of gestation. Her birth weight was 1930 grams (< 10th percentile), her length and head circumference were within normal ranges. She was the third child of healthy non-related parents. One sibling died suddenly, at the age of 22 days, due to a cardiogenic shock with an unexplained hyperchloremic metabolic acidosis.

On day of life (DOL) 7, the girl vomited and had a decreased state of consciousness. Further physical examination and cardiorespiratory parameters were normal. Venous blood gas analysis showed hyperchloremic metabolic acidosis with a pH of 7,24 (reference range 7,35-7,45); base excess (BE) of -10,9 mmol/L; lactate of 1,23 mmol/l (normal < 2 mmol/l); chloride of 134 mmol/l (reference range 101-109 mmol/l) and bicarbonate of 15,6 mmol/l (reference range 21-35 mmol/l). An intravenous bolus of NaCl 0,9% and sodium bicarbonate were given with normalization of the pH and neurologic status. C-reactive protein (CRP) was negative. Gastro-intestinal and renal losses of bicarbonate were excluded. On DOL 14, the girl developed central cyanosis with arterial saturations measured by pulse oximetry around 85-90%. There was tachycardia with normal capillary refill and no respiratory distress. Her neurological status was normal. Capillary blood gas analysis showed metabolic hyperchloremic acidosis (pH 7,29; BE -2,7 mmol/l; lactate 2,7 mmol/l; sodium 146 mmol/l, chloride 124 mmol/l, bicarbonate 22 mmol/l). Blood examination showed a hemoglobin of 10,9 g/dl, no leukocytosis and CRP was negative. Lactate increased to 8,2 mmol/l. Administration of 100% of oxygen through nasal cannula had no effect on the oxygen saturation. Echocardiography showed a hyperdynamic heart without structural abnormalities. Because we thought of a hemoglobinopathy, methemoglobin level was determined using a blood gas analyzer (ABL90 FLEX PLUS, Radiometer Medical ApS, Bronshoj, Denmark). Methemoglobin level was 72% (normal < 1%). Urgently methylene blue was administered intravenously (1 mg/kg). Saturation raised within 20 minutes to 100%. There were no arguments for provoking medications or feedings that can cause acquired methemoglobinemia. Because of the young age and the unexplained death of the sibling, it is likely that this is a congenital form of methemoglobinemia. Nevertheless, there were no pathogenic mutations in the CYB5R3, CYB5A, HBB, HBA1, HBG1 and HBG2 gene. Glucose-6-phosphate deficiency (G6PD) and hemoglobinopathy M were excluded. Hemoglobin electrophoresis of both parents was normal. During hospitalization, the girl needed administration of methylene blue twice more because of symptoms and recurring elevated methemoglobin of 28% and 39%. Maintenance therapy with vitamin B2 (4 mg/kg/day) was started. At the age of 6 weeks, she was discharged home. Currently, she is ten months old and her methemoglobin levels remains low.

The second case is a girl born at 28 weeks of gestation. She received endotracheal surfactant administration through a less invasive surfactant application because of respiratory distress syndrome. Thereafter, her respiratory parameters were stable on non-invasive continuous positive airway pressure without supplemental oxygen. On DOL 10, her oxygen saturations dropped to 85-90% and did not respond to supplemental oxygen. Radiography of the chest, abdomen and echocardiography were normal. Antibiotics were started because of suspicion of a late onset sepsis with a CRP of 15 mg/l (normal < 10 mg/l) and diarrhea. Culture of the stools were positive for two different Escherichia coli species (without Shiga producing toxins). Hemoculture was negative as well as viral cultures. Total hemoglobin level was 9,1 g/dl (reference range 10-17 g/dl). Arterial blood gas analysis showed a partial oxygen pressure of 143 mmHg after oxygen administration (with a simultaneous pulse oximetry oxygen saturation of 86%) and detected sulfhemoglobin. Hemoglobin electrophoresis showed that 3,5% of the hemoglobin was sulfhemoglobin. As cause of the sulfhemoglobinemia we considered the E. coli. The girl nor her mother received sulfur containing medications or were exposed to sulfites. Breast milk tested negative for sulfites. The girl was treated with two packed cell transfusions. Her oxygen saturation gradually improved and respiratory support was ceased on DOL 56.

## Discussion

### Etiology

A variety of medications, chemicals and high nitrate food can cause acquired methemoglobinemia (7). Newborns are at risk for acquired methemoglobinemia because fetal hemoglobin is oxidized more rapidly and their CYB5R activity is only 50-60% of the activity in adults (3,7). Also, individuals with G6PD deficiency are more prone to methemoglobinemia (3,7). Monitoring of the methemoglobin level in neonates treated with higher doses of inhaled nitric oxide is therefore suggested (21). The acquired forms of methemoglobinemia are beyond the scope of this article.

CYB5R deficiency, the most frequent form of congenital methemoglobinemia, is very rare and the actual incidence is not known. In type 1 of this autosomal recessive condition only the red blood cells are deficient (7). These children have a normal life expectancy and have only well-tolerated cyanosis that can cause later on fatigue, headache and dyspnea with exertion (7). In a type 2 CYB5R deficiency all cells are deficient (7). These children have severe neurological damage, failure to thrive and usually die before one year of age (7). Cytochrome b5 deficiency is another, very rare, autosomal recessive form of methemoglobinemia (8). Genetic deficiencies of the NADPH-methemoglobin reductase pathway usually do not result in methemoglobinemia because of the minor role it plays in methemoglobin reduction (3). Another cause of congenital methemoglobinemia is hemoglobin M, in which an amino acid substitution in the alfa or beta (or gamma) chain of hemoglobin makes it more difficult for the enzyme to transform Fe3+ to Fe2+ (9). It is an autosomal dominant condition and most people are asymptomatic (9).

Sulfhemoglobinemia is usually drug-induced (10). But the source of sulfur is not always apparent. Although rare, it can originate from hydrogen sulfide released by intestinal organisms, e.g. in patients with constipation, Morganella morganii or Escherichia coli infection (11-13). Endogenous glutathione may also serve as a sulfur donor (3,14).

### Diagnosis

As the ability of heme to bind oxygen is decreased in meth- and sulfhemoglobin, cyanosis is often the first clinical sign (1). Cyanosis develops when methemoglobin or sulfhemoglobin exceeds 15% or 5% of the total hemoglobin level respectively (3,10). As was in our case, the cyanosis is out of proportion to a given oxygen saturation level. Normally, pulse oximetry measures light absorbance at two distinct wavelengths (660 and 940 nm) to determine the ratio of oxyhemoglobin to deoxyhemoglobin (15). Methemoglobin absorbs the light equally at both wavelengths, while sulfhemoglobin has a greater absorbance at 660 nm (10). This distorts the ratio of oxyhemoglobin to deoxyhemoglobin measured by pulse oximetry and give stable saturations around 85% (3,15). There is a poor response of the saturation value measured by pulse oximetry to supplemental oxygen (15). In contrast, supplemental oxygen falsely increases the partial arterial oxygen pressure and the calculated saturation of an arterial blood gas (3). If this oxygen saturation gap exceeds 5%, the patient's hemoglobin may be abnormal (15) (see Table 1). At a neonatal intensive care unit or pediatric ward, there is easy access to point of care capillary blood samples, while obtaining arterial samples is more challenging. In neonates the calculated oxygen saturation range on a capillary blood sample is 80,5±8,5% with a pulse oximetry saturation of 98±1,9% (16). So, the oxygen saturation gap is useless in capillary samples, as in our case. Therefore, we recommend to obtain an arterial blood sample in case of an abnormal pulse oximetry result to aid in the differential diagnosis. Clues for diagnosis of dyshemoglobinemias are summarized in table 1.

**Table 1:** Clues for the diagnosis of dyshemoglobinemias in patients with cyanosis

| *Clues for the diagnosis of dyshemoglobinemias in patients with cyanosis* |
|---|
| Cyanosis out-of-proportion to oxygen saturation |
| Oxygen saturation gap ($SaO_2$ – $SpO_2$) > 5% |
| No change in pulse oximetry with supplemental oxygen administration |
| Normal arterial oxygen pressure and low $SpO_2$ |

$SaO_2$: calculated arterial oxygen saturation from a blood gas; $SpO_2$: arterial oxygen saturation read from a pulse oximetry

The gold standard for the diagnosis of dyshemoglobinemias is co-oximetry. Co-oximetry measures the concentration of different types of hemoglobin through spectrophotometry using different wavelengths (3). Not all co-oximeters can differentiate between meth- and sulfhemoglobin as they have spectrophotometrically similarities (17). In our cases an ABL90 FLEX PLUS (Radiometer Medical ApS, Bronshoj, Denmark) was used, which is accurate till sulfhemoglobin exceeds 10%. Diagnosis of sulfhemoglobinemia is confirmed by spectrophotometry or gas chromatography/mass spectrometry (17).

Besides central cyanosis, other symptoms of methemoglobinemia in neonates are dyspnea, discomfort, lethargy and tachycardia. In older children also coughing, headache, dizziness and weakness are reported (3,7). These symptoms appear when the methemoglobin level increases to 20-45%. An increase above 45% causes acidosis, arrhythmias, heart failure, convulsions or coma; levels above 70% are usually lethal (3,7). In contrast, symptoms of sulfhemoglobinemia are usually milder (14). Levels of sulfhemoglobin above 60% are associated with mortality (11).

Another clinical clue is the chocolate-brown color of the blood of a patient with a meth- or sulfhemobloginemia (3). In case of methemoglobinemia, a drop of blood does not change with light exposure (3). In case of application of potassium cyanide, methemoglobin turns bright red while sulfhemoglobin stays dark brown (15).

We found no clear explanation for the hyperchloremic metabolic acidosis in our first patient. Older publications suggest that hyperchloremia facilitates the conversion of hemoglobin to methemoglobin (18,19). Additional suggested risk factors in neonates are: weight below the tenth percentile, as was in our case, immature enzyme systems which are less efficient in acidotic environments and higher intestinal pH which promotes growth of gram-negative bacteria who convert dietary nitrates to nitrites (3,18,20). But others found no association between pH, chloride, dehydration and methemoglobinemia (18).

### Treatment

Methylene blue 1-2 mg/kg intravenously is recommended in symptomatic patients with a methemoglobin above 20% and in asymptomatic patients with levels above 30% (3-4). Methylene blue accelerates the reduction of methemoglobin through the NADPH-methemoglobin reductase pathway (7) (See Figure 1). An important contra-indication for methylene blue is G6PD deficiency, as it can induce hemolysis (3,7). Also, in patients with hemoglobin M or flavin reductase deficiency it is ineffective. Maintenance therapy is possible with methylene blue 50-250 mg/d orally (7). There is a variable gastro-intestinal absorption and adverse effects include gastro-intestinal symptoms, discomfort (headache and confusion are reported in older individuals), dyspnea, blue saliva, stool or skin, hemolysis and paradoxical increase of methemoglobin (4,7). Other therapeutic options are vitamin C 200-500 mg/d, which reduces oxidant compounds and decreases methemoglobin production, and vitamin B2 20 mg/d, which activates NADPH flavin methemoglobin reductase (4,5,7). If the patient is unresponsive or unsuitable for methylene blue administration, an exchange transfusion or hyperbaric oxygen therapy can be considered (7). Furthermore, it is important to avoid provoking agents (7).

In contrast, sulfhemoglobin cannot be reduced to hemoglobin because of irreversible sulfur binding (17). Treatment is supportive with removing the cause and giving blood transfusions. In severe cases, exchange transfusion can be necessary. Symptoms resolve over one to six months (3).

## Conclusion

The diagnosis of a dyshemoglobinemia should be considered in neonates with central cyanosis out of proportion to the oxygen saturation and not responding to supplemental oxygen. Think of dyshemoglobinemias if the saturation gap exceeds 5%. Nowadays the diagnostic challenge has become less exciting as all modern co-oximeters have the ability to distinguish between common dyshemoglobinemias but clinical suspicion is the rate-limiting step. Early recognition of dyshemoglobinemias is vital as early therapy can be life-saving.


### Conflicts of interest

The authors have not disclosed any potential conflicts of interest or financial support from any pharmaceutical company.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# The Flemish milk ladder: a tool for home-based cow's milk reintroduction in children with non-IgE-mediated cow's milk allergy

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## Keywords

cow's milk allergy, non-IgE mediated, management and milk ladder

## Abstract

Cow's milk allergy is one of the most prevalent food allergies in young children affecting 2 to 5 % of the infants in developed countries. The classic treatment of this food allergy consists of a strict avoidance diet. However, literature states that 70% of cow's milk allergic children can tolerate extensively heated (baked) milk products and that incorporating baked milk products into the diet accelerates tolerance towards unheated milk. In this paper, we focus on the gradually reintroduction of cow's milk using a Flemish milk ladder for children with non-IgE mediated cow's milk allergy. Hereby, we examined the utility and user-friendliness of this tool to guide both clinicians and parents through the reintroduction of cow's milk, since there is still a wide variety in clinical practice on how and when to introduce cow's milk in these children. The Flemish milk ladder was evaluated through surveys, open interviews and expert panels composed of academics, clinicians and dieticians. In total we received 22 surveys from regional pediatricians and parents, in which the overall feedback on the utility and user-friendliness of the milk ladder was positive. The suggestions that we received of the experts in the field and parents regarding this milk ladder were incorporated into a new version, which included a reduction of the number of steps, availability of more recipes and healthier options within each step. In conclusion, we present a helpful and safe guide to gradually reintroduce cow's milk-containing products at home in children with non-IgE mediated cow's milk allergy, considering the eating habits of the Belgian population.

## Introduction

Cow's milk allergy (CMA) is one of the most common food allergies in early childhood with an overall prevalence of 2 to 5% (1). This food allergy is defined by a hypersensitivity reaction to one or more cow's milk proteins (CMP), which are in most cases β-lactoglobulin or caseins (1). The immunological response of CMA can be IgE-mediated or non-IgE mediated or in some presentations a combination of both (2). As a result, this food allergy is characterized by a wide spectrum of clinical presentations ranging from mild, moderate to severe (1,2). In case of IgE-mediated CMA, symptoms can rapidly evolve within minutes to several hours after ingestion of cow's milk-containing products and may even result in a potentially life-threatening anaphylaxis (1,2). Hereby, IgE-mediated reactions are mainly manifested at the level of the skin, gut and/or respiratory tract (1,2). Non-IgE mediated CMA encompasses a wider range of disorders mostly affecting the gastro-intestinal system (protein-induced allergic proctocolitis (FPIAP), protein-induced enterocolitis (FPIES), gastrointestinal dysmotility & cow's milk protein-sensitive enteropathy (FPE)), skin (eczema) or in very rare cases the lungs (Heiner syndrome) (1,2). Symptoms may vary from mild to moderate (e.g. reflux, colic, diarrhea, constipation, blood in stool) to severe forms of non-IgE mediated CMA (e.g. severe eczema, failure to thrive, anaemia, hypovolemic shock) (1,2). An overview of the different manifestations of CMA are given in Table 1.

**Table 1 :** *Table 1: Overview of the different manifestations of cow's milk allergy (1,2)*

| IgE-mediated CMA | Non-IgE mediated CMA | Mixed mechanism |
|---|---|---|
| Urticaria and angio-edema | Allergic dysmotility: reflux, diarrhea, constipation, colic's | Atopic dermatitis |
| Gastro-intestinal symptoms: vomiting, abdominal pain, diarrhea | FPIAP: well infant with bloody stools | Eosinophilic esophagitis: abdominal pain, dysphagia, reflux with eosinophilic infiltration in the esophagus |
| Airway symptoms: stridor, cough, wheeze | FPIES: severe vomiting, pallor, hypotension | |
| Shock, anaphylaxis | FPE: chronic diarrhea, vomiting, failure to thrive | |
| | Heiner syndrome: recurrent pneumonia | |

CMA: cow's milk allergy, FPIAP: protein-induced allergic proctocolitis, FPIES: protein-induced enterocolitis, FPE: cow's milk protein-sensitive enteropathy

The prognosis of CMA is usually favourable, with the majority of children being able to tolerate cow's milk by the age of 5 (2). Hereby, tolerance will develop faster in case of non-IgE mediated CMA, while IgE-mediated responses are known to be more persistent (2). Risk factors for a delayed or persistent form of CMA are severe symptoms on initial presentation, presence or persistence of high specific IgE's to cow's milk (> 20 kU/l), multiple food allergies and the presence of respiratory allergies (3). In case of IgE-mediated CMA, tolerance development can be monitored by use of skin prick tests and measurement of cow's milk specific IgE levels (3–5). When tolerance is suspected, an oral food challenge with cow's milk (baked milk e.g. boiled for 20 minutes or unheated fresh milk) can take place in a controlled hospital environment (3–5). Unfortunately, there are no reliable tests available to predict tolerance in non-IgE mediated CMA (3–5). Moreover, the timing of tolerance development seems to be variable and dependent on the clinical picture (Table 2) (3–5). Infants with mild gastro-intestinal symptoms, atopic dermatitis or FPIAP seem to develop tolerance by their first birthday whereas children with FPIES and FPE only develop tolerance by the age of 2 to 3 years (4,5).

**Table 2 :** *The timing of tolerance development in function of the clinical presentation of cow's milk allergy (3–5)*

| Manifestations of CMA | Age of tolerance development |
|---|---|
| GI-dysmotility | Mostly resolved by the age of 6-12 months |
| FPIAP | Mostly resolved by the age of 9-12 months to 3 years |
| Atopic dermatitis | Sensitivity to cow's milk mostly resolved by the age of 12-24 months |
| FPIES | Mostly resolved by the age of 2 years |
| FPE | Mostly resolved by the age of 2-3 years |
| Eosinophilic esophagitis | Unsure, possibly no tolerance development |

GI: gastro-intestinal, CMA: cow's milk allergy, FPIAP: protein-induced allergic proctocolitis, FPIES: protein-induced enterocolitis, FPE: cow's milk protein-sensitive enteropathy
Note: Adapted from Nowak-Wegrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. J Allergy Clin Immunol. 2015 May;135(5):1114-24. doi: 10.1016/j.jaci.2015.03.025. PMID: 25956013.

The classic treatment of CMA consists of a strict elimination diet. However, recent studies have shown that 75% of CMA children are able to tolerate extensively heated (baked) milk products (e.g. cookie/biscuit, muffin…) and that incorporating baked milk into the diet accelerates tolerance towards unheated milk (6). In 2013, a British expert panel developed a milk ladder as a tool to gradually reintroduce milk-containing foods, from lowest to highest allergenicity, for children with non-IgE mediated CMA (7). This is based on the evidence that thermal processing of CMP and the interaction with carbohydrates and fats reduces the allergenicity (8). To date, no evidence suggests that the British milk ladder could accelerate tolerance induction. However, it has proven to be a useful tool for healthcare professionals as it provides a uniform practical guidance for the reintroduction of cow's milk (9). It should be noted that the British milk ladder still requires country-specific adjustments (9). In this article we present a Flemish version of this milk ladder and evaluate the utility and user-friendliness of this tool by means of surveys, open interviews and expert panels.

## Materials and method

### Development of the Flemish milk ladder

Considering that the British milk ladder contained some traditional British dishes (e.g. Shepherd's Pie) a group of dieticians and doctors from the Department of Paediatric Allergy and Gastroenterology of UZ Leuven collaborated with Mead Johnson to develop a Flemish version of this milk ladder. The main modifications included: replacing the regional products of England, substituting the high-sugar and fat foods with healthier alternatives and combining a number of steps. Originally, the Flemish milk ladder was developed for two age groups, children aged 1-1.5 years (Figure 1a) and 1.5 years and older (Figure 1b). In the youngest children cow's milk was reintroduced through 15 steps, while in older children the milk ladder contained 17 steps. It was recommended that each step should take a minimum of 3 days in agreement with the physician and/or dietician.

### The use of the Flemish milk ladder in clinical practice

The goal of the Flemish milk ladder entails the home reintroduction of cow's milk in children with mild to moderate non-IgE-mediated CMA. An observational study (S59587) was started in 2017 to evaluate the user-friendliness of the Flemish milk ladder in clinical practice. Specifically, our aim was to determine whether parents and pediatricians would find this an easy and helpful tool to guide them through the reintroduction of milk-containing foods. This study was approved by the Ethics Committee Research of UZ/KU Leuven (study nr. S59587).

The goal of this observational study was to evaluate the Flemish milk ladder by means of 50 anonymized questionnaires to the physician and parents. Hereby, each questionnaire was filled out on the experience of a single child. The inclusion criteria included the following: age 1 year and older, a clinically established non-IgE mediated CMA and the absence of positive IgE's and/or positive skin prick test to cow's milk. The survey for the parents included questions on: the demographics of the child, the different steps (duration, arising difficulties, allergic reactions…), findability of the products on the Flemish market and tolerance after completing the milk ladder (final step reached, total duration…). In addition, parents were free to give additional remarks on the Flemish milk ladder. The survey for the physicians consisted of clinical data on: demographics, initial reaction towards cow's milk (age, presentation, preferred diagnosis…), results of allergy tests (skin prick test and sIgE levels), cow's milk provocation test, nutrition history (breastfeeding, infant formula...), multiple food allergies, their recommended duration of each step and the indication for which they opted to use the milk ladder. After completing the milk ladder, physicians filled out additional information on: the different steps (duration, clinical manifestations…), the use of rescue medication, final step reached (total duration, reason of stopping earlier, was the stop rightfully…), satisfaction score and adjustments that they would recommend.

The Flemish milk ladder was presented and distributed along with the questionnaires during the local quality evaluation group (LOK/GLEM) meetings of the pediatricians in Flanders. Representatives of Mead Johnson were partially responsible for the distribution and collection of the closed envelopes with anonymous questionnaires from the regional pediatricians. An additional assessment was accomplished by using the thinking aloud test and expert panel groups (10). In the thinking aloud method, an open interview (not recorded) was conducted to assess the opinion of various experts in the field of allergy (10). Concerning the expert panel groups, these were composed of academics, clinicians and dieticians involved in the treatment and/or research of food allergy. The first expert panel was part of the Pediatric Allergy and Asthma Meeting in 2017 in London where several experts from Flanders and Netherlands attended. A second expert panel took place in Leuven in 2017 with the help of the postgraduate course 'Allergy and Clinical Immunology' organized by UZ Leuven. A final expert panel was held in 2021 in Leuven, with the original group of experts that developed the Flemish milk ladder, to incorporate the received feedback into a new version.

## Results

### Surveys

A total of 150 surveys were distributed among 30 pediatricians. However, only 22 envelops with anonymized surveys from the pediatrician and parents were returned to us, of which 16 for the young child and 6 for the older child. The ultimate goal of 50 questionnaires was not achieved. Most of the pediatricians reported not having enough time to process them or did not receive the surveys back from the parents.

The pediatricians used the Flemish milk ladder to reintroduce milk in children with mild to moderate non-IgE mediated CMA presented as FPIAP, gastrointestinal dysmotility or FPE. The majority of these children were exclusively breastfed for 2 to 6 months and switched to a hypoallergenic infant formula afterwards. Only a small number of mothers followed an elimination diet over a longer period of time and kept breastfeeding after 6 months. The main symptoms at initial presentation included gastro-intestinal complaints (e.g. cramps, anal blood loss, diarrhea, constipation, vomiting…) in combination with reflux, eczema, restless behavior and/or suboptimal weight. Four children already tolerated baked milk while 18 children reintroduced milk into their diet for the first time on introduction of the milk ladder. The cow's milk sIgE levels were measured in 15 of the 22 children of which all were below the cut-off value of 0.10 kU/L. The skin prick test was performed in 13 children, of which three had a positive result. However, these three children had cow's milk sIgE's below the 0.10 kU/L. In total, most of these children had concomitant hen's egg, soy, peanut and/or treenuts allergy while only eight were exclusively diagnosed with CMA.

Eighteen of the 22 children spent 2 to 4 days on each step of the Flemish milk ladder, which was in line with the advice of their pediatrician or dietician. However, four children needed 7 to 14 days to complete each individual step. In three children this prolonged time duration was attributed to a previously failed reintroduction, picky eating behavior or practical issues for the parents

**Figure 1 :** *Flemish milk ladder for children aged 1-1.5 years (a) and 1.5 years and older (b)*


during the week. The fourth child prolonged step 1 from 3 to 7 days by advice of their pediatrician due to symptoms (eczema, cramps and diarrhea) when reintroducing baked milk in step 1. Ultimately, seventeen children developed complete cow's milk tolerance and reached the final step of the milk ladder. During the reintroduction of cow's milk, only four of these 17 children experienced symptoms (diarrhea, eczema). In general, most of the symptoms occurred during the last steps of the milk ladder for both age categories. In addition, seven children replaced or skipped a step of the milk ladder since they disliked a product, ate larger quantities of a product from the start or replaced cow's milk by growth milk or follow-up formula. Five of the 22 children had to stop the reintroduction of cow's milk by advice of their pediatrician due to diarrhea, cramps and/or eczema. The majority of these children were between 1 and 1.5 years of age and experienced more severe symptoms (e.g. diarrhea, vomiting, anal blood loss, suboptimal weight) at the initial time of diagnosis. In addition, two of these five children reached partial tolerance for fermented milk (e.g yoghurt), while the other children were put on an elimination diet again.

The overall feedback from the regional pediatricians on the Flemish milk ladder was positive, with an average satisfaction score of 75%. Recommendations and comments made by the clinicians included reducing the number of steps, eliminating the sugar-rich products (e.g. baby cereals, pancakes), lowering the portions for the smallest children and eliminating the step with pasteurized milk since several parents indicated that they weren't familiar with this product. In addition, parents mentioned the need of alternative products for children with concomitant hen's egg allergy and/or gluten intolerance.

### Thinking aloud method

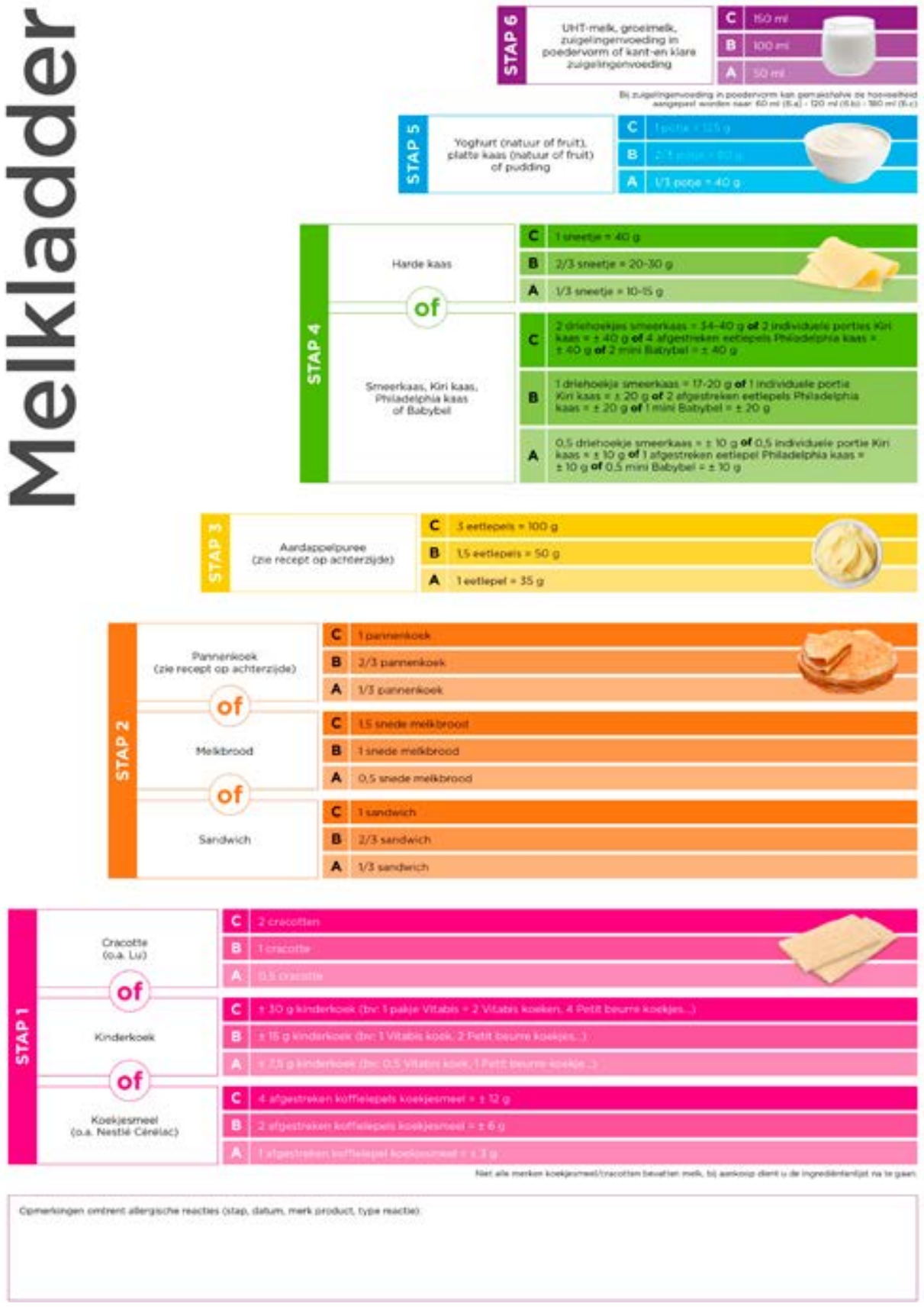
Both clinicians and dieticians reported that the Flemish milk ladder was a valuable and user-friendly tool for the reintroduction of milk. This applies for children with non-IgE-mediated CMA who already tolerated baked milk and those who reintroduced milk into their diet for the first time on introduction of the ladder. There were no negative remarks on the number of steps the milk ladder contains. Parents even mentioned to their physician that they felt more comfortable since the stepwise induction was spread over a longer period of time. The children who had a mild allergic reaction during the reintroduction of milk, usually had this during the last steps of the milk ladder. In these circumstances, the child temporarily returned to a previous step or the time period of 3 days was extended by advice of their treating physician. The most recurring remarks were that parents weren't familiar with pasteurized milk, the high-sugar content of some products, not listing growth milk or follow-up formula and the lack of alternative products for children with multiple food allergies or when children don't like a product.

### Expert panels

In the first expert panel, Belgian and Dutch pediatricians, allergists and dieticians focused on comparing the Flemish and Dutch version of the milk ladder. The Dutch milk ladder was an initiative from the dietician's alliance in food hypersensitivity (DAVO) and similar to the Flemish milk ladder based on the Milk Allergy in Primary (MAP) Care guidelines published in 2013. The tolerance induction takes place through 12 steps, with the advice to contact a dietician after completing step 4, 7 and 10. Each step requires 1 week of reintroduction, and when children can finally tolerate small amounts of unprocessed sterilized milk or follow-up formula the Dutch milk ladder refers to the recommended number of dairy products for each age category. However, this milk ladder again contains a number of regional brands (e.g. knappertjes van Verkade, sprinkles of Venz) that are less known in Belgium which highlights the need for different versions of the milk ladder customized to the eating habits of each region. In general, the experts advised to reduce the number of steps in the Flemish milk ladder starting with the deletion of pasteurized milk. Furthermore, they indicated that it would be interesting to incorporate the advised number of dairy products and highlight the role of the dietician, as was done in the Dutch milk ladder.

In the last two expert panels, Belgian pediatricians, allergists and dieticians tried to incorporate the feedback that we received into a new version of the Flemish milk ladder (Figure 2). Hereby, we created an official leaflet with explanatory notes, which is going to be distributed by Mead Johnson. In this newest version, the two milk ladders for different age categories are combined into one and the number of steps reduced to six. It should be noted that within each step of this new milk ladder the corresponding milk-

**Figure 2 :** *New version of the Flemish milk ladder for children aged 1 year and older*



containing products are still introduced gradually. Furthermore, similar to the first version each step (e.g. 1a, 1b & 1c) requires 3 days of reintroduction. As in the Dutch milk ladder, we have provided different options of milk-containing foods within each step, giving families a broader range of foods to choose from including some healthier options. In addition, the parents are provided with recipes for some of the products (Figure 3). For practicality reasons, the quantities of the foods are also provided in the form of spoons. In the last step of the milk ladder, we have added the reintroduction of growth milk and infant formula on top of sterilized milk (UHT – 140 to 150°C for 2 seconds). After successfully completing all six steps children can eat all milk-containing products safely except for pasteurized milk which is not part of the newest version of the Flemish milk ladder. Parents need to consult their physician or dietician before reintroducing this product, since pasteurized milk is only heated for 15 seconds at 72 degrees. Additional alternative products for children with multiple food allergies are going to be provided in a supporting website. Finally, in the newest version we place more emphasis on the fact that the milk ladder is intended for the treatment of children with non-IgE mediated CMA and not for IgE-mediated CMA.

## Discussion

In general, we received positive feedback on the user-friendliness and safety of the Flemish milk ladder as a tool to reintroduce milk at home in children with non-IgE mediated CMA. Hereby, the suggestions of experts and parents were incorporated into a new version of the Flemish milk ladder which includes a reduction of the number of steps, availability of more recipes, healthier options within each step and the removal of pasteurized milk. However, it should be noted that the milk ladder is not an evidence-based tool, but rather a tool based on the opinion of experts and the knowledge that by heating CMP and the interaction with carbohydrates and fat the allergenicity of CMP reduces (8). Nevertheless, the Flemish milk ladder seems to be a useful and safe guide to help both clinicians and parents through the gradual reintroduction of cow's milk by means of surveys, interviews and expert panels. This applies for children who already tolerated baked milk as well as those who introduced cow's milk into their diet for the first time. However, one drawback of our observational study was that we only received 22 surveys instead of the intended 50. On the other hand, we were able to obtain feedback from a considerable number of clinicians, dietitians and researchers who used the Flemish milk ladder in clinical practice by interviews and expert panels.

Although full cow's milk tolerance is not always achieved when using the milk ladder, it is possible that children can reach partial tolerance for baked milk or fermented milk products while still reacting to raw milk. Consequently, the Flemish milk ladder is also helpful to broaden the diet of children with non-IgE mediated CMA without reaching full milk tolerance. By doing so, children can avoid unnecessary restrictions of baked milk or fermented milk-containing foods, which may improve the nutrition as well as the quality of life of both children and parents. It is recommended that each step takes at least three days, as symptoms can occur up to 72 hours after ingestion. In case a child experiences symptoms during the reintroduction, we advise to return to a previous step in the milk ladder or stop the introduction of cow's milk completely. Depending on the age of the child a new attempt of cow's milk reintroduction can be made after a period of 3 to 6 months. In general, guidance by a dietician is recommended when using the milk ladder, this to provide safe alternatives, avoid deficiencies when following a cow's milk-free diet and to explain the use of the milk ladder especially in case of multiple food allergies.

To date, no severe allergic reactions have been reported during the home-reintroduction of milk by use of the Flemish milk ladder. However, we should emphasize that this tool can only be used in children with mild to moderate non-IgE mediated CMA presented as FPIAP, gastrointestinal dysmotility or FPE. Hereby, caution is advised when using this tool for more severe presentations of non-IgE-mediated CMA, with the possibility of an acute allergic reaction at home. This can be the case for acute FPIES, where the child is at risk of experiencing delayed repetitive vomiting and diarrhea usually within 1 to 4 hours after ingestion of the offending food which can ultimately lead to a hypovolemic shock (11). On the other hand, children with chronic FPIES who present with chronic diarrhea, vomiting and failure to thrive due to a chronic exposure to the food trigger can also react with acute symptoms upon reintroduction of cow's milk after following a cow's milk-free diet (12). In addition, 25% of children with FPIES may develop IgE antibodies of which some can evolve to an acute food allergy (13). It is therefore recommended to assess allergic sensitization to cow's milk in these children by either performing a skin prick test or measuring the specific IgE levels. In case of severe symptoms, the presence of IgE antibodies or a positive skin prick test to cow's milk, a hospital-based provocation of baked cow's milk is usually warranted and the use of the milk ladder contraindicated. This is also the case for mixed forms of CMA, such as eosinophilic esophagitis, where the child has to follow a cow's milk elimination diet over a longer period of time and reintroduction is only considered after consulting a pediatric gastroenterologist.

Finally, although 75% of the children with IgE-mediated CMA can become tolerant towards baked cow's milk, the general advice is to perform the baked milk challenge in the hospital due to the risk of severe symptoms (6). In contrast to non-IgE mediated CMA, where the introduction can take place at home by use of the milk ladder as there is no risk of an anaphylactic shock. This was recently supported by a worldwide survey of healthcare professionals, where the majority of the clinicians considered the home setting as unsafe for the performance of a baked milk challenge or use of the milk ladder in IgE-mediated CMA (9). In the management of IgE-mediated CMA, the physicians are therefore advised to frequently evaluate the cow's milk sIgE levels and skin prick test. Based on the results of these allergy tests and the severity of the initial symptoms, the physician can decide whether to perform an in-hospital oral food challenge to test for acquired baked milk tolerance. Hereby, the recent study of De Boer et al. showed that cow's milk sIgE levels were a better predictor for baked milk tolerance in comparison to the skin prick test (14).

## Conclusion

The Flemish milk ladder is an adapted tool that physicians and dieticians can use to gradually reintroduce cow's milk at home in children with mild to moderate non-IgE-mediated CMA. This reintroduction takes place through six steps, of which each step requires a minimum of 3 days. Although it is not an evidence-based tool parents, clinicians and dieticians consider it to be a helpful guide to reintroduce cow's milk-containing products.

### Conflicts of Interest

DMAB received consulting fees from Mead Johnson. KC and MR participated in webinars organized by Mead Johnson. LDV, TB, MD, LN, JL and SV declare to have no conflict of interest.

**Figure 3 :** *Accompanying recipes for the new version of the Flemish milk ladder*



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# Palmar, plantar and palmoplantar erythema in children

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## Keywords

plantar erythema, palmar erythema, palmoplantar erythema, children, diagnosis

## Abstract

Palmar, palmoplantar and plantar erythema are important clinical entities in children. These findings may be diagnostic clues to an underlying pathology. Palmar erythema has been described for decades and has a broad differential diagnosis. However, plantar erythema is a less known phenomenon and has only been described in several articles. Our aim is to give an overview of the most frequent and well-known causes of palmar, palmoplantar and plantar erythema in children and their specific presentation. We also included a list with further investigations that can be performed in order to come to the right diagnosis.

## Introduction

Palmar erythema is a well-known symptom in children but is often overlooked (1). It usually presents as a symmetric, slightly warm, painless, non-pruritic and non-scaling superficial reddening of the skin on the palmar side of the hands. The thenar and hypothenar eminences are most frequently affected (1, 2). Erythema on the plantar surface of the feet (plantar erythema) can also occur, however it is less known and reported. The combination of plantar and palmar erythema is common and comes with an extensive differential diagnosis. The broad differential diagnosis makes the evaluation of palmar, palmoplantar or plantar erythema quite challenging (2). We use the abbreviation PE for these three possible presentations of erythema. We focused on the mere presentation of palmar, plantar and palmoplantar erythema, as previously described. If the erythema is not the only or predominant dermatologic feature, it will be indicated. A classification of conditions associated with PE can be found in table 1. Our aim is to give an overview of the causes of PE in children and their specific presentation.

**Table 1 :** *Classification of PE in children.*

| |
|---|
| **Physiologic or primary** |
| Palmar<br>Idiopathic |
| Plantar<br>Idiopathic |
| Palmoplantar<br>Erythema palmare hereditarium, Idiopathic |
| **Pathologic or secondary** |
| Palmar<br>Hepatic<br>Cholestasis, Liver cirrhosis, Hemochromatosis, Wilson disease<br>Autoimmune<br>Systemic lupus erythematosus<br>Endocrine<br>Graves disease, Thyrotoxicosis, Diabetes mellitus<br>Infectious<br>Human T-lymphotropic Virus-1 associated myelopathy, Chronic HBV/HCV<br>Drug-related<br>Topiramate<br>Neoplasia<br>Hepatic tumors, Brain tumors and Lymphoproliferative disorders |
| **Plantar**<br>**Juvenile plantar dermatosis, Allergic contact dermatitis** |
| Palmoplantar<br>Infectious<br>Papular Pruritic Gloves and Sock Syndrome, Epstein Barr virus infection, Mycoplasma pneumoniae, Hand Foot Mouth disease, Erythema infectiosum, Secondary syphilis, Respiratory syncytial virus, Adenovirus, Human Parecho-Virus 3, Meningococcal septicemia, Toxic shock syndrome, Rocky mountain spotted fever, SARS-Cov-2, Varicella, Measles, Erythema subitum, Rat bite fever, Chikungunya.<br>Atopic<br>Atopic dermatitis<br>Autoimmune<br>Systemic arthritis, Kawasaki disease, Graft-versus-host disease<br>Drug-induced<br>Chemotherapy-induced acral erythema, Drug Reaction with Eosinophilia and Systemic Symptoms syndrome |

## Physiologic or primary

Palmar and plantar erythema can be a primary physiologic finding or a secondary marker of systemic pathology in children. This physiologic palmar or plantar erythema presents as diffuse mottling and involves the entire palmar or plantar surface with specking of pale areas of 1 mm or more in diameter. The pattern alters with pressure, atmospheric temperature, emotional state and elevation or position of the limb.

### Palmar erythema

Isolated palmar erythema in children is usually idiopathic. When all other possible causes are excluded, this diagnosis by exclusion can be made.

### Plantar erythema

Isolated plantar erythema is mainly considered idiopathic. Literature on primary causes of isolated plantar erythema is very scarce. This could be partially due to the lack of attention for the soles in general, especially in comparison to the more visible hands, and the lack of attention of clinicians and patients to the soles when there is no specific complaint in that area. In addition, people are inclined to attribute the cause of redness of the soles of feet to pressure that the soles experience during walking or running.

### Palmoplantar erythema

There are two primary causes of palmoplantar erythema: idiopathic palmoplantar erythema and Erythema Palmare Hereditarium (EPH).

EPH or Lane disease, is a very rare rash that presents as a symmetric, persistent, slightly bluish to vivid scarlet colored erythema of the palms and, less frequently, the soles (2-4). It usually appears at birth and remains stable throughout life. No specific treatment should be administered. It shows an autosomal dominant pattern of inheritance. Therefore, it is important to consider EPH in all children presenting with palmar erythema, especially if at least two relatives within the same family are affected (4). There is no inflammatory infiltrate on histology, however, dilated vessels in the entire dermis can be observed. Capillaroscopy shows an increased number of capillary loops running parallel to the surface (5). Dermoscopy shows red structureless areas with arborizing vessels that mainly run in parallel along follicular openings (4). The diagnosis of idiopathic palmoplantar erythema can be made when all other possible causes are excluded.

## Pathologic or secondary

### Palmar erythema

Palmar erythema can be a symptom of many different conditions (2).

The etiology of the underlying disease may be hepatic, autoimmune, endocrine, infectious, drug-induced or neoplasia related. As the pathogenesis of these diseases is often age-related, the age of onset can guide the clinician in making the most appropriate differential diagnosis.

When palmar erythema is present in the newborn or young child, a pathologic cause must be considered.

### Hepatic

Palmar erythema in liver disease can present as generalized redness of the palms, the dorsum of the hands, fingertips and nail bed. The erythema blanches when pressure is applied and it is commonly accompanied by pruritus (6).

In children, the most frequent hepatic diseases associated with palmar erythema are cholestasis (e.g. in primary sclerosing cholangitis or obstructive gallstone disease) and less commonly liver cirrhosis (2, 6). Alpha-1-antitrypsin deficiency, cholesterol ester storage disease and tyrosinemia can all present for the first time with signs and symptoms of cirrhosis, including palmar erythema, in late childhood or early adolescence. A relatively common hepatic disease that causes palmar erythema is Wilson disease. It mainly presents in the school-aged child. Hemochromatosis and hepatitis (B, C) can also lead to liver cirrhosis (2).

However, neonates and young children with underlying liver disease are less likely to present with palmar erythema and other signs of chronic liver disease than adolescents and adults (7). Treatment depends on the type of liver disease.

### Autoimmune

Children and adolescents with systemic lupus erythematosus can develop a rash with a variable morphology and location. It therefore remains a diagnostic challenge for the primary care physician, especially if the malar rash is absent. A skin biopsy for histology may facilitate accurate diagnosis (8). Treatment consists mainly of immunosuppressive drugs.

### Endocrine

Palmar erythema can also be present in patients with Graves disease, a cause of thyrotoxicosis. Aside from the infrequent occurrence of postnatal thyrotoxicosis due to maternal antibodies, the incidence of spontaneous Graves disease in children before the age of 10 is very low. However, the incidence increases with each decade until about the age of 60. The hand of the thyrotoxic person is erythematous, moist and in a state of hot hyperhidrosis (9).

Thyrotoxicosis, without an autoimmune cause such as pituary adenoma or iatrogenic by administration of iodide, is an endocrine disorder with several cutaneous manifestations including palmar erythema. It has been found in up to 18% of patients with this disorder (2). Treatment depends on the cause of thyrotoxicosis.

Diabetes mellitus is associated with palmar erythema in up to 4% of patients with type 1 and type 2 diabetes. Nevertheless, this presentation in children is rare given that cutaneous involvement is especially seen in prolonged disease (2, 10, 11). Treatment consists out of dietary measures and anti-diabetic medication (e.g. insulin).

### Infectious

Juvenile human T-lymphotropic virus-1 associated myelopathy or tropical spastic paraparesis (HAM or TSP), a chronic myelopathy characterized by slow progressing spastic paraparesis, severe sphincter disturbances and mild sensorial involvement, is frequently associated with palmar erythema. Although many authors suspect a relatively high frequency of HAM/TSP in childhood and puberty, only a scarce number of cases can be found in literature (12-14). Treatment is symptomatic. Chronic Hepatitis B or Hepatitis C infection can also present with palmoplantar erythema, however chronic disease in children is rare.

Drug induced

Palmar erythema may be observed as a result of hepatic damage related to the use of medication. However, topiramate is one of the few drugs that directly causes palmar erythema without causing liver dysfunction.

### Neoplasia

Palmar erythema has been reported as a paraneoplastic finding. The study of Noble et al. suggests an association between acral erythema and malignant tumors. It has been reported in brain tumors, hepatic tumors and lymphoproliferative disorders e.g. Hodgkin lymphoma (2, 15). However, the correlation between palmar erythema and cancer seems to be infrequent. Palmar erythema due to therapeutic regiments for neoplasia will be discussed later.

## Plantar erythema

Juvenile plantar dermatosis and shoe dermatitis are secondary causes of isolated plantar erythema. As with palmar erythema, it is also important to be differentiated from the physiologic diffuse red mottling over the entire plantar surface. These two clinical entities are included because of the clinical relevance. They both, however, present mainly with scaling and therefore can't be considered as mere plantar erythema.

Juvenile plantar dermatosis (JPD), chapped fissured feet or sweaty sock syndrome, appears with shiny or glazed erythema, increased skin markings and fissuring of the dorsal and plantar aspects of the forefeet. The rash is mainly scaling. Children complain of pain but not of itching. Some children who have JPD will exhibit features of atopic dermatitis. JPD generally occurs between the age of 3 to 14 years (16). The cause is not yet known, however some believe it to be a frictional dermatitis. The treatment consists of avoiding skin irritants, the administration of petroleum jelly and in severe cases topical glucocorticosteroids (16).

Shoe dermatitis, a form of allergic contact dermatitis, appears as a pruritic inflammation with redness and usually scaling on the toes and dorsa of feet and less frequently, on the soles of feet. The soles are often spared because the thickness of the skin is more resistant to allergens. It can appear at any age. Avoidance of the causative agent is necessary and results in resolution in 2 to 3 weeks (16).

## Palmoplantar erythema

Most causes of palmoplantar erythema are secondary and can be infectious, atopic, autoimmune or drug-induced.

### Infectious

A well-known entity is the papular-purpuric gloves and socks syndrome (PPGSS), which may present as erythema on the hands and feet in a gloves and socks distribution. It can also manifest as purpuric papules on the soles of feet. It is described in infections with parvovirus B19, Epstein Barr virus, cytomegalovirus and Mycoplasma pneumonia (17-21). In young children, hands may be more involved than feet. In addition, the petechial component may be less prominent in children (22).

PPGSS caused by Epstein Barr virus may present as a maculopapular eruption that is initially located on the trunk and then extends to the face and extremities. Other possible presentations are an urticarial eruption, a scarlatiniform eruption and a vesicular or purpuric eruption (19, 20, 23). Treatment is symptomatic. Spontaneous resolution occurs in several weeks.

The typical hand foot mouth disease (HFMD, most commonly caused by coxsackievirus CVA16 or enterovirus EV71) also presents as a maculopapular rash. It typically involves the face, trunk, breech, arms, legs, palms and feet. The rash can turn into vesicles and there is usually a history of fever. The atypical presentation of HFMD caused by coxsackievirus CVA6 is generally observed in children younger than 5 years and presents as lesions of the oral mucosa, palms and soles (22-25). Spontaneous resolution can be expected within 2 weeks.

Erythema infectiosum is the most common manifestation of parvovirus B19. It is typically associated with an erythematous rash on the trunk and extremities, including palms and soles and knows a spontaneous resolution within weeks (22, 26).

Involvement of the palms and soles in secondary syphilis is common. It usually begins as small macular lesions that evolve into macular brownish red papules (27). Treponema pallidum infection within the first 4 months of life causes a palmoplantar erythema that is often accompanied by bullae on the soles. The palmoplantar erythema has a shiny appearance and subsequently results in desquamation. Antibiotic treatment should be administered (2).

Palmar and plantar erythema has been observed in our centre in a 5-month-old and a 4-year-old girl infected with respiratory syncytial virus (RSV, figure 1) and adenovirus (figure 2), respectively. The erythema in the RSV infected infant presented 1 week after the acute clinical phase, initially as an erythema on the trunk and shoulders and subsequently as palmar and plantar erythema. The onset of the palmoplantar erythema in the preschool child infected with Adenovirus was after 3 days of fever. Differentiation with exanthema subitum should be made. Treatment is supportive. There was spontaneous resolution within 2 weeks in both cases.

Human parechovirus-3 infection presents typically with an erythematous rash that is limited to the palms and soles and is associated with hyperferritinemia. The palmoplantar erythema appears on day 3 to 5 after the onset of fever and most frequently occurs in infants below the age of 3 months. Due to the association between human parechovirus-3 and sepsis-like illness and/or meningoencephalitis, it is important to differentiate with exanthema subitum given the very similar clinical picture. Nevertheless, exanthema subitum commonly spares the extremities. The distinction with Kawasaki disease is sometimes difficult. Kawasaki disease is more common in toddlers and not in neonates (28, 29). Spontaneous resolution of the rash can be expected and treatment is supportive.

Meningococcal septicemia often presents with fever and dermatitis in infants and young adults. The rash may be maculopapular, petechial or purpuric and can involve the palms and soles. It is not considered as mere palmoplantar erythema but must be included in the differential diagnosis. The recognition is of primordial importance since the presence of a rapidly progressive hemorrhagic dermatitis, usually starting on the lower extremities, is mostly indicative of sepsis. Antibiotics should be administered immediately (27, 30). The toxic shock syndrome, caused by Staphylococcus aureus or group A Streptococcus, can present as palmar erythema, mostly together with palmar edema. Plantar erythema can also be present(27). Antibiotics

**Figure 1 :** *Palmoplantar erythema in a child with respiratory syncytial virus.*

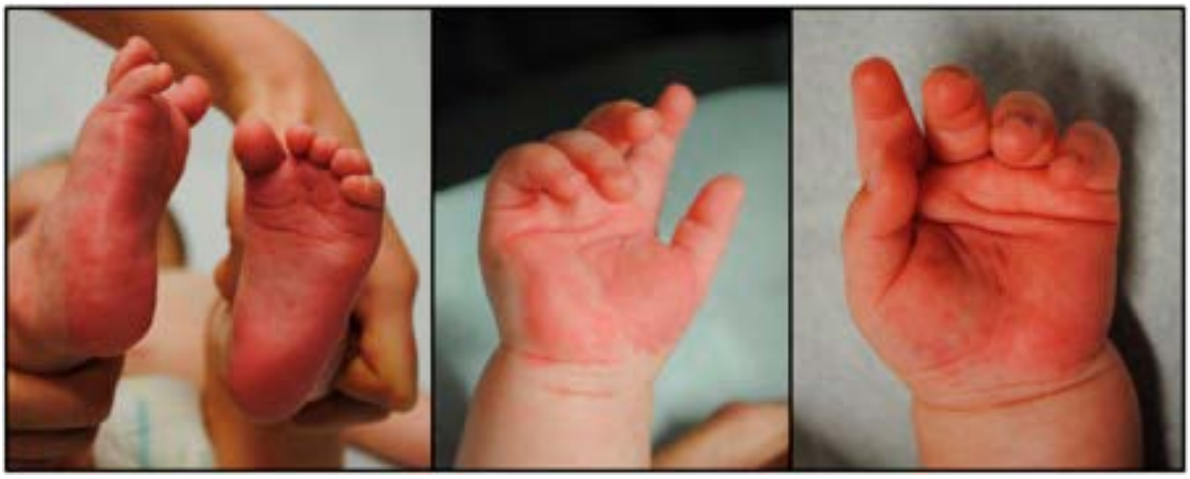
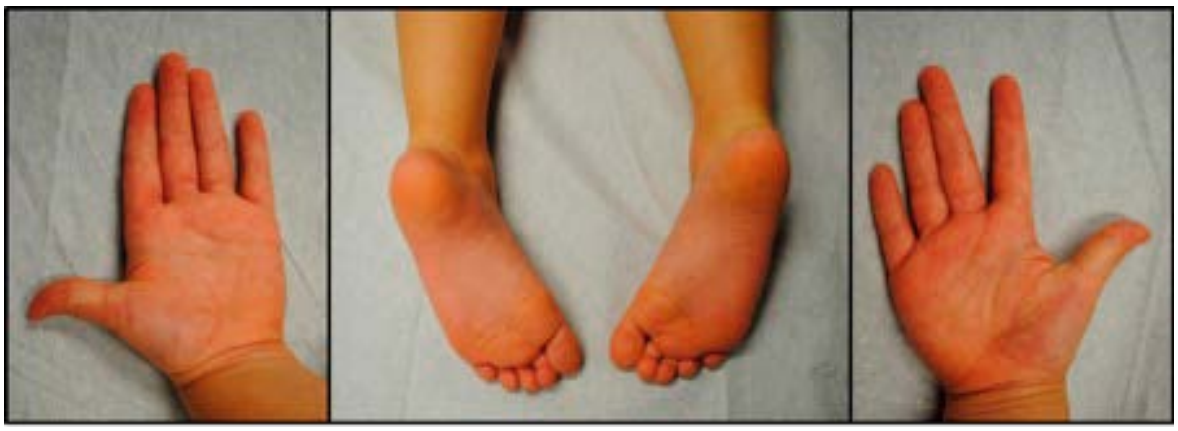


**Figure 2 :** *Palmoplantar erythema in a child with adenovirus.*



should be urgently administered. Another important disease to recognize is the Rocky Mountain spotted fever (RMSF), given a 23% mortality when the start of treatment with antibiotics is delayed. It is caused by the intracellular bacterium Rickettsia rickettsi which is endemic in the South Atlantic, the Pacific and West South-Central part of the United States. It has a median incubation period of 7 days and up to 95% of children develop a rash within the first 2 days of illness. It typically presents with fever, rash and history of tick exposure. The rash consists of 1 to 4 mm erythematous blanching macules of the ankles and wrists that can spread centripetally to involve the trunk. It involves the soles and palms in 65% of cases. In two-third of the pediatric RMSF cases with rash, the child develops petechiae. Screening for tick exposure and recent travel in endemic areas may facilitate an early diagnosis (27, 31). Antirickettsial therapy should be administered.

In children in the late phase of SARS-CoV-2 infection, a Kawasaki-like hyperinflammatory syndrome has been observed. The child presents with persistent fever and mucocutaneous involvement as seen in Kawasaki disease (among which palmoplantar erythema) and other symptoms like prodromal diarrhea, capillary leak syndrome and myocardial dysfunction (32). Neri et al. described an increase in palmar and plantar erythema during the COVID-19 pandemic. An association with SARS-CoV-2 infection however is not yet demonstrated (33).

Erythema of the palms and soles is also observed in measles and varicella. It is rarely observed in exanthema subitum, chikungunya, rat bite fever caused by Streptobacillus moniliformis, ehrlichiosis and murine typhus (22, 27, 30, 34, 35).

#### Atopic

In atopic dermatitis, palmoplantar erythema is a frequent finding. This involvement is even included in the minor diagnostic features of atopic dermatitis (36, 37). It can manifest on the palms as pronounced, erythematous maculae or reticulated erythema surrounding pale, angiospastic foci (36). In the study of Lee et al., where the presentation of atopic hand-foot dermatitis was investigated in 108 children with atopic dermatitis, about half of the children had both hand and foot dermatitis, and 43% showed solely foot involvement. The age of onset of hand-foot dermatitis was between the age of 3 and 5 years. Genetic factors play an important role in the pathogenesis of atopic dermatitis. Cholinergic hyperreactivity and susceptibility to cutaneous irritation are also believed to play an important role. Hand-foot dermatitis is mostly caused by irritation and related to nonallergic etiology (37, 38).

The study of Schuster et al. showed an increased tendency to vasoconstriction and decreased circulation of the small blood vessels both in atopic dermatitis affected skin areas as well as disease-free skin areas. The vascular pattern of the palms was not associated with other clinico-morphological features like inflammatory infiltration, papules, vesicles or clinical symptoms like itching or burning (36). Treatment is mainly local, with hydrating regiments and, depending on the severity, dermocorticoids.

#### Autoimmune

Systemic arthritis, also called adolescent-onset Still disease, accounts for 5–15% of children with juvenile idiopathic arthritis. It is characterized by arthritis with daily fever for at least 2 weeks that follows a quotidian pattern and at least one of the following features: an evanescent, erythematous rash, generalized lymphadenopathy, hepatomegaly, splenomegaly or serositis (39). Cutaneous findings occur in 90% of the patients manifesting as well-circumscribed, transient, non-pruritic, salmon-pink, macular or urticarial rash over the trunk, neck and proximal extremities (39, 40). The lesions can also develop on the face, palms or soles and they typically occur during the daily fever spikes together with joint pain or fatigue (39-41). It is frequently observed over pressure areas and can be associated with marked dermatographism or Koebner phenomenon. This may help in differentiating the rash from drug-induced or viral exanthemas (39). Referral to a rheumatologist is indicated.

Kawasaki disease is an important vasculitis with systemic symptoms in the young child and risk of coronaropathy if not recognized. It has a typical presentation with fever, conjunctival injection, oral involvement, acute cervical adenopathy, polymorphous rash and changes in the extremities (figure 3). Erythema of the palms and soles often occurs in the acute phase. A firm and sometimes painful induration of the hands or feet may also occur (42). Recent case reports describe an association between Kawasaki disease and COVID-19 (SARS-CoV-2) in children, which makes the recognition of this disease even more important (43). Administration of intravenous immunoglobulins and aspirin is indicated as soon as possible after diagnosis.

In graft-versus-host disease, cutaneous manifestations are often one of the first symptoms. Erythema on the palmoplantar regions is commonly preceded by a burning sensation or pruritus. In case of graft-versus-host disease after bone marrow transplantation, palmoplantar erythema manifests typically between day 7 and day 21. As the disease progresses, the maculopapular exanthema can involve the thorax, neck and cheeks. It can also lead to a violaceous coloration of the ears. Urgent referral to the attending hematologist is indicated (44).

#### Drug-induced

Chemotherapy induced acral erythema (hand foot syndrome, palmar-plantar erythrodysesthesia) is a symmetric, painful erythema of the palms and soles, which progresses to blistering and desquamation. It usually appears within 1 day to 3 weeks of initiation and resolves within 1 to 2 weeks after discontinuation of chemotherapy. Numerous chemotherapeutic agents have been described, including 5-fluorouracil, cytarabine, methotrexate, cyclophosphamide, paclitaxel, mercaptopurine, mitotane, hydroxycarbamide, etoposide and doxorubicin. Methotrexate is the most commonly implicated agent in children (45).

Erythema of the palms and soles rarely presents in children with drug reaction with eosinophilia and systemic symptoms syndrome (DRESS syndrome) (46-49).

## Approach to a child with palmar and/or plantar erythema

#### Recommended Investigations

In children with palmar or plantar erythema, a thorough history is paramount and should include the initial presentation, evolution and associated symptoms of the erythema. A careful family history should not be forgotten since some types of erythema have a genetic cause. This should be followed by a complete clinical examination with attention for the erythema but also for associated symptoms. Attention for specific clinical features and possible risk factors can facilitate adequate diagnosis. For example, a child with a history of transplantation that presents with palmoplantar erythema, should always receive further investigations to rule out graft-versus-host disease. In a child presenting with conjunctivitis, lymphadenopathy, fever for more than 5 days and palmoplantar erythema, the possibility of Kawasaki disease should be considered.

When the patient presents solely with plantar erythema, no further examinations are required given the known benign nature of isolated plantar erythema. However, further investigations in patients who present with persistent palmar or palmoplantar erythema without any clues are strongly recommended. Although most forms of PE have a good prognosis, in some cases the occurrence of palmar and/or plantar erythema can be an important presenting feature of a possibly life-threatening condition (e.g. cancer).

A blood sample can help to rule out the most frequent causes of PE. In table 2, a comprehensive but still incomplete list of recommended tests can be found. It can be used to guide clinicians in tackling the diagnostic odyssey for PE.

When the initial investigations are normal, more targeted investigations may be necessary, especially when there is a high clinical suspicion for a particular underlying disease. For example, in patients with respiratory symptoms, a polymerase chain reaction test (PCR test) for Mycoplasma pneumoniae and, depending on the clinical picture, a chest X-ray should be performed. In a neonate with PE with a mother with an unknown infection status, a serologic test for congenital syphilis should be done.

#### Therapy

In patients with primary PE, no treatment is indicated. If the erythema is secondary, the patient is treated according to the identified underlying cause.

For example, in Kawasaki disease, intravenous immunoglobulins and aspirin should be administered.

## Conclusion

The finding of PE in children is an important clinical sign and should not be disregarded or neglected. It has an extensive differential diagnosis with mostly reassuring causes such as viral infections that do not require treatment. However, palmar and or plantar erythema can be an important sign that indicates the presence of a possibly life-threatening underlying condition. Hence the strong recommendation for further investigations when a thorough anamnesis and clinical examination raise even the slightest suspicion for a possible underlying cause (table 2).

This article aims to remind the clinician of the significance of the presence of erythema on the palms and soles of the child. It aims to help undertake the necessary action in excluding a possible underlying cause of the encountered erythema, depending on the clinical suspicion. Overall, it is clear that cases of palmar, palmoplantar and especially plantar erythema are still largely underreported.

The lack of mentioning the presence of erythema of the palms and soles in most studies, the assumption that erythema of the palms and soles is almost always likely due to a physiologic pressure reaction and the lack of knowledge about PE as a clinical entity make the recognition and undertaking of appropriate action difficult. There is a major need for more research to confirm known associations (e.g. between PE and DRESS syndrome) and to discover new associations to have a more comprehensive view of the prevalence, epidemiology, therapy and prognosis of the child with PE. Overall, the therapy and prognosis are largely dependent on the underlying cause of PE.

The global awareness for PE is rising and should continue to rise given the possibly life-threatening underlying causes. Case reports play a very important role in the further exploration and identification of PE as a clinical symptom in different pathologies. Their publication on this issue should therefore be encouraged.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

**Figure 3:** *Palmoplantar erythema in a child with Kawasaki disease.*

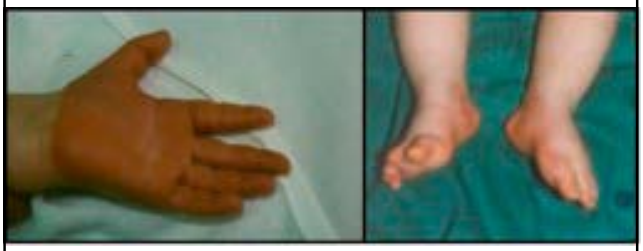


**Table 2 :** *Recommended investigations in a child with PE where an indication for further diagnostic investigation is present.*

| Location | Investigation type | Specific tests | Associated disease |
|---|---|---|---|
| Palmoplantar | Laboratory | Complete blood count, CRP | Infectious |
| | | Liver function test (AST, ALT, GGT), Bilirubin, APTT, PT, fibrinogen, INR, Vitamin K | Liver dysfunction<br>Viral infection |
| | | RF, ANA, anti-CCP, anti-SSA, anti-SSB, HLA-B27 | Juvenile idiopathic arthritis |
| | | Rapid plasma reagin, Fluorescent treponemal antibody absorption assay | Syphilis (congenital) |
| | | Serology Ricketssia antigen, VZV antigen, Chikungunya, Parvovirus IgM/IgG | RMSF , Varicella, Chikungunya<br>PPGSS |
| | | Proalbumin, Albumin, ESR | Kawasaki |
| | Blood culture | Aerobe and anaerobe tube | Meningococcal septicemia, Rat bite fever |
| | Nasopharyngeal aspirate | Viral and bacterial PCR | Mycoplasma pneumoniae infection, SARS-Cov-2 infection, Enterovirus infection, RSV, Human Parechovirus 3, Hand foot mouth disease, PPGSS |
| | Imaging | Cardiac ultrasonography | Kawasaki disease |
| | | Chest X-ray | Mycoplasma pneumoniae |
| | Anatomopathological | Bone marrow biopsy | Lymphoproliferative disease |
| Palmar | Laboratory | Complete blood count | Infectious |
| | | Ferritin, Iron | Hemochromatosis |
| | | (Fasting) glucose, HbA1C | Diabetes mellitus |
| | | TSH, (T4, T3) | Thyrotoxicosis, Graves |
| | | Bilirubin (total + direct), Alkaline phosphatase, GGT | Cholestasis |
| | | Ceruloplasmin, Cu, MRI | Wilson disease |
| | | ANA, anti-Sm, anti-DNA, anti-ENA (anti-SSA, anti-SSB), anti-RNP | Systemic lupus erythematosus |
| | | Anti-human t-lymphotropic virus-1 IgM, IgG | Juvenile Human T-lymphotropic Virus-1 associated myelopathy |
| | | Serology: Hepatitis C, Hepatitis B, Epstein-Barr Virus, Rickettsia Ag, SARS-Cov-2 | Hepatitis, Epstein-Barr virus infection, RMSF, PPGSS, Erythema infectiosum, SARS-Cov-2 infection |
| | Blood culture | Aerobe and anaerobe tube | Toxic shock syndrome |
| | Imaging | Abdominal ultrasonography | Lymphoproliferative disease, Liver cirrhosis |
| | | CT chest, abdomen, pelvis | Neoplasia |
| | | MRI brain | Neoplasia, Hemochromatosis |

*CRP (C-reactive protein), AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), GGT (Gamma-glutamyl transferase, APTT (Activated partial thromboplastin time), PT (Prothrombin time), RF (Rheumatoid factor), ANA (Anti-nuclear antibodies), anti-CCP (Anti-cyclic citrullinated peptide), anti-SSA (Anti-Sjögren syndrome related antigen A), anti-SSB (Anti-Sjögren syndrome related antigen B), HLA-B27 (Human Leucocyte Antigen), VZV (Varicella zoster virus), RMSF (Rocky Mountain Spotted Fever), PPGSS (Papular-pruritic gloves and socks syndrome), ESR (Erythrocyte sedimentation rate), RSV (Respiratory syncytial virus), HbA1C (Hemoglobin A1C), TSH (Thyroid stimulating hormone), Cu (Copper), MRI (Magnetic resonance imaging), ANA (Antinuclear antigen), anti-Sm (Smith antibody, specific marker for systemic lupus erythematosus), anti-ENA (Extractable nuclear antigen antibody), anti-RNP (Ribonucleoprotein antibody).*

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**PRIX PUBLIQUE 86.52€**

# VACCINEZ EN CONFIANCE CONTRE LE MenB

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

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

**RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT** Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT** Bexsero suspension injectable en seringue préremplie Vaccin méningococcique groupe B (ADNr, composant, adsorbé) EU/1/12/812/001 EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004 Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09 **COMPOSITION QUALITATIVE ET QUANTITATIVE** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de *Neisseria meningitidis* groupe B [1,2,3] : **50 microgrammes** - Protéine recombinante NadA de *Neisseria meningitidis* groupe B [1,2,3] : **50 microgrammes** - Protéine de fusion recombinante fHbp de *Neisseria meningitidis* groupe B [1,2,3] : **50 microgrammes** - Vésicules de membrane externe (OMV) de *Neisseria meningitidis groupe* B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4 [2] : **25 microgrammes.** [1]produite dans des cellules d'*E. coli* par la technique de l'ADN recombinant [2]adsorbée sur hydroxyde d'aluminium (0,5 mg $Al^{3+}$) [3]NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H) **Indications thérapeutiques** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration** Posologie **Tableau 1. Résumé de la posologie - Age lors de la première dose : Nourrissons de 2 à 5 mois**[a] **- Primovaccination :** Trois doses de 0,5 ml chacune- **Intervalles entre les doses de primovaccination :** 1 mois minimum - **Primovaccination :** Deux doses de 0,5 ml chacune - **Intervalles entre les doses de primovaccination :** 2 mois minimum - **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel [b,c] - **Age lors de la première dose : Nourrissons de 6 à 11 mois - Primovaccination :** Deux doses de 0,5 ml chacune - **Intervalles entre les doses de primovaccination :** 2 mois minimum - **Rappel :** Oui, une dose au cours de la deuxième année avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel [c] - **Age lors de la première dose : Enfants de 12 à 23 mois - Primovaccination :** Deux doses de 0,5 ml chacune - **Intervalles entre les doses de primovaccination :** 2 mois minimum - **Rappel :** Oui, une dose au cours de la deuxième année avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel [c] - **Age lors de la première dose : Enfants de 2 à 10 ans - Adolescents (à partir de 11 ans) et adultes*** **- Primovaccination :** Deux doses de 0,5 ml chacune - **Intervalles entre les doses de primovaccination :** 1 mois minimum - **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d] – [a]La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b]En cas de retard, la dose de rappel ne doit pas être administrée audelà de l'âge de 24 *mois*. [c]Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'une dose de rappel n'ont pas encore été déterminés. [d]Voir rubrique 5.1 du RCP complet * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, souscutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **Mises en garde spéciales et précautions d'emploi** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entraîner le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vasovagales (syncope), de l'hyperventilation ou des réactions en rapport avec le stress peuvent survenir lors de la vaccination comme réaction psychogène à l'injection avec une aiguille (voir rubrique « Effets indésirables »). Il est important que des mesures soient mises en place afin d'éviter toute blessure en cas d'évanouissement. Ce vaccin ne doit pas être administré aux patients ayant une thrombocytopénie ou tout autre trouble de la coagulation qui serait une contreindication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination par Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation. Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles postvaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique. Les personnes ayant des déficits hétréditaires du complément (par exemple les déficits en C3 ou C5) et les personnes recevant un traitement inhibiteur de l'activation de la fraction terminale du complément (par exemple, l'éculizumab) ont un risque accru de maladie invasive due à *Neisseria meningitidis* du groupe B, même après avoir développé des anticorps après vaccination par Bexsero. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. Traçabilité Afin d'améliorer la traçabilité des médicaments biologiques, le nom et le numéro de lot du produit administré doivent être clairement enregistrés. **EFFETS INDÉSIRABLES** Résumé du profil de sécurité La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6837 étaient des nourrissons et des enfants (de moins de 2 ans), 1051 étaient des enfants (entre 2 et 10 *ans*) et 2677 étaient des *adolescents* et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3285 ont reçu une dose de rappel au cours de leur deuxième année de vie.. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69% à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et *Haemophilus influenzae* de type b), contre 44% à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) Fréquent : (≥ 1/100 à < 1/10) Peu fréquent : (≥ 1/1 000 à < 1/100) Rare : (≥ 1/10 000 à < 1/1 000) Très rare : (< 1/10 000) Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles) Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans)** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Troubles du métabolisme et de la nutrition Très fréquent : troubles alimentaires Affections du système nerveux Très fréquent : somnolence, pleurs inhabituels, céphalée Peu fréquent : convulsions (y compris convulsions fébriles) Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire) Affections vasculaires Peu fréquent : pâleur (rare après le rappel) Rare : syndrome de Kawasaki Affections gastrointestinales Très fréquent : diarrhée, vomissements (peu fréquents après le rappel) Affections de la peau et du tissu souscutané Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel) Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans) Peu fréquent : eczéma Rare : urticaire Affections musculosquelettiques et systémiques Très fréquent : arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité Peu fréquent : fièvre (≥ 40 °C) Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois) **Adolescents (à partir de 11 ans) et adultes** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Affections du système nerveux Très fréquent : céphalée Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire) Affections gastrointestinales Très fréquent : nausées Affections de la peau et du tissu sous-cutané Fréquence indéterminée : rash Affections musculosquelettiques et systémiques Très fréquent : myalgies, arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois) Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique** Agence fédérale des médicaments et des produits de santé Division Vigilance Boîte Postale 97 B-1000 Bruxelles Madou Site internet: www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be **Luxembourg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy - Hôpitaux de Brabois Rue du Morvan 54 511 VANDOEUVRE LES NANCY CEDEX Tél : (+33) 3 83 65 60 85 / 87 Fax : (+33) 3 83 65 61 33 E-mail : crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments Allée Marconi - Villa Louvigny L-2120 Luxembourg Tél. : (+352) 2478 5592 Fax : (+352) 2479 5615 E-mail : pharmacovigilance@ms.etat.lu Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie **DATE D'APPROBATION DU TEXTE** 02/07/2020 (v11) **MODE DE DELIVRANCE** Sur prescription médicale. **Référence :** SmPC Bexsero

**PM-BE-BEX-ADVT-210007 - Juillet 2021 |** E.R.: GlaxoSmithKline Pharmaceuticals s.a./n.v. Site Apollo Avenue Pascal, 2-4-6 1300 Wavre Belgium

Case Report

# Acute asphyxic asthma: beware of a potential killer

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## Keywords

Severe asthma; sudden-onset asthma attack; life-threatening asthma; child

## Abstract

Acute asphyxic asthma is a rare but severe presentation of an acute asthma exacerbation, not well known in children. We report the case of an eleven-year old girl, who presented with acute dyspnea at night, quickly evolving to cardiorespiratory arrest, for which cardiopulmonary resuscitation was required. An acute asphyxic asthma attack was diagnosed as the cause of the cardiopulmonary arrest. Acute asphyxic asthma has been previously described in adults, but studies in children are scarce. Further studies are needed to identify children at risk for acute asphyxic asthma and guide preventive measures. Awareness of this entity is crucial. If promptly recognized and treated, a near-fatal attack usually resolves rapidly and completely.

## Introduction

The prevalence of asthma is high, with five to ten percent of children estimated to be affected. Only few children present with life-threatening episodes, but these are associated with potential mortality, morbidity and a high cost of treatment (1). Severe attacks of asthma may have a sudden or slow onset. Acute asphyxic asthma (AAA) is characterized by a sudden onset that may rapidly progress to a near-arrest state. This is a rare entity previously described in adult patients (2-3). There is evidence that AAA also occurs in children (1).

With this case report, we want to raise awareness of this rare but severe presentation of an acute asthma exacerbation in children. In addition, we want to describe the specific subgroup of patients who present with this type of exacerbation and highlight the differences in therapy and outcome in comparison to a classic asthma exacerbation.

## Case Report

We report the case of an 11-year old girl, with previously known allergic rhinitis and asthma (total IgE 5814 kU/l, with sensitization for dog, cat, dust mite, tree pollen, grass pollen and weed), partly controlled with medium dose inhaled corticosteroids (ICS) and long acting beta2 agonist (LABA), but with moderate therapy compliance. She was exposed to second-hand tobacco smoke daily. No other environmental risk factors were identified. She had regular complaints of cough and was treated for asthma since the age of five, but without any need for oral corticosteroids or hospital admissions in the past. On January 4, 2019, 1 month before admission, therapy was increased to high dose ICS plus LABA and a leukotriene receptor antagonist was started because of daytime symptoms. Spirometry at that time showed a FEV1 of 83%, with an obstructive curve and significant reversibility after administration of SABA (short acting beta2 agonist) (figure 1).

On February 9, 2019, she was admitted to the pediatric intensive care unit (PICU) after an out of hospital cardiorespiratory arrest. She had developed acute dyspnea at night, without previous complaints during the day or evening. Her mother tried to administer salbutamol via inhaler, which was unsuccessful due to severe dyspnea. An ambulance was summoned. She subsequently rapidly lost consciousness and developed central cyanosis. Upon arrival of the ambulance, she was unresponsive, with apnea and extreme bradycardia (heart rate 20 bpm). CPR was started and she was intubated and managed according to standard pediatric advanced life support guidelines, with return of spontaneous circulation after administration of intravenous adrenaline. Intravenous corticosteroids were administered. She was transported to the PICU in stable condition where intensive treatment with inhaled bronchodilators (salbutamol, ipratropium bromide) was started. Investigations showed severe combined respiratory and lactic acidosis (pH 7.068, pCO2 72 mmHg, lactate 51 mg/dl) and a normal chest x-ray (figure 2). Her respiratory condition improved rapidly, with extubation after merely 9 hours of invasive mechanical ventilation (IMV). There were no signs of respiratory distress after extubation. Initial cardiological screening showed a prolonged QT(c) interval, which normalized spontaneously. Investigations for anaphylaxis showed a peanut sensitization but there was no history of recent ingestion of peanuts, and the attack happened at night. Unfortunately, the level of tryptase at admission was not performed. An AAA attack was diagnosed as the cause of the cardiopulmonary arrest. Thirty six hours after admission, spirometry was within normal range (figure 3) and she was discharged. Further investigations showed positive specific IgE for peanut h3, h8 and ara h2, but provocation test one month later was negative.

## Discussion

When studying reports of life threatening asthma or near-fatal asthma, there is evidence that severe asthma can present with acute onset and rapidly progressive respiratory failure (1,2). This phenomenon is not rare, as 15 to 26 percent of asthma deaths in adults are attributed to sudden-onset asthma attacks (3). In near-fatal asthma in children, 17 percent of cases presented with sudden collapse without previous deterioration, while in an Australian asthma mortality study 79% of children presented with sudden collapse (2,4).

AAA or sudden-onset asthma attacks have been defined as respiratory arrest or failure within three hours after the onset of the attack (3). This type of asthma exacerbation is more frequently observed in young male adults and is characterized by a brief duration of symptoms (<3h), few identifiable triggers and a rapid progression to respiratory failure. Sudden onset asthma attacks are characterized by severe mixed respiratory-metabolic acidosis, reflecting circulatory compromise besides acute hypercapnic respiratory failure. There is a higher incidence of respiratory arrest, and silent chest upon admission (1,3,5).

Studies in a pediatric population are scarce, but there is evidence suggesting that AAA in children shares characteristics with adults presenting with this type of asthma attack (1). It is unclear from the current literature, whether usual risk factors for asthma exacerbation like poor adherence and tobacco smoke exposure, as were present in the reported case, increase the risk for an AAA attack in children.

The exact pathophysiological differences between a sudden and a slow-onset asthma attack are not well-described. However, immunohistological differences have been described. Post mortem airway mucosa specimens from fatal asthma patients showed eosinophilic predominance in slow-onset asthma, and predominantly neutrophils in sudden-onset asthma (3). Other studies suggest bronchospasm as a predominant factor of deterioration (5,6). It is notable that in contrast with slow-onset attack, an upper respiratory tract infection or viral trigger is rarely found in AAA (6). It has been suggested that inhalation of large quantities of allergens by patients with high levels of specific IgE to this allergen may cause a sudden-onset asthma attack (3). However, anaphylaxis and AAA are distinct entities with differing treatments so a correct diagnosis is essential (7).

Despite the severity of the presentation, sudden-onset asthma attacks usually resolve rapidly with adequate treatment, both in adults and in children. The principles of the treatment do not differ between AAA and other asthma exacerbations, with bronchodilatory agents and corticosteroids being the first line of therapy. However, due to the rapid progression to respiratory failure, there is a higher need for IMV. Duration of IMV is shorter than in slow-onset attacks, with more rapid improvement of gas exchange (1,3,5). However, patients with a history of AAA are more at risk for a fatal asthma-related outcome (3). Therefore, we advise a strict follow-up for these patients, and would advise a careful approach when considering a step-down in therapy. To further guide preventive measures and treatment choices for pediatric AAA, further studies are warranted.

## Conclusion

In conclusion, AAA is a distinct form of life-threatening asthma, that can occur in the pediatric population. In adults, it is characterized by a sudden onset of symptoms, few identifiable triggers and rapid progression to end-stage respiratory failure (1,3,5). Pediatric AAA shares certain characteristics with adult AAA but in this case poor adherence and smoke exposure were possible triggers. If promptly diagnosed and treated, a near-fatal attack usually resolves rapidly and completely, with most often early hospital discharge. Further studies are required to better define asthma patients at risk for AAA to guide both preventive measures and treatment choices.

### Conflict of interest statement

The authors of this case report declare that they have no conflict of interest. They do not have any affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter of materials discussed in this case report.

**Figure 2 :** *Chest X-ray after intubation in the field. In the upper right lobe, we see an atelectasis, due to deep tube positioning (clinically evident, already corrected at the moment of the X-ray)*

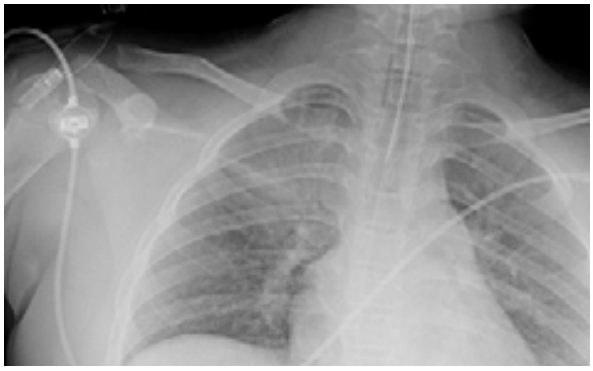


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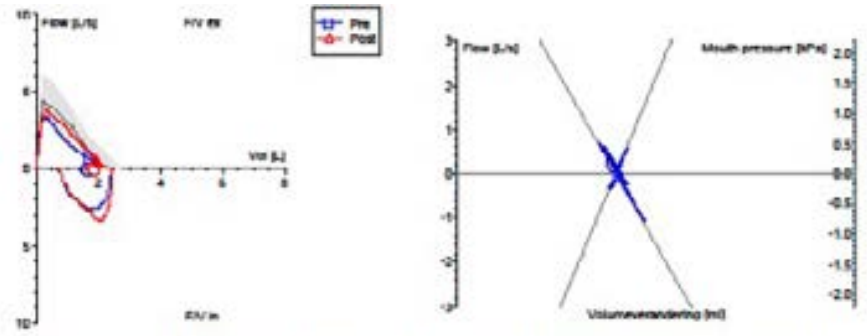
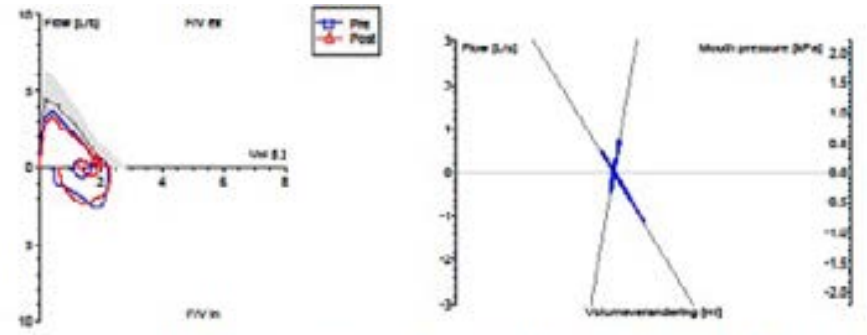
**Figure 1 :** *Spirometry one month before admission. Note the obstructive curve before administration of SABA and the 14.5% reversibility in FEV1 after administration of SABA.*




| | | Voorsp | Pre | % | Post | % | % Chg | z-score |
|---|---|---|---|---|---|---|---|---|
| R tot | kPa/(L/s) | 0.35 | 0.71 | 202.2 | | | | 3.97 |
| SR tot | kPa²s | | 1.89 | | | | | |
| ITGV | L | 1.40 | 2.40 | 164.3 | | | | 4.57 |
| RV Pleth | L | 0.77 | 1.86 | 241.8 | | | | 6.19 |
| TLC Pleth | L | 2.99 | 4.22 | 141.9 | | | | 4.63 |
| ERV | L | 0.72 | 0.54 | 74.8 | | | | -1.74 |
| RV%TLC | % | 25.4 | 44.0 | 173.5 | | | | 4.77 |
| ITGV % TLC | % | 47.20 | 56.78 | 120.3 | | | | 2.38 |
| VC | L | 2.21 | 2.36 | 107.1 | | | | 0.67 |
| VC IN | L | 2.21 | 1.80 | 81.7 | 1.86 | 84.3 | 3.2 | -2.10 |
| FVC | L | 2.23 | 2.40 | 107.6 | 2.42 | 108.8 | 1.1 | 0.64 |
| FEV 1 | L | 1.86 | 1.60 | 83.1 | 1.85 | 95.1 | 14.5 | -1.43 |
| FEV 1 % VC MAX | % | 89.37 | 68.69 | 76.9 | 77.76 | 87.0 | 13.2 | -2.64 |
| PEF | L/s | 4.36 | 3.60 | 82.4 | 3.79 | 86.8 | 5.3 | -1.25 |
| MEF 25 | L/s | 1.23 | 0.47 | 37.9 | 0.69 | 56.0 | 47.5 | -2.53 |
| MEF 50 | L/s | 2.77 | 1.32 | 47.7 | 2.05 | 74.1 | 55.1 | -3.84 |
| MEF 75 | L/s | 3.92 | 2.60 | 66.4 | 3.21 | 81.9 | 23.5 | -2.43 |
| MFEF 75/25 | L/s | 2.66 | 1.11 | 41.7 | 1.70 | 64.0 | 53.4 | -2.90 |
| PIF | L/s | | 2.66 | | 3.40 | | 27.8 | |
| FIV 1 | L | | 1.79 | | 1.73 | | -3.3 | |

**Figure 3 :** *Spirometry 36 hours after admission. Note the absence of obstruction and reversibility.*




| | | Voorsp | Pre | % | Post | % | % Chg | z-score |
|---|---|---|---|---|---|---|---|---|
| R tot | kPa/(L/s) | 0.34 | 0.34 | 101.5 | | | | 0.00 |
| SR tot | kPa²s | | 0.80 | | | | | |
| ITGV | L | 1.52 | 2.19 | 144.6 | | | | 3.17 |
| RV Pleth | L | 0.79 | 1.53 | 192.1 | | | | 4.02 |
| TLC Pleth | L | 3.09 | 3.83 | 124.1 | | | | 2.67 |
| ERV | L | 0.75 | 0.67 | 88.9 | | | | -0.77 |
| RV%TLC | % | 25.2 | 30.8 | 157.8 | | | | 3.73 |
| ITGV % TLC | % | 47.32 | 57.18 | 120.8 | | | | 2.45 |
| VC | L | 2.29 | 2.31 | 100.8 | | | | 0.05 |
| VC IN | L | 2.29 | 1.79 | 78.0 | 1.69 | 73.8 | -5.3 | -2.53 |
| FVC | L | 2.31 | 2.24 | 96.9 | 2.30 | 99.5 | 2.6 | -0.26 |
| FEV 1 | L | 2.05 | 1.84 | 89.8 | 1.81 | 88.3 | -1.7 | -0.87 |
| FEV 1 % VC MAX | % | 89.29 | 82.37 | 92.3 | 78.01 | 88.4 | 4.2 | -1.13 |
| PEF | L/s | 4.51 | 3.69 | 81.7 | 3.21 | 71.2 | -12.9 | -1.30 |
| MEF 25 | L/s | 1.27 | 0.81 | 63.4 | 0.71 | 56.0 | -11.6 | -1.30 |
| MEF 50 | L/s | 2.85 | 2.24 | 78.3 | 2.02 | 70.9 | -9.5 | -1.50 |
| MEF 75 | L/s | 4.04 | 3.42 | 84.5 | 2.92 | 72.2 | -14.6 | -1.12 |
| MFEF 75/25 | L/s | 2.73 | 1.90 | 69.9 | 1.70 | 62.3 | -10.7 | -1.44 |
| PIF | L/s | | 2.62 | | 2.33 | | -11.2 | |
| FIV 1 | L | | 1.75 | | 1.67 | | -4.5 | |

Case Report

# Distal intestinal obstruction syndrome and mechanical small bowel obstruction : a rare but life-threatening combination in cystic fibrosis patients

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## Keywords

cystic fibrosis - distal intestinal obstruction syndrome - mechanical small bowel obstruction – children

## Abstract

This case report illustrates a distal intestinal obstruction syndrome in a child with cystic fibrosis, complicated by an adhesive small bowel obstruction. Both conditions can occur simultaneously in cystic fibrosis patients.

Early recognition and appropriate multidiciplinary medical management are essential to avoid complications.

## Introduction

Distal intestinal obstruction syndrome (DIOS) is a common complication associated with cystic fibrosis (CF). The prevalence is estimated around 5 to 12 episodes per 1000 patients per year in children (1). DIOS results from an accumulation of viscous faecal material with sticky mucous secretions in the bowel lumen that adheres to the intestinal wall of the terminal ileum and caecum, and was first described by Jensen in 1962 (1-3).

In 2010, a consensus gave rise to a definition of the syndrome with a distinction between the incomplete and complete form (4). The incomplete form is characterised by history of abdominal pain and the presence of a subostructive faecal mass in the right colic quadrant. The complete form is more severe, with signs of complete intestinal obstruction such as bilious vomiting and secondary mechanical ileus with hydro-aeric distension of the intestines visible on plain radiographs.

Most cases resolve with medical treatment. However, in case of a lack of improvement despite conservative management, an alternative diagnosis should be considered, such as an adhesive small bowel obstruction. We describe the occurrence of both DIOS and mechanical small bowel obstruction due to adhesions in a child with CF and a history of abdominal surgery in the neonatal period.

## Case report

A 9-year-old boy with CF, genotype F508del/R1162X, with a pancreatic insufficiency and a history of meconium ileus leading to bowel resection at birth, was admitted at the emergency department for abdominal pain and gastric fluid vomiting. Abdominal radiographs revealed hydro-aeric levels with stercoral stasis. The abdominal ultrasound did not show any sign of bowel ischaemia. Blood tests was normal apart from hyponatremia at 127 mmol/L (normal value: 135-145mmol/L). Initial management consisted of saline enemas and oral macrogol administration. The hyponatremia was corrected through intravenous fluid therapy. The patient was transferred to a CF reference centre 72 hours after the initial management.

On admission, the clinical examination revealed a tense and bloated abdomen. The bowel sounds were weak and the abdominal palpation was painful. Blood tests were normal. Management consisted in placing a nasogastric tube and the administration of gastrografin enemas, without success. Barium enema showed faecal impaction in the right lower quadrant with small intestinal distension. 48 hours after, due to persistent abdominal pain, bile stained gastric residuals, increase of inflammatory markers and ascites with evidence of small bowel obstruction on ultrasound (Figure 1), surgical intervention by laparotomy was indicated. A significant intestinal dilatation proximal to an ileal stenosis with numerous adhesions and bowel impaction was found. A complete adhesiolysis and a 10 cm necrotic ileal resection were performed. There were no complications in the immediate post-operative period and a residue-free diet was progressively introduced. 72 hours after refeeding, signs of obstruction reappeared. A re-intervention was performed and consisted of a 15 cm resection of intestinal stenosis (due to bowel impaction) and ileostomy. After re-intervention, refeeding was well tolerated. Due to high stoma output and salt loss, electrolyte replacement was necessary, first with parenteral administration and then with enteral feeding. The patient left the hospital after 6 weeks. The ileostomy was closed 3 months after the surgery, following imaging assessment (radiography and barium enema) confirming the recovery of a normal intestinal calibre upstream and good permeability downstream of the ileostomy.

## Discussion

DIOS can occur at any age, but is most common after the age of 15, with a peak in young adults of 20-25 years old (3). The principal differential diagnosis of DIOS is constipation, also common in patients with cystic fibrosis.

The diagnosis is often clinical. Sometimes, an abdominal radiograph may help to show the faecal mass in the bowel lumen with multiple air-fluid levels in the dilated small bowel (1-3). Risk factors include cystic fibrosis genotype with non-functional CFTR-protein (cystic fibrosis transmembrane conductance regulator protein), pancreatic insufficiency, a history of meconium ileus at birth as this could share the same pathophysiology, irregular pancreatic enzyme intake and dehydration or dietary changes (3). After lung transplant, the incidence is also higher and this may be due to a post-operative ileus and use of analgesics (like opioids) (1).

The management is often symptomatic and conservative (91% of episodes of non-

complicated of DIOS are successfully treated) (3). In a case series of 80 patients a surgical treatment was required in less of 3.9% (3). In mild or moderate DIOS, a combination of orally administered laxatives and osmotic laxative enemas are recommended (3). A nasogastric tube may be required to give large volumes of oral laxatives or to decompress the abdomen in cases of complete intestinal obstruction. Prokinetics have been suggested, but there is a lack of evidence to use them in cases of DIOS (3). In rare cases, when oral treatment fails, a gastrografin enema can be used to clear the impacted faecal mass in the terminal ileum (3). This procedure must be performed by an experienced radiologist to minimize the related complications such as intestinal perforation, shock or necrotising enterocolitis (1).

In our case, surgical treatment was required because conservative treatment failed.

DIOS probably worsened a chronic small bowel subocclusion in an abdomen full of adhesions. In this case, the adhesions around the neonatal surgery probably contributed to the concomitant involvement of digestive stenosis. We can also imagine that there were previous incidents of repetitive intussusceptions which may have contributed to acute incident.

If conservative management fails, a diagnosis of mechanical small bowel obstruction due to adhesions must be considered. According to Subhi et al., the risk of surgical intervention in patients with a history of meconium ileus was statistically significant, maybe due to previous laparotomy (5). Surgery for DIOS is rare in the paediatric population and may be necessary if oral treatment fails or if there are complications such as intussusception or volvulus (3-6). In severe cases, a surgical procedure is required with laparotomy and intestinal lavage often without ileostomy (3). In some cases, bowel resection with stoma is required to allow intestinal recovery (3). In all cases, the patient must be referred to a CF centre with a multidisciplinary team. Early recognition and appropriate medical management are necessary to avoid complications (such as intussusception) or surgical treatment (3).

Frequent in acute situation among CF patients and especially in case of digestive problems, hyponatremia may contribute to create a third space which helps to underline the gravity of the situation. Further investigations are required to quickly reach the diagnosis.

There is a lack of research analysing options to prevent DIOS in CF patients (3). It is important to follow these patients in CF centres, to monitor their feeding habits to achieve good hydration status, and to supplement pancreatic insufficient patients with fat-soluble vitamins and pancreatic enzymes. Early detection of signs of constipation and prevention of possible faecal impaction are essential in CF patients.

## Conclusion

This case report highlights that DIOS, a classical gastrointestinal complication in cystic fibrosis, and adhesive small bowel obstruction can occur concurrently, making the diagnosis more difficult. Early recognition and appropriate multidiciplinary medical management are essential to avoid complications. The purpose of this case report was to demonstrate that clinical deterioration despite medical treatment must raise the suspicion of another diagnosis such as an obstruction due to adhesions.

**Conflict of interest statement:** The authors have declared that no conflict of interest exists.

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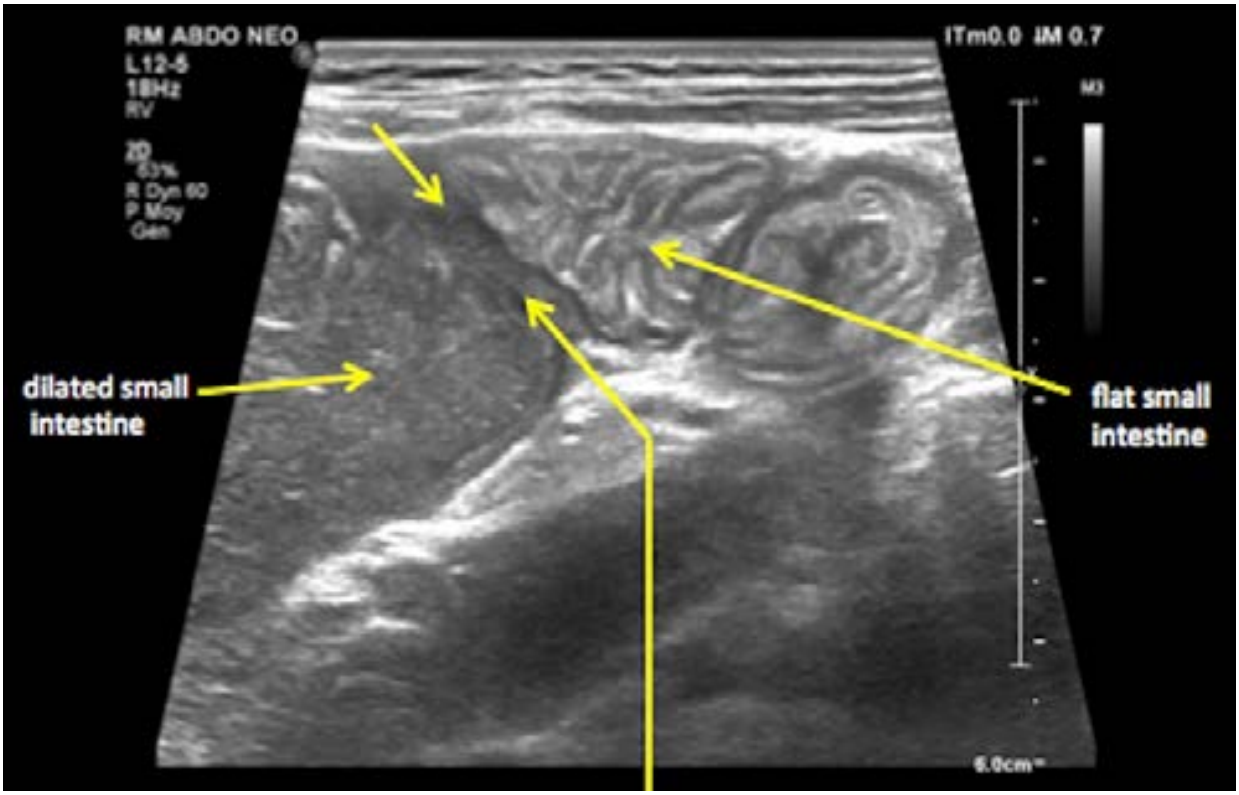
**Figure 1:** *Ultrasound of DIOS described by an impaction of faecal mass with bowel distension complicated by a small bowel obstruction described by a bridle imprint*

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Case Report

# Iron Deficiency and Iron Deficiency Anemia due to cows' milk consumption: a case report

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## Keywords

Iron deficiency, anemia, iron supplementation, cow milk, case report

## Abstract

Iron deficiency is the most frequent micronutrient deficiency among children, affecting two billion people in the world. It can be associated with anemia. Iron deficiency has different etiologies, among them we can find early introduction of cows' milk and late weaning from breastmilk.

We describe a case of severe iron deficiency anemia with early cows' milk introduction as major risk factor for its development.

The aim of this article is to put emphasis on the importance of screening the children at risk of developing iron deficiency and iron deficiency anemia and to make a review of the literature about their diagnosis and treatment.

## Introduction

Iron deficiency (ID) is the most frequent micronutrient deficiency among children (1). It can be associated with anemia. ID has different etiologies including early introduction of cows' milk and late weaning.

We describe a case of severe iron deficiency anemia (IDA) in which early cows' milk introduction was one of the risk factors leading to the development of anemia.

## Case

We report the case of a 15-month-old Syrian boy presenting with a severe isolated microcytic anemia (hemoglobin (Hb) 6.1g/dl (10.5-13.5g/dl), mean corpuscular volume (MCV) 49.7fL (70-86fL)) discovered during a pre-operative work-up.

After 11 months of exclusive breast feeding, the child started to drink cows' milk mainly due to difficulties in starting the alimentary diversification. He was also suffering from pica, eating first his mother's hair and then cotton fiber, paper and cardboard. There was no failure to thrive with a weight of 11.9 kg (75th percentile) and a height of 80 cm (90th percentile).

The initial biological work-up showed a severe iron deficiency (serum iron (SI) 13µg/dl (50-120µg/dl), transferrin saturation (TSAT) 3% (20-55%), serum ferritin (SF) 3µg/l (30-400µg/l)). There was no sign of lead or zinc intoxication and the hemoglobin electrophoresis was normal.

A first attempt of oral iron supplementation was initiated with a therapeutic dosage of polysaccharide-iron complex (Ferricure®, 4mg/kg/day) without response after one month of treatment (Hb 6g/dl, MCV 50.2fL, SI 21µg/dl, SF 3µg/l). Probably this lack of response was due to poor compliance.

The child was then hospitalized to complete the work-up, excluding parasitic infection, gastrointestinal blood loss, celiac disease and folic acid deficiency. Finally, he received a parenteral therapy with ferric carboxymaltose (Injectafer®, 10mg/kg) with pursuit of the oral supplementation.

One week after the injection, the eating disorder improved with biological improvement of the IDA (Hb 7.5g/dl, Reticulocytes (Rc) 222.500/mm³ (35-100 10³/mm³), SI 46µg/dl, SF 39µg/l). One month later, blood results were still improving (Hb 9.8g/dl, MCV 63.8fL, SI 86µg/dl, SF 27µg/l).

## Discussion

Iron deficiency is defined by the World Health Organization's (WHO) as a serum ferritin under 12 µg/l (1). It affects more than two billion people worldwide, its prevalence is evaluated to reach 12% at 12 months of life and up to 15.2% of the toddlers in the United States (1,2). Iron deficiency anemia, where anemia is defined by the WHO as a hemoglobin concentration inferior to 11 g/dl for children aged 12-35 months, has a prevalence of 2-4% in Europe (2).

ID can be due to insufficient iron intake or absorption, excessive iron requirement or abnormal loss (3). Its development can be attributed to economic, dietary and neonatal risk factors (table 1) (2,4). Our case illustrates the importance of investigating the dietary history in the prevention and assessment of ID in infants and young children. Indeed, during the first months of life, the major sources of iron are breastmilk, cows' milk or formula feeds : human and cows' milk containing a similar amount of iron with a lower bioavailability for cows' milk (10% versus 50%) and iron-fortified formula having a better bioavailability than non-fortified ones (2). Vegetarian and vegan diets also increase the risk of iron, zinc, calcium, omega-3 polyunsaturated fatty acids, vitamins B12 and D deficiencies if growing children do not have an adequate meal plan or dietary supplements (5).

**Table 1 :** Risk factors associated with development of ID and IDA (adapted from Ferrara et al. (2) and Mc Carthy et al. (4))

- Dietary history (2)
  - Low family income
  - Early introduction or excessive consumption of cows' milk
  - Delayed weaning (after 6 months)
  - Low intake of iron-fortified products
  - Overweight
  - Vegan/vegetarian diet (5)
- Antenatal and prenatal history (4)
  - Premature birth (<37 weeks of gestation)
  - Low-birth-weight (LBW) (<2700g)
  - Pregnancy complication (diabetes and fetal growth retardation)
  - Maternal lifestyle factors (obesity, smoking)
- Medications (e.g. proton pump inhibitors) (6)

The prenatal and neonatal history must also be taken into account because some factors may have a negative impact on the infant iron stores as preterm and low birth weight infants are at higher risk of ID because of the higher post-natal iron requirement needed for the rapid growth and the early onset of erythropoiesis (4).

ID and IDA may be associated with non-hematological complications that are important to know because some might not completely recover after supplementation. Indeed, many studies have highlighted the possible causal relation between ID, IDA and delays in cognitive, behavioral and motor development, insisting on the necessity of preventing ID and IDA in young children. The age of onset, severity and duration of the ID as well as the association to anemia may have an impact on the child's development and on the supplementation's efficacy. Although, more evidence is needed to evaluate the efficacy of iron supplementation to correct those symptoms (2,6).

It's also believed that ID increases the infectious risk and can be associated with growth retardation and weight impairment (7).

IDA can also be associated to pica, which is defined as the compulsive ingestion of non-nutritive materials such as plaster, soil, ice, paper, cinder… for more than 1 month. The link between ID and pica needs to be further investigated. Some authors suggest that pica is a consequence of ID and others think that pica is its cause. However, it can be considered as an alert for possible ID and can be resolved after a few days of iron supplementation (8).

Different approaches have been proposed to prevent ID. In a position paper, the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends delayed umbilical cord clamping, use of iron fortified formulas (iron concentration 4-8mg/l) and of iron supplementation (1-2mg/kg/day between 2000-2500g and 2-3mg/kg/day under 2000g) up to 6 months of life. From the age of six months, they recommend sufficient intake of iron fortified complementary food including meat, iron-fortified follow-on formulas and iron-fortified foods (e.g. cereals), and the eviction of cows' milk as the only milk drink up to 12 months (with maximal intake of 500ml/day for toddlers). In their opinion, there is no benefit in using iron supplementation for pregnant women or in exclusively breast-fed normal birth weight children under six months of life (7).

The Swiss Pediatric Oncology Group proposes to evaluate the iron load for all children presenting signs and symptoms of ID or IDA (6) whereas the American Academy of Pediatrics recommends a systematic screening of anemia at 12 months or a selective screening at any age when risk factors are identified, including risk of inadequate iron intake based on dietary history (1).

Almost all recommendations suggest the use of serum ferritin level for the diagnosis of ID (1), taking into account that inflammation could increase SF (9). Transferrin saturation can be used as a complementary testing with a threshold under 20% (9).

The treatment of IDA should include the treatment of the underlying cause (3). Oral therapy is preferred over intravenously administration. The dosage of elemental iron recommended for children range from 3 to 6mg/kg/day depending on the active iron compounds Fe2+/ Fe3+ (3,6,10). Different formulation of ferrous (Fe2+) and ferric iron (Fe3+) are available. In Belgium, the only formulation commercially available for young children is a solution of polysaccharide-iron complex (Fe3+) which has a lower absorption than ferrous sulfate or gluconate (Fe2+). In table 2, we propose a preparation based on ferrous sulfate tablets that can be used to prepare magistral solution.

The therapy can be considered as effective when there is an elevation of the hemoglobin of 1g/dl after one month of treatment (3). It should be taken sober because its absorption can be reduced by some food components (e.g. phytates, calcium, cows' milk). In addition, medications inhibiting gastric acid secretion (e.g. proton pump inhibitors) will diminish iron absorption. On the other hand, some food components such as vitamin C can enhance iron absorption (2,6). The treatment should be maintained for 3-6 months to restore the iron stores. In case of non-response, poor compliance or absorption of the oral treatment or other causes of iron deficiency should be evaluated. Poor adherence can be increased by the gastro-intestinal side effects (such as diarrhea, constipation, abdominal discomfort, dyspepsia, and vomiting) (3,10). In those cases of poor response or compliance to polysaccharide-iron complex, a change of formulation could be tried.

**Table 2 :** Oral iron suspension (Fe 18,7 mg/ml / FeSO4 57,7 mg/ml))

Qualitative and quantitative composition

- Tardyferon pills : Fe2+ 80mg /Fe SO4 dehydrated 247,25mg =7 pills
- Citric acid monohydrate ..... 0,2462 g
- Simple syrup ..... 24,410 g
- Raspberry aroma ..... 0,45 ml
- Water for injection ..... ad 30 ml

A parenteral therapy could be considered in case of poor tolerance, inefficacy or poor absorption of oral iron or need for rapid hemoglobin correction (3,10). Its advantages are that it has less gastro-intestinal side-effects, a better adherence, and the possibility of administrating a greater amount of iron in a shorter time (9). The immediate side-effects include headache, vomiting, abdominal pain, flushing, myalgia, pruritus, and hypophosphatemia (10). The major risk of parenteral therapies is anaphylactic reaction whose severity is variable and which is mostly encountered with the high-molecular-weight iron dextran (3,9). It can be reduced by slow injection and close monitoring. The use of antihistaminic premedication is still under debate but antianaphylaxis medication should be available and ready to use without delay during the infusion (6,10).

The increase of the reticulocytes after 5-10 days is an early sign of response to parenteral therapy (6).

Transfusion should be considered according to the hemoglobin level and the clinical state of the patient. There isn't any standard recommendation regarding its indication in case of IDA (3).

There is no universal recommendation about the monitoring after iron supplementation, but some authors recommend to follow the total blood count every three month during one year (3).

## Conclusion

Iron deficiency anemia can be associated with complications such as delays in cognitive and behavioral development, growth retardation and pica. Thus, it is of great importance to prevent it and to detect the children at potential risk, more especially by taking the nutritional history into account. Indeed, early introduction or excessive consumption of cows' milk associated with late weaning or delayed food diversification are risk factors for the development of ID and IDA.

The authors have no conflict of interest to declare.

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Case Report

# Umbilical venous catheterization: a fatal complication in a term neonate

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## Keywords

Neonatal intensive care; complication; catheter malposition; liver failure; liver injury

## Abstract

This case report describes a newborn with pulmonary hypertension who developed liver failure and multi organ failure due to extravasation through a malpositioned umbilical venous catheter. Although placement of an umbilical venous catheter is a commonly used technique, correct positioning is difficult, particularly since x-ray confirmation is often unreliable. Acceptance in suboptimal position, not at the junction of the inferior vena cava and the right atrium, can lead to serious morbidity and mortality. With this case report we want to raise awareness of the risk of complications following improper tip placement of an UVC and promote the use of ultrasound in confirming the catheter position.

## Introduction

Insertion of an umbilical venous catheter (UVC) is a commonly used procedure to establish central venous access in neonates. It is widely used as a quick intravenous access to be able to administrate intravenous fluids such as parenteral nutrition, medication and transfusions. However, caution is warranted as complications can occur, especially if placed in suboptimal position or if kept into place longer than a period of 7-14 days (1, 2). Catheter-related infection, thromboembolic events and complications due to malpositioning of the UVC such as cardiac arrhythmias and extravasation in the hepatic parenchyma are the most common complications. Complications related to the liver parenchyma are rare, but have a high rate of morbidity and mortality (3, 4).

The aim of this case report is to raise awareness of the risk of complications following improper tip placement of an UVC. Furthermore, we discuss how these complications can be prevented.

## Case Report

A term neonate, born at 38 weeks and 4 days gestational age after a repeat caesarean section with a birthweight of 3445 grams, presented with respiratory distress within fifteen minutes postpartum. Initially, nasal CPAP was started and intravascular access was obtained through UVC and umbilical arterial catheter (UAC) placement. X-ray confirmed a correct position of the UAC and showed the tip of the UVC on the right side of the T11-12 vertebra on anteroposterior X-ray (figure 1). No profile X-ray was made. Although the tip position of the UVC was not correct, it was not repositioned. Because of respiratory deterioration, the neonate was intubated at day one of life and mechanically ventilated from then on. Hypertonic parenteral nutrition was started. Persistent pulmonary hypertension of the neonate (PPHN) was diagnosed by echocardiography. Inhaled NO and intravenous levosimendan were started as treatment. High doses of intravenous noradrenaline and dopamine were needed to treat severe hypotension. All intravenous medication was administered through the UVC. Although the initial clinical improvement and resolution of the PPHN on echocardiography, his clinical condition deteriorated rapidly on day 3 of life with development of cardiorespiratory failure. On clinical examination at that time hepatomegaly and abdominal distension were noted. An abdominal ultrasound showed extensive multifocal lesions in the left liver lobe, suggestive of necrotic or haemorrhagic lesions, as well as free fluid in the abdominal cavity, suggestive of extravasation (figure 2). The UVC was visualised in the vena umbilicalis. The tip was suspected to be in the portal vein, although not clearly visualised on ultrasound. The UVC was removed after these findings and was replaced by a peripherally-inserted central catheter. Despite removal of the UVC, there was a rapid evolution to fulminant hepatic failure and secondary multiple organ failure with the need for haemodialysis. A cranial ultrasound showed an extensive subdural haemorrhage in the left frontotemporal lobe as well as an intraventricular haemorrhage causing midline shift and cerebral oedema. The haemorrhage was caused by extensive coagulopathy reflected biochemically by abnormal APTT and PT values as well as clinically by prolonged bleeding after procedures. After careful consideration of the severe clinical condition with poor prognosis, taking into account the opinion of the parents, the decision was made to withhold further intensive care. The patient died at day five postpartum. At post-mortem examination, there was diffuse ischaemic liver necrosis of more than 50 percent of the parenchyma, in both the left and right liver lobes (figure 3). Necrosis of the vena umbilicalis and ductus venosus was observed and there was diffuse intestinal transmural ischaemic necrosis with peritonitis. The kidneys showed signs of acute tubular necrosis. Lung pathology was consistent with congenital alveolar dysplasia, explaining the initial presentation of respiratory distress and PPHN. Although often a fatal condition, the congenital alveolar dysplasia did not explain the rapid clinical deterioration with multi organ failure as seen in our patient.

## Discussion

Umbilical venous catheter placement is one of the most frequently used methods for obtaining an urgent venous access in neonates since it has been first described in 1947. The correct position of an UVC is at the junction of the inferior vena cava (IVC) and the right atrium, but is not always easy to achieve. Repeated manipulations should be avoided keeping in mind the clinical condition and

**Figure 1 :** *Anteroposterior X-ray showing the position of the umbilical arterial catheter and the umbilical venous catheter, with the tip of the umbilical venous catheter on the right side of the T11-12 vertebra.*

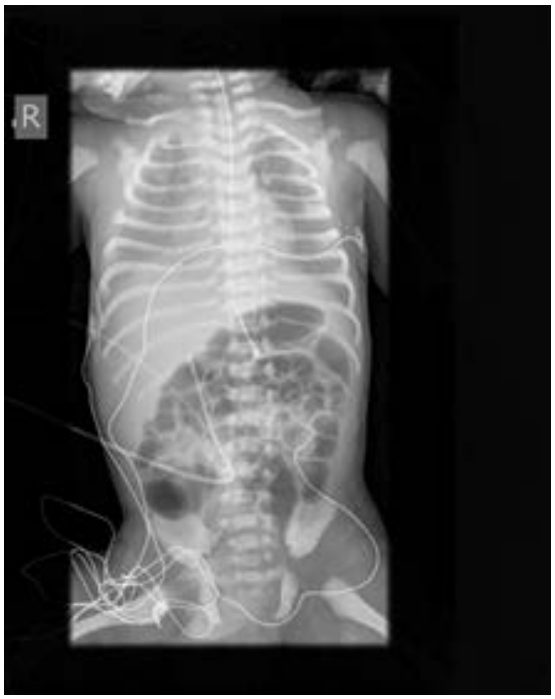



**Figure 2 :** *Abdominal ultrasound showing heterogenous liver parenchyma, with wide spread necrotic and haemorrhagic zones (Blue arrow).*

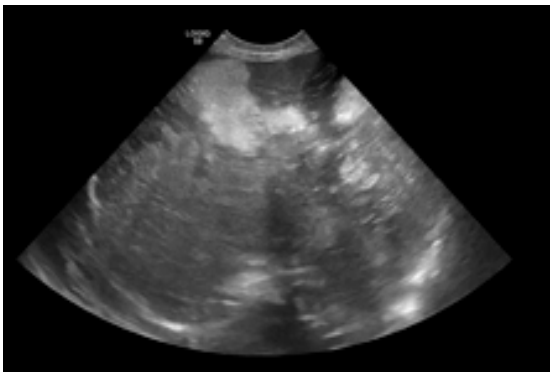
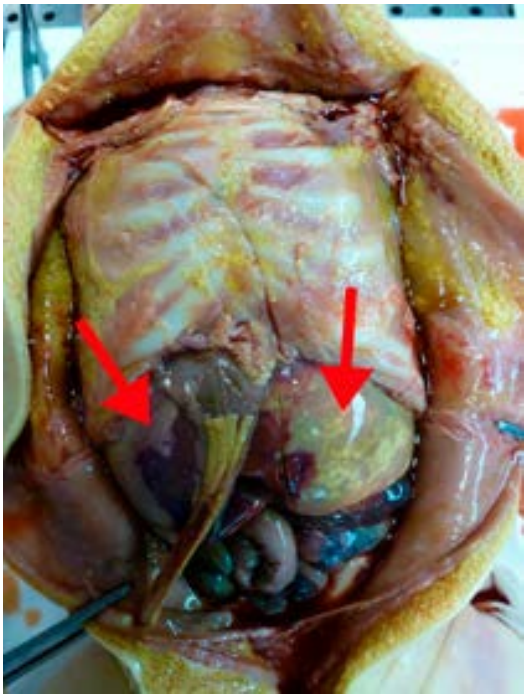


**Figure 3 :** *Anteroposterior X-ray showing the position of the umbilical arterial catheter and the umbilical venous catheter, with the tip of the umbilical venous catheter on the right side of the T11-12 vertebra.*



stability of the patient. In such a case a suboptimal position, i.e. downstream of the ductus venosus in the umbilical venous, is sometimes accepted (5). If so, the UVC needs to be handled as a peripheral catheter and no hypertonic parenteral nutrition nor hyperosmolar drugs should be administered through it.

Complications after UVC placement are not rare. Blood stream infections are the most frequently reported serious adverse events, although the reported incidence varies from 3 to 36% (6). Portal venous thrombosis (PVT) is slightly less common with a reported incidence between 2 and 43%, although probably underreported because of lack of symptoms (7). PVT should not be ignored because of the possible evolution to portal hypertension. Therapy is usually conservative since more than half of the cases show spontaneous resolution, although there is a tendency to treat large obstructive thrombi with low molecular weight heparin (8, 9). Furthermore as a complication of catheters with an atrial position, cardiac arrhythmias have been described and most often show resolution after repositioning of the UVC in the correct position (4, 6).

With this case report, we focus on the hepatic parenchyma complications related to UVC placement. Hepatic complications occur less often than other complications, with a reported incidence of 0.8%. (10). However, they are associated with higher morbidity and mortality than other complications. Furthermore there is a strong association between malpositioning of the catheter in the liver and subsequent extravasation of hypertonic fluids (3-5).

If hepatic injury occurs, abdominal distension or clinical deterioration and hypotension may arise (10). The diagnosis is made by abdominal ultrasound, showing heterogeneously echogenic intrahepatic lesions or cyst-like well-margined liver lesions with hyperechoic rims (10, 11). Fortunately in most cases, after removal of the umbilical catheter, follow-up ultrasounds show resolution of the hepatic lesions. However if persistent, these lesions can lead to portal hypertension, liver lobe atrophy and development of hepatic cavernoma (12). Some neonates even need laparotomy in case of perforation of the hepatic vessels and mortality due to liver failure and bleeding has been described (5, 10).

Considering the possible severe complications, correct tip positioning of the UVC is paramount. To assess the position of the UVC, antero-posterior chest-abdominal radiograph is the most widely used technique. There are two ways of assessing the correct position on the radiograph. Firstly, the vertebral body method in which the position of the tip relative to the vertebral bodies is assessed. Optimal positioning would be on T8-T9. Secondly, the cardiac silhouette method in which the position of the tip relative to the supposedly cavo-atrial junction is assessed. Optimal positioning would be at the junction of the IVC with the right atrium (13). However, errors do occur when using chest-abdominal radiograph to determine the UVC position. Recent studies have shown the superiority of ultrasound to X-ray in detecting the actual catheter position. A study by Michel et al. showed a sensitivity of 93% and specificity of 95% concerning correct tip positioning when using ultrasound, compared to a sensitivity of 66% and specificity of 63% when using antero-posterior radiography. A more recent study of Grizelj et al. supports these data (10, 14). Besides being more reliable, it is also bedside available which allows frequent control of catheter position since even after initial correct placement, catheter tips seem to migrate in 50 to 90% of the cases (13, 15). Additionally, the use of ultrasound leads to less X-ray exposure and fewer manipulations of the catheter (3). Despite these advantages, ultrasound still is not widely used to analyse the location of the UVC tip. It is of great interest to train

neonatologists to use this technique seeing the great advantage it holds in correct positioning of the UVC and thereby reducing catheter related complications. (16)

Our case report illustrates severe morbidity with fatal outcome following acceptance of suboptimal position of an UVC. The placement of the UVC in the hepatic circulation and infusion of hypertonic and inotropic fluids caused extravasation in the hepatic parenchyma with extensive caustic and ischaemic necrosis as a result. This resulted in fulminant liver failure, evolving to multi organ failure with coagulopathy and subsequently intracranial haemorrhage.

This case report reminds us that umbilical venous catheterization cannot be considered harmless. It should be correctly placed, catheter tip position should be checked on a regular basis and the use of an UVC should be limited in time to a maximum of 7 to 14 days. Although not free of complications either, percutaneous central venous catheters are recommended whenever prolonged infusion is anticipated.

## Conclusion

We presented a case of severe morbidity with fatal outcome after misplacement of an UVC. Awareness should be raised of the potentially severe complications when keeping an UVC in aberrant position. Verifying the tip position of the UVC by X-ray may be unreliable. Therefore, the use of ultrasound to determine the UVC position should be used on a regular basis, especially when there is doubt about the correct position on X-ray.

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Case Report

# Flexor tenosynovitis in a 6-month-old infant after penetrating trauma: case report

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## Keywords

Septic flexor tenosynovitis, pediatric, infection

## Abstract

We present the case of a 6-month-old infant with flexor tenosynovitis of the ring finger after penetration of a splinter in the distal interphalangeal fold. Thorough irrigation and debridement were necessary after ineffective conservative antibiotic treatment of 48 hours. This is the youngest case ever described in literature. Children present differently from adults in terms of route of inoculation and causative pathogens. The Kanavel signs and inflammatory blood markers have a lower sensitivity than in adults. A high index of suspicion is needed because of the poor clinical and biochemical reliability in infants.

## Introduction

Septic flexor tenosynovitis is an infection of the flexor tendon sheath which can lead to tissue necrosis, stiffness and amputation. Dr Allen Kanavel, a Chicago surgeon, treated this kind of infection before the existence of antibiotics. His extensive research of potential spaces of the hand is still the mainstay in the treatment of hand infections (1, 2). The Kanavel signs are a semiflexed position of the finger, fusiform swelling, excessive tenderness over the flexor tendon sheath and pain on passively extending the finger. Because of the low incidence, there are no studies validating the sensitivity or specificity of these signs, especially not in the pediatric population. There is discussion, even in adults, which signs are the most useful (3, 4). This study discusses the current literature of septic flexor tenosynovitis in children on the basis of a case report of a 6-month old infant and highlights the differences with the adult population.

## Case report

A 6-month-old infant presented at the emergency department with a two-day history of a painful swollen ring finger on the right hand. There was no relevant past medical history. Her father recently made a wooden cradle for his daughter, of which a sharp splinter entered her finger. She became febrile with peaks of temperature of 38.6°C. The general practitioner removed the visual part of the splinter and started empirical oral antibiotic treatment with 250 mg amoxicillin/clavulanic acid three times a day. Examination by the pediatrician in the emergency department two days later revealed a fusiform swelling of the fourth finger, which was held in a slight flexion. There was also an extension of erythema to the palmar space. A possible entry point was noticed in the distal interphalangeal fold (Fig. 1). Pain was observed on palpation and with passive finger extension. The white blood cell (WBC) count was 14,7 x10*9/L (normal: 6-13,0 x 10*9/L) and C-reactive protein (CRP) level was 54.1 mg/dL (normal: 0-1 mg/dL). Plain radiographs (Fig.2A) and an ultrasound showed no remaining foreign body but the ultrasound was positive for synovial thickening and mild fluid effusion in the tendon sheath (Fig 2B). She was admitted to the pediatric department after administration of intravenous (IV) amoxicillin/clavulanic acid with continuation every 8 hours. Because there was no clinical improvement after two administrations, the hand surgeon proceeded to perform an irrigation and debridement. Sheath irrigation was used with distal opening of the sheath and proximal syringe irrigation. Symptoms disappeared after 24 hours and she was discharged home with peroral amoxicillin/clavulanic acid therapy. A follow-up examination one week later showed no remaining signs of infection. Antibiotic treatment was stopped after a total treatment of ten days. Hand function turned back to normal and there were no problems at six weeks follow-up.

## Discussion

Flexor tenosynovitis is a well-known medical condition requiring prompt surgical and antibiotic treatment in adults (1). Although clinical decision making has been copied to children, it is less reliable due to the lack of cooperation and variable presentations (5, 6). The 6-month-old infant described in this case report is so far the youngest case described in literature. Brusalis et al. reported that of thirty-two patients with flexor tenosynovitis, with an average age of 9.5 years, 25% had no antecedent injury (6). Hematogenous flexor tenosynovitis is rare in adults and when this occurs disseminated gonococcal infections are often considered (1). This is however quite rare in the pediatric population. An alternative route of introduction in children is digital sucking or nail biting. Predominant mouth flora, Eikenella species, has often been detected in upper-extremity infections in children (7).

Staphylococcus species are the most frequently cultured organisms accounting for 50% to 80% of cases in both adult and pediatric hand infections (7). In children, methicillin-resistant Staphylococcus aureus (MRSA) has been documented in 38% of cases (6). Comorbidities such as diabetes, vascular disease or smoking are less frequent in children, but polymicrobial infections still account for 28% of cases (6). Possible explanations for high percentages of resistant and polymicrobial infections could be the differences between the adult and the maturing immune system or differences in hand hygiene between adults and children (7). These results are based on a study from the United States of America, but global variations in skin colonization methods should be accounted for.

The four cardinal signs by Kanavel for flexor tenosynovitis are a useful diagnostic tool but have never been prospectively validated in children (2, 4, 8). Pang et al. found that uniform, symmetric swelling has a prevalence of 97% in adults (3). In our opinion, this is the only objective sign to use in very young children as tendon sheath tenderness, partial flexion at rest and pain with passive extension are more difficult to objectivate and match with flexor tenosynovitis in an infant. An infant's hand resting position is always in a semiflexed posture, so isolated partial finger flexion is difficult to determine.

**Figure 1 :** *Dorsal (left) and palmar (right) photo of the right hand with fusiform swelling of digit 4 with erythema extending to the palmar space and puncture wound in the distal interphalangeal fold.*

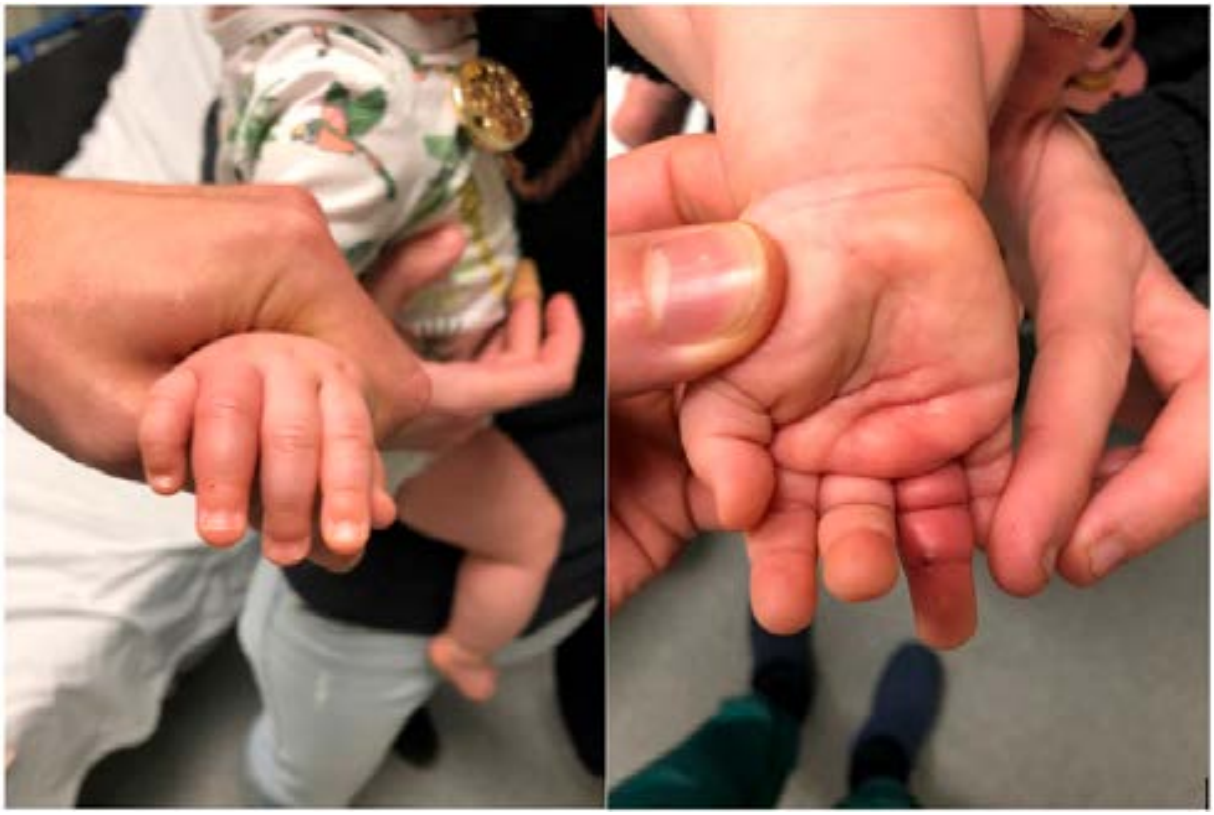
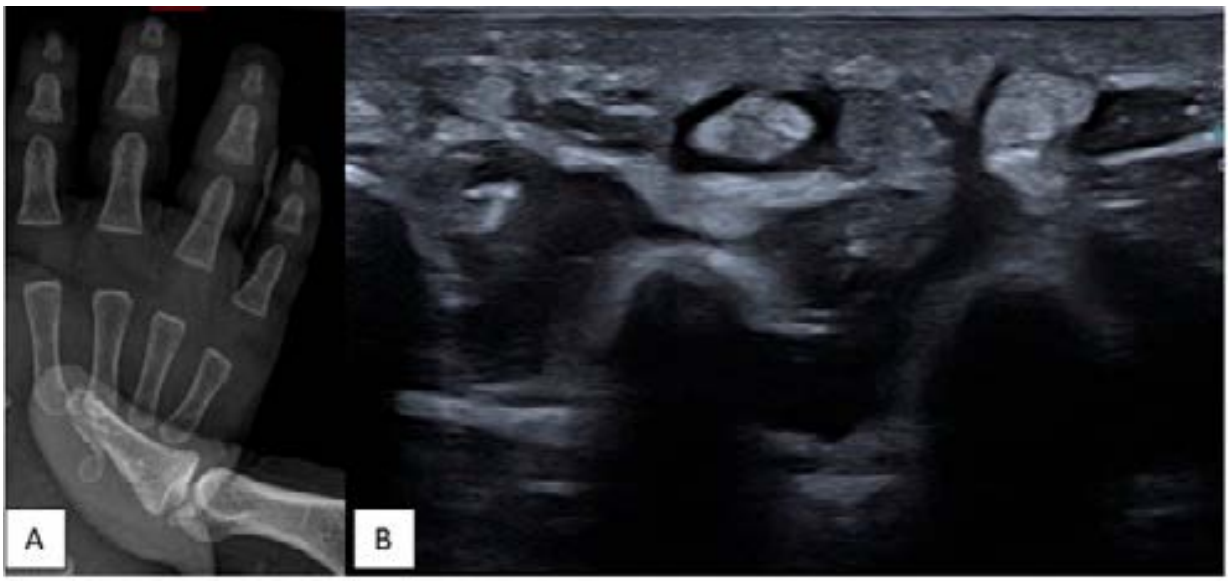


**Figure 2 :** *A: Plain X-ray of the right hand showing no remaining foreign body. B: Ultrasound showing circumferential hypoechogenicity around a thickened flexor tendon.*



Because of these reasons, the Kanavel signs are less reliable in a pediatric population. Literature shows that for children three signs are apparent in 63% of cases, but reports have been made of children with no positive signs, indicating a great variation in the pediatric population (5, 6). In a case series by Brusalis, children were febrile (> 38°C) in 22% of cases, had elevated CRP in 5%, elevated erythrocyte sedimentation rate (ESR) in 28% and elevated WBC count in 44% (6). Sensitivity of inflammatory blood markers in adults is 76% for CRP, 41% for ESR and 39% for WBC count (9). The difference in sensitivity for CRP level between children and adults is remarkable and consequently we advise ordering ESR as well.

Differential diagnosis must include other infections such as felon, paronychia and herpetic whitlow. These can easily be ruled out based on clinical presentation around the nail or in the finger pulp. Diffuse edema and pain not restricted to only one digit are signs of cellulitis with or without deep space infection (1). Non-infectious etiology (dactylitis) should be accounted for if no entry point is visible. Ultrasound is safe and fast way of identifying tenosynovitis in emergency settings. It can show the thickening of tendon fibers and circumferential areas of hypoechogenicity representing fluid effusion in the tendon sheath (10). In our case, it was important to compare these results with the contralateral or neighboring digits. Septic arthritis is typically caused by a dorsal penetrating wound instead of a volar puncture.

In conclusion, we would like to emphasize the importance of other clinical signs for flexor tenosynovitis in children such as erythema, skin scaling or dryness and the presence of a puncture wound, rather than focusing solely on the Kanavel signs, on account of the poor reliability and variation in the pediatric population. It is important not to dismiss the diagnosis of flexor tenosynovitis because some Kanavel signs are lacking. Empirical broad-spectrum antibiotic therapy with for example amoxicillin/clavulanic acid has to be started immediately and surgical treatment without delay is essential in suspect cases.

The authors have no conflict of interest to declare.

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# The management and outcomes of neuroblastoma in South African children

PhD thesis presented on 5 January 2021 at Stellenbosch University, Faculty of Medicine and Health Sciences, Cape Town, South Africa

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## Keywords

Neuroblastoma, South Africa, middle-income country, limited resources, adapted management protocol

## Introduction

After brain tumours, neuroblastoma is the most diagnosed childhood solid tumour in high-income countries (1). Yet the incidence of this metabolically active sympathetic system malignancy has not accurately been described in low- and middle-income countries (2). One reason is the heterogeneous clinical picture and spectrum of patho-physiology that lends itself to misdiagnosis and underdiagnosis (3,4). This contributes to children with neuroblastoma often presenting in advanced stages of the disease with poor outcomes (2). Other contributing factors are the limited treatment modalities, and poorly understood biology of neuroblastoma in children living in low- and middle-income countries (2,3,4).

In the South African context national research into the epidemiological and clinical characteristics as well as management outcomes have not been conducted. Paired with the initiative of the South African Children's Cancer Study Group to develop prospective cancer-based protocols, we investigated neuroblastoma in South Africa with the aim to improve overall survival.

Our retrospective study showed that South Africa has a higher-than-average number of patients with high-risk (HR) tumours (75.6%), mainly because of advanced disease (70%) and a 54% *MYCN*-amplification of tumours (5). These findings were higher than high-income countries (HIC), but comparable to other low- and middle-income countries (LMICs) such as India and Brazil (4,6). Belgium, part of the SIOPEN (International Society of Paediatric Oncology European Neuroblastoma) group, about 53% of neuroblastoma (NB) tumours are stratified as HR, with 20% *MYCN*-amplification (7). Between 2000 and 2016 the incidence for neuroblastoma in South Africa was estimated to be 1.74-2.6 cases/million children (8). This is much lower than the 10.4 cases per million children reported in HICs and the 12.6 cases/ million children in Belgium (9). Very low risk disease had a 2-year overall survival (OS) of 94.1%, low risk (LR) disease 81.6%, intermediate risk (IR) disease 66.7% and HR disease 27.6% ($p<0.001$, 95% CI) (5). This contrasts to the higher five-year OS of 84.6% observed for all risk stratifications, and a two-year OS of 70% for high-risk disease for Belgian patients (10). We hypothesised that the poorer outcomes in the IR cohort was due to inclusion of patients with HR disease in this cohort. A limited number of tumours were tested for *MYCN* (38.4%) and an inability to determine neuroblastoma related genetic characteristics made risk stratification more difficult.

In the limited cohort of patients with LR disease (n = 30; 7.7%), we concluded that there was no prognostic advantage to high intensity chemotherapy. Therefore, we recommended a surgical approach in LR disease with chemotherapy in specific indications (11). In IR disease a doxorubicin-based chemotherapy regimen was recommended, with surgery and radiotherapy according to the degree of surgical tumour resection (11). During the study evaluating induction chemotherapy for HR disease, the OPEC/OJEC (carboplatin, cisplatin, etoposide, cyclophosphamide and vincristine) regimen proved the most advantages with regards to toxicity and metastatic remission rates (12). In the absence of autologous stem cell transplants, both surgery and radiotherapy had prognostic significance during management (11). Patients with HR disease who could be operated with a complete resection of 90% or incomplete resection of between 50% to 90% had an improved five-year OS of 32.1% versus 5.9% without surgery ($p<0.001$) (11). Patients who had been irradiated without surgery had a marginally better five-year OS of 12.5% as opposed to 5.4% ($p<0.001$) (11).

Our research confirmed the value of non-specific tumour marker lactate dehydrogenase (LDH) and ferritin in the risk stratification of neuroblastoma and predicting outcomes such as metastatic complete remission (mCR) rate and OS (13). Our study reproduced the prognostic cut-point values recommendations of 750 U/L for LDH and 120ng/dl for ferritin proposed by the International Society for Paediatric Oncology's Committee for Developing Countries (SIOP-PODC) (2,13). Ferritin proved to have predictive value, comparable to modified Curie scores, in determining mCR (13). LDH was comparable to modified Curie scores when predicting 2-yr OS. Age at diagnosis remained a significant prognostic factor, as recommended in HICs, even with a delayed age at diagnosis in LMICs (14).

Our findings could serve as a roadmap for other low- and middle-income countries to develop their own resource-based neuroblastoma management initiative. In South Africa, with our findings, policy makers and medical systems can justify initiatives to optimise resources in the country and encourage multi-disciplinary collaborations to ensure that patients diagnosed with neuroblastoma have access to all treatment options. With the implementation of a national neuroblastoma protocol, South Africa continues the target of decreasing the mortality of childhood malignancies according to the World Health Organisation's 2030 goals and supports the SIOP-PODC motto of "every child deserves a chance".

The thesis consisted of nine chapters that have been published as individual articles.

***"The management of neuroblastoma in limited-resource settings" (15)***

Neuroblastoma is the most common solid tumour in HICs, but in LMICs, limited knowledge is available about NB beyond data published in abstracts and reports by single institutions. The last report on NB in South Africa was published by Hesseling et al in the 1990s (16). From these few reports, patients in LMICs present at a later mean age at diagnosis, more advanced disease and with more high-risk prognostic indicators. The resource-poor settings limit the scope of management, resulting in treatment approaches not being standardised. This narrative review provided an extensive overview of the regional approaches of LMICs towards NB, summarised the presenting symptoms, disease characteristics at diagnosis and the prognostic factors. Due to the non-standardised reporting of outcomes between LMICs and HICs the comparison was not feasible, and an overview of reported results was analysed. Finally, the review reflected on the barriers to the implementation of evidence-based treatment protocols and socioeconomic variables that influenced the diagnosis, management and follow-up of patients with NB.

***"Reporting incidences of neuroblastoma in various resource settings" (8)***

NB contributes to approximately 7% of all childhood malignancies that are diagnosed yearly worldwide. For various reasons accurate incidences of paediatric malignancies in sub-Saharan countries, have not been documented including inaccurate recording in tumour registries. In South Africa, underreporting of up to 50% has been reported compared to HIC statistics. The heterogeneous spectrum of NB disease poses a diagnostic challenge and the subsequent inclusion into tumour registries in limited-resourced settings. This study evaluated the context of NB in LMIC if HIC reporting standards were applied and the expected incidences were calculated. South Africa has two tumour registries that include childhood malignancies. We evaluated the NB data of patients diagnosed between 2000 and 2016, which included clinical file data from ten paediatric oncology units (POUs) and NB patients in South Africa who were included in the two registries. The same methodology was applied for the age at diagnosis and sex in patients diagnosed with NB.

***"Overall survival for neuroblastoma in South Africa between 2000 and 2014" (5)***

For the development of a standardised prospective national management protocol for NB in South Africa, it was necessary to evaluate the local OS against international data to formulate management recommendations. The hypothesis was that the various NB treatment strategies had varying outcomes in South Africa. A national multicentre chart review of newly diagnosed NB patients between 2000 and 2014 in nine POUs of South Africa was done. The data that were sourced retrospectively were the known risk factors of NB including age, stage, non-specific and specific tumour markers, pathology and biological disease characteristics. Numerous treatment modalities that were applied during management were evaluated. The outcomes, mCR, EFS (event free survival) and OS were determined for all patients registered with the SACTR (South African Children's Tumour Registry) during the 14-year period. This information was used to evaluate the various treatment protocols used in South Africa and to facilitate the development of the prospective management protocol aligned with both international guidelines and local resources.

***"Age at diagnosis as a prognostic factor in South African children with neuroblastoma" (14)***

Age at diagnosis has consistently remained an important prognostic factor in determining treatment risk classifications of NB despite the advances in treatment options. LMICs had reported older median ages at diagnosis compared to HICs (*Figure 1*). During the retrospective study the same delay in the age at diagnosis was reported in South Africa. Internationally, children under the age of 12 months have a favourable prognosis regardless of tumour biology and patients older than five years have poor outcomes. The research hypothesis is that the delayed age of presentation in South Africa would have prognostic implications for the risk stratification and therefore for the management. In keeping with international findings, the study team determined that the 18-month cut-point value was of prognostic significance in South African children diagnosed with NB as well.

***"The correlation of tumour markers and 123I-mIBG-studies in South African children with neuroblastoma" (13)***

An mIBG scan is part of the gold standard in the diagnosis and evaluation of NB treatment response, but is not freely available in LMICs. Furthermore, the production of radioisotopes is not reliable. In NB, it is important to administer chemotherapy at the indicated intervals and therefore it is important to be able to perform tests at the correct point of evaluation. Blood-based tests are part of the standard of care, are cheaper and need limited technology to perform. Non-specific tumour markers lactate dehydrogenase (LDH) and ferritin have extensively been validated in the prediction of treatment response and OS. The *MYCN*-gene is a NB specific tumour marker and has been validated in predicting treatment response and outcomes as well. *MYCN*-amplification can be determined on both tissue from the NB tumour as well as the NB-cells in bone marrow aspirates yet requires lab-based technology that is often centralised in countries and more expensive than LDH and ferritin. In our study both LDH and ferritin predicted two-year OS, where the modified Curie scores did not. We concluded that LDH and ferritin may serve as surrogate tumour markers to the gold standard of mIBG-scans to assist in the management of NB in LMICs with limited resources.

***"Induction chemotherapy for high-risk neuroblastoma in South African children" (12)***

Seventy-eight percent of patients diagnosed in South Africa between 2000 and 2016 with NB, had high-risk tumours. As metastatic remission after induction therapy in high-risk neuroblastoma (HR-NB) was of prognostic importance, this study investigated mCR after induction chemotherapy during the three standard induction protocols for NB in the South African setting. The objective was to identify an induction regimen for HR-NB based on remission rate, toxicity and OS that could be administered in al POUs in South Africa. There was no significant difference in the mCR and OS between the three induction regimens but OPEC/OJEC had the most favourable toxicity profile for the South African setting. The same outcomes were drawn between the Rapid COJEC (SIOPEN protocol) and N5-MSKCC (St Jude's Hospital, North American protocol) with the N5-MSKCC induction protocol causing greater toxicity (10).

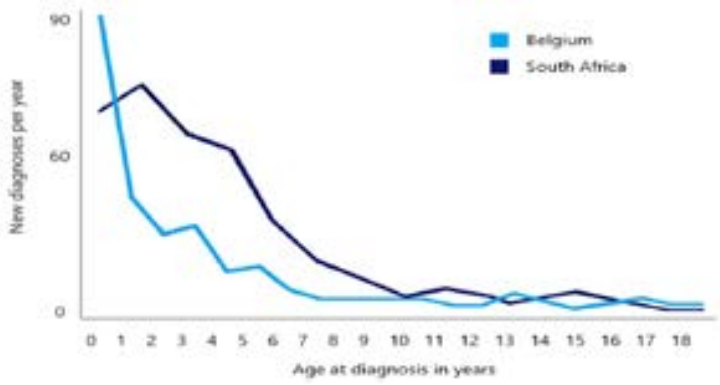
***"The importance of local control management in neuroblastoma in South Africa" (11)***

Surgery and radiotherapy are important in the local tumour management of NB. In patients with low-risk tumours, surgery is curative, whilst in patients with intermediate-risk tumours, surgery, chemotherapy and, in cases of residual tumours, radiotherapy are curative. HR-NB trimodal therapy (chemotherapy, surgery and radiotherapy) only has an OS of up to 20-25% (*Figure 2*). In higher-resourced settings, autologous stem cell transplants, molecular targeted therapies and maturation therapy have increased the outcomes up to 60-65% OS but made the significance of local therapies unclear. The role of surgery in NB in South Africa, especially the degree of resection, has never been evaluated. The relevance of radiotherapy in curative and palliative management in the absence of surgery has not been explored in the South African paradigm. The study concluded that a surgical resection between 90% to 100% had better outcomes than no surgery and that radiotherapy in the absence of surgery increased the progression-free survival.

***"The implementation of a national paediatric oncology protocol for neuroblastoma in South Africa" (17)***

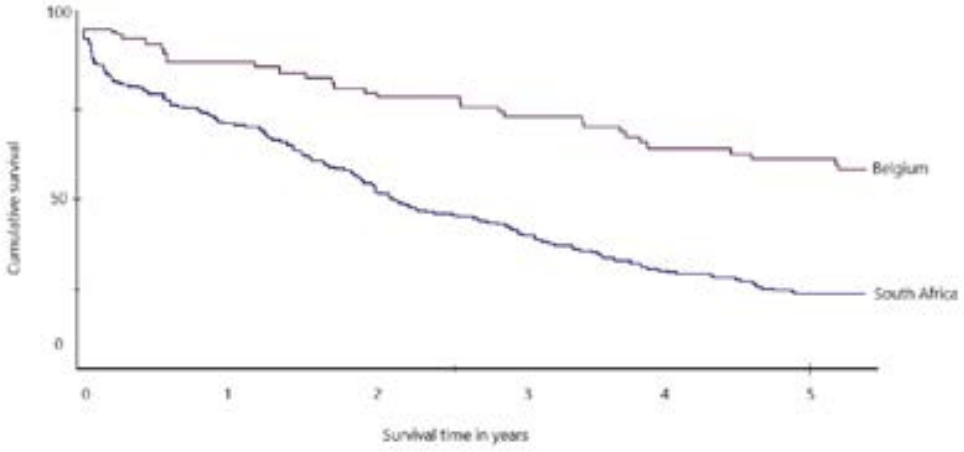
Collaborative guidelines are important in establishing a standard of paediatric oncology care in South Africa. The South African Children's Cancer Study Group (SACCSG) has embarked on developing national management protocols for individual childhood malignancies. The evaluation of the development process of the neuroblastoma protocol by the NB-working group of South Africa, valuable resources and methodologies for future protocol development were documented. The SACCSG NB-2017 protocol was an example where multiple international guidelines were incorporated for the local setting as an adapted management protocol. The implementation research of this article may provide insight into the development and implementation of similar treatment guidelines in other LMICs.

**Figure 1:** *A comparison of the age at diagnosis for neuroblastoma in a high-income country (Belgium) compared to a resource limited country (South Africa)*




**Graph:** Created by J van Heerden and M Kruger. **Sources:** The Belgian graph is based on data from the Belgian Cancer Registry. The South Africa graph is based data from the retrospective study in this thesis.

**Figure 2:** *The Kaplan Meier curve representing the five-year overall survival for high-risk neuroblastoma in South Africa compared to Belgium*




**Graph:** Created by J van Heerden and M Kruger.

***"Inequality in paediatric oncology in South Africa – the neuroblastoma case study" (18)***

South Africa adopted its first democratic Constitution in 1996. The Bill of Rights included a section protecting children's rights beyond the constitutional right to life and equality. With the guarantee of access to health services enshrined in the Constitution, lifesaving treatment for neuroblastoma should be included in the right to life-saving medical treatment. With a more equitable population-based distribution of the country's budget and various administrative reforms, the national health services should after 20 years have established equal health care access to children with cancers. Based on the data from our retrospective NB study between 2000 and 2014, we evaluated the equity of the human resources, the level of paediatric oncology services and the access to these services based on distance and travel duration. We concluded that inequity to access these resources for children with cancer in South Africa, was still a large problem.

***"An interim assessment of the prospective national neuroblastoma protocol (SACCSG NB-2017) in South Africa".***

The running of a successful trial and recruitment of patients depends on many contributing factors. The interim analysis of the SACCSG NB-2017 clinical trial and the sub-optimal inclusion of patients were evidence to this. The factors that contribute to investigator trial participation are institutional, national and/ or individual to single investigators. Although many factors can be mitigated, others are not and flexibility towards the research should be adopted with a greater emphasis on co-operative participation. South African universities have no standardised or shared ethics application procedure. Neither are reciprocal ethics approvals between universities in place for more efficient cooperation. This leads to excessive, burdensome administration in a system where research is already challenging. The personal experience of co-investigators led to the exclusion of study eligible patients because participating POUs have felt the psycho-emotional situation such as pre-terminal presentations, not conducive for including patients on the palliative aspect of the study. The interest in the subject matter, number of staff to oversee the clinical workload and a resistance to work in a research study group added many degrees of complexity in executing the study. The responsibility of co-investigators familiarising themselves with a new national treatment protocol in combination with the infrequent diagnosis of a rare disease, such as NB, in a single POU contributed to low retention of the study protocol. Since the outbreak of the COVID-19 pandemic an already overburdened South African medical system, increased pressures arose.

This relegated academic and administrative responsibilities secondary to the pandemic's management responsibilities.

***The value of neuroblastoma research done in LMICs for HICs***

With increasing evidence of genetic and epigenetic variations in NB, questions regarding the population-based genetic profiles in NB are still unanswered. One conclusion in our thesis is that South Africa might truly have a lower incidence of NB, independent from the resource and delayed health seeking behaviour limitations. With the limited to no genetic and molecular data available from LMICs, conclusions cannot be made regarding local profiles.

Fundamental clinical research, including translational research, is possible in LMICs because of the higher need for clinical applications of advanced tests to improve outcomes, but at a lower cost. The value of resource allocation is acutely present in LMICs compared to HICs, yet the experienced gained regarding resource management is valuable to HICs as well.

Most HICs collaborate in study groups who utilise trial protocols based on standard of care and interventions with clear indications. In LMICs the possibilities are greater for treatments with favourable evidence to be studied outside the study group trials. This opens avenues for developing more strategies to treat NB with locally available resources which can be used in HICs.

## Conclusion

This thesis highlights the landscape of NB in LMICs through the lens of the South African experience. NB is often underdiagnosed and under reported, which leaves basic epidemiological questions on NB in limited resource settings unanswered. The high burden of advanced and high-risk disease not only represents the unique pathology in limited resource settings, poses significant challenges in the management of NB, often with poor outcomes. Achieving early diagnosis remains a challenge in LMICs which includes South Africa. Therefore, advocacy to improve public awareness should increase and include the early warning signs of childhood cancer in the integrated management of childhood illnesses (IMCI) to assist all level of health care workers to recognize childhood cancer with an immediate referral (19). The methodical development of a national protocol indicated the possibility of managing NB, but with the conclusion that the use of local therapies, such as surgery and radiotherapy, should be optimised for improved outcomes. Both the COVID-19 pandemic and reluctance to recruit advanced stage patients limited the recruitment of patients into the national NB clinical trial. Of great importance is to encourage initiatives towards bio-banking in South Africa to study the genetic profiles of diseases unique to the region. With the diversity of the genetic landscape in South Africa and the ever-increasing research into genetic and epigenetic targets in NB, biological knowledge could contribute to a greater understanding in the outcome variations as well as research into the pharmacokinetics and dynamics in the treatment of NB (20).

By promoting collaborative research efforts and relevant research questions, rare diseases such as neuroblastoma in South Africa could be managed in national management protocols, with the goal of improving the survival rates and eventually being able to cure high-risk disease.

### Conflict of interest

There is no conflict of interest to disclose.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# Transient tachypnea of the newborn

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## Question

Are restricted fluid therapy or treatment with salbutamol effective and safe to treat transient tachypnea in neonates?

## Context

Transient tachypnea of the newborn (TTN) is characterized by abnormally fast breathing and signs of respiratory distress starting shortly after birth. It is caused by delayed clearance of fluids in the lungs and typically occurs in term and late preterm newborns. Although TTN is usually self-limiting, it does result in many neonatal intensive care unit admissions for supportive care and sometimes even respiratory support. Several Cochrane reviews have already been published about possible treatments for this condition, such as diuretics, steroids and epinephrine, but at the moment the only treatment for TTN remains supportive care, primarily intravenous fluid and oxygen therapy. Recently two new Cochrane reviews were published investigating the effectiveness and safety of fluid restriction therapy and salbutamol treatment respectively (Gupta 2021, Moresco 2021). Both treatments may accelerate the clearance of fluids from the lungs, resulting in faster resolution of symptoms and decreased need for supportive care and/or hospitalization.

## Criteria for study selection

The first review compared the use of restricted versus standard fluid therapy in term and preterm neonates with TTN. Restricted fluid therapy consisted of a total fluid intake that was 90% or less than the standard amount for at least 24 hours in the first week of life. The salbutamol review compared the use of salbutamol to placebo, no treatment or any other drugs in infants born at least 34 weeks' gestational age. The primary outcomes in both reviews were duration of supplemental oxygen therapy and the need for non-invasive or invasive ventilation.

## Summary of the results

### Fluid restriction

Four studies with 317 infants were included in the review. Three studies included late preterm and term neonates with TTN and the fourth trial included only term neonates. The infants were on different additional respiratory support methods (room air, oxygen, nasal continuous positive airway pressure). The neonates in the fluid restriction group received 15 to 20 mL/kg/day less fluid than those in the standard fluid therapy group. Typically, term infants would receive 40, 60 and 80 mL/kg/ day in the fluid restricted group, and 60, 80 and 100 mL/kg/day in the standard group on day 1, 2 and 3 of life. The duration of the intervention varied.

We are uncertain whether fluid restriction therapy, compared to standard fluid therapy, decreases or increases the duration of oxygen therapy (control: range 6-53 hours vs intervention: on average 13 hours less (95% CI*: 33 hours less to 7 hours more); 2 studies, 172 neonates, very low-certainty evidence), the need for invasive ventilation (control: 57 per 1000 vs intervention: 42 per 1000 (95% CI*: 13 to 128 per 1000); 3 studies, 242 neonates, very low-certainty evidence) or the need for non-invasive ventilation (control: 250 per 1000 vs intervention: 100 per 1000 (95% CI*: 35 to 292 per 1000); 2 studies, 150 neonates, very low-certainty evidence). Similarly, there is uncertainty for the incidence of hypernatremia and hypoglycemia, length of hospital stay and cumulative weight loss at 72 hours of age.

### Salbutamol

Seven studies with 498 neonates compared a nebulized dose of salbutamol to normal saline. Either a single dose was administered (4 studies), 3 to 4 doses (2 studies) or additional doses were administered if needed (1 study). The duration of oxygen therapy was significantly reduced in the infants receiving salbutamol (control: range 26-77 hours vs intervention: on average 19 hours less (95% CI*: 24 to 15 hours less); 4 studies, 338 neonates), but the level of certainty about this effect was downgraded to very low because of risk of bias, inconsistency of results between studies, and small sample size. The use of salbutamol may also decrease the length of hospital stay by about 1.5 days (control: range 5-9 days vs intervention: on average 1.5 days less (95% CI*: 1.8 to 1.2 days less); 4 studies, 338 neonates, low-certainty evidence). We are uncertain about the effect of salbutamol on the need for continuous positive airway pressure (control: 533 per 1000 vs intervention: 389 per 1000 (95% CI*: 203 to 741 per 1000) 1 study, 46 neonates, very low-certainty evidence) or the need for mechanical ventilation (control: 25 per 1000 vs intervention: 15 per 1000 (95% CI*: 3 to 71 per 1000); 3 studies, 254 neonates, very low-certainty evidence). We are also uncertain about the effect on the duration of respiratory support and the occurrence of pneumothorax. Duration of mechanical ventilation was not reported in any of the studies.

## Conclusion

Only limited evidence was available for both interventions. It is still uncertain whether fluid restriction therapy or salbutamol treatment have any positive effects on the duration of oxygen therapy and the need for invasive of non-invasive ventilation. Salbutamol may shorten the length of stay at the hospital. Five trials with salbutamol are still ongoing and given the simplicity of the fluid restriction intervention, a well-designed trial should be considered to evaluate its effectiveness and safety.

## Implications for practice

As of now, it still remains unclear whether fluid restriction therapy or treatment with salbutamol are effective or safe.

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Entretien avec Arnaud Collignon, Water Ressources Manager, chez SPA® qui explique les mesures de protection des zones de captage dans les Fagnes et les contrôles réalisés pour garantir un eau pure, très faiblement minéralisée et d'une composition constante.

### UNE ZONE DE CAPTAGE SANS AUCUNE ACTIVITÉ HUMAINE

***AC:*** *La zone de protection de l'eau minérale de Spa s'étend sur plus de 13 000 hectares. A l'intérieur de ce périmètre, il n'y a aucune activité industrielle, pas d'agriculture, pas de pesticides afin de garantir une très grande pureté des eaux. Depuis la source jusqu'à la bouteille, l'eau reste en circuit fermé et ne voit pas la lumière du jour. Tous les matériaux en contact avec l'eau, conduites ou emballages, sont très régulièrement testés et analysés pour garantir leur caractère inerte et non polluant. Les emballages garantissent également une qualité de l'eau et une pureté préservée. Un suivi continu des lignes de production est assuré. Toutes ces procédures et ces contrôles, permettent d'offrir et de garantir une eau de grande qualité et d'une pureté irréprochable.*

### DES ANALYSES QUOTIDIENNES ASSURÉES PAR UN LABORATOIRE AGRÉÉ

***AC:*** *L'eau de Spa respecte en tous points les exigences de la réglementation européenne en la matière. Ainsi, l'eau est analysée quotidiennement pour évaluer sa qualité microbiologique et sa composition chimique. Elle est contrôlée aussi bien à la source qu'avant ou après sa mise en bouteille. Dans un souci d'excellence, le contrôle de l'eau est poussé au-delà de la réglementation avec des contrôles réguliers sur un large éventail de paramètres microbiologiques, physico-chimiques et organiques par le Laboratoire de Spadel (certifié ISO 17025). De plus, des laboratoires indépendants contrôlent régulièrement l'absence de contaminants émergents (pesticides et leurs métabolites, résidus de médicaments, perturbateurs endocriniens, virus,...). Sans compter les contrôles microbiologiques hebdomadaires, Spadel a analysé en 2020 quelques 53.204 paramètres sur les eaux de Spa.*


### LES CRITÈRES POUR LE LABEL «CONVIENT POUR LA PRÉPARATION DES ALIMENTS POUR NOURRISSONS»

***AC:*** *Pour bénéficier du label « convient pour la préparation des aliments pour nourrissons », une eau doit répondre à différents critères : une très grande pureté, constante dans le temps et une composition faible en minéraux, ce qui est le cas pour Spa® Reine puisqu'elle est faiblement minéralisée avec une très faible teneur notamment en calcium, fluor, chlorures, sodium mais aussi en nitrates et en nitrites. Autant de critères auxquels Spa® Reine répond parfaitement. Pour ces raisons, Spa® Reine est une eau de premier choix pour la maman allaitante et pour le nourrisson.*

www.spa.be

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