BJP
Belgian Journal of Paediatrics
Publication of the Belgian Society of Paediatrics

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

2022 - Volume 24 - number 3 - September

Articles

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Paediatric Cochrane Corner

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Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

QUARTERLY
ISSN 2466-8907 (printed version)
ISSN 2566-1558 (digital version)

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De Belgische Vereniging voor Kindergeneeskunde

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de gezondheid van onze kinderen

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BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
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Editorial

An apple a day keeps the doctor away !

September 2022... back to school and to work.. Fall and winter are knocking on our doors...

September 2022 also sees a page of history turn. Through our editorial and our cover, we want to pay tribute with a touch of humor, of respect and of trust above all, to a personality and a reign that has seen many pages of history written, including that of medicine. Elizabeth II passed away on September 8, 2022 at the age of 96 after being the Queen of the United Kingdom and other Commonwealth realms for more than 70 years. She was born (April 21, 1926) almost at the same time as our Belgian Pediatric Society (January 14, 1923). Few years later, the British Alexander Fleming discovered accidentally penicillin (1928). In 1952, the year of Elizabeth II's accession to the throne, the first kidney transplant from a living donor took place. Immunology was still in its infancy and the patient died 21 days later. It was not until 1954 that the first successful kidney transplant was performed on monozygotic twins. The first bone marrow transplant was performed in 1957, and the first liver transplant took place in 1963. In 1953, Queen Elizabeth II was officially crowned. The same year, Watson and Crick described the double helix structure of DNA. In the early 1980s, Her Majesty celebrated the wedding of her children and became a grandmother. This time also corresponds to the introduction of surfactant in clinical practice. This transformed the vital prognosis and morbidity of newborn respiratory distress associated to prematurity. Let's bet that, with a birth weight of 3.250kg and 2.8kg respectively, Princes William and Harry did not need it. More recently in December 2020, a few days before the beginning of the vaccination campaign in Belgium and while Europe and particularly the United Kingdom were facing a peak of contaminations by the coronavirus, Elizabeth II and her husband Prince Philip, were among the first to be vaccinated. Usually quite discreet about her state of health, the monarch decided to make this information public to avoid any possible rumors.

The exceptional length of Elizabeth II's reign, the place that King Charles II will now take, and the massive tribute paid by the British people also put into perspective the questions of continuity and change. In our medical practice, we have all known, or perhaps still know, personalities, professors, doctors, managers who have had an impact on their unit through their length of tenure, their charisma, or their vision. The importance of these people in the development of a department is indisputable. The questions that arise are rather the transition, the evolution during or afterwards. How to leave a place for other points of view, other sensibilities? These remarks also apply to ideas. Certain theories, practices or habits may change or evolve. How to position yourself? What is preferable? a break? a slower and progressive transition? So many questions that are possibly echoed in our pediatric community, the one that accompanies adolescents in their passage from childhood to adulthood...

The cover of this September issue, once again illustrated by Serge Ernst, is also the opportunity to confirm another British secret: the positive role of fruits and vegetables in children's diets. This is discussed more objectively discussed in our Cochrane Corner section.

In addition, this issue also features several clinical case reports described by young pediatricians and colleagues from all over Belgium: a neonatal acute myeloid leukemia revealed by a Blueberry Muffin syndrome, a case of fetal and neonatal ventricular arrythmias in Long QT type 2 syndrome, a report of erythromelalgia in a young adolescent and a rare cause of liver dysfunction and malabsorption. We also publish several studies on compounded hydrocortisone preparations for children with congenital adrenal hyperplasia, prophylactic azithromycin in preschoolers with chronic respiratory symptoms, congenital long-segment tracheal stenosis, pediatric fluid resuscitation and risk of anaphylaxis in children with Ig E-mediated allergy. Our “Made in Belgium” section is also very rich with the summary of 3 thesis: Congenital cytomegalovirus infection in Flanders by Annelies Keymeulen (University of Ghent), the influence of maternal antibodies on the immune responses of term and preterm born infants by Marlolein Orije (University of Antwerp) and visuoperceptual profiling and game-based rehabilitation in children with cerebral visual impairment by Nofar Ben Itzhak (University of Leuven).

We hope you will enjoy reading this issue and on behalf of the entire editorial board, we wish you a bright and colorful fall !

Christophe Chantrain and Marc Raes, Editors-in-chief

Uw vragen of commentaar
Vos questions ou commentaires

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VOOR KINDERGENEESKUNDE
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CLIMATE CHANGES IN PEDIATRICS: FROM SOCIETY TO ENVIRONMENT

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Health literacy among caregivers of children with IgE-mediated allergy at risk of anaphylaxis

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As per every year's wont, the joy of the return to school for parents of children with a food allergy (FA) mingles with many adrenaline peaks inherent in their quest for the best possible safety for their offspring in nurseries or schools. Most of the information transmitted to the communities is unfortunately done only via the parents of allergic pupils instead healthcare professionals, such that the pediatrician or allergo-pediatrician, prescriber of eviction diets and emergency kit, remains under the impression of having thrown a bottle into the sea for want of knowledge about the follow-up to their recommendations. FA, which mainly affects children, is becoming a real public health problem in Europe given the increase in its prevalence over the past two decades and an age of spontaneous recovery that occurs increasingly later (1). It affects up to 8% of children, or about two children in a class of 25 students (2). Whilst it is estimated that around 20% of children with FA experience a reaction at school, it is of greater concern that 25% of allergic reactions occurred in children who were not known to have previously had FA or who had an allergy that had not been disclosed to school staff (3, 4). Subsequent to the demise of allergic children in the school environment, recommendations have been published emphasizing the essential role of information and training for staff in nurseries and schools (5).

As documented in this volume's article devoted to the topic of FA, the benefits of short multidisciplinary training courses (allergo-pediatrician, dietitian, psychologist) received by community personnel, have been substantiated in numerous European studies, notably in Italy and Spain (6, 7). For a better integration of children, France adopted in 1999 the project of individualized reception, which outlined the adjustments to be made in community to the life of infants at risk of allergy. In the US and Canada, recent laws require nurseries and schools to have unassigned epinephrine auto-injectors, like the automatic external defibrillators present in public places (9,10).

In Belgium, one of the last countries in Europe where allergology is not yet recognized as a medical specialty, there are no FA prevalence figures nor anaphylaxis registry, in spite of the infant casualties reported in rare publications (10). What is being done at the federal or regional level to avoid dramatic situations in nurseries and schools? Not much to be fair, apart from the local initiatives, such as that of Allergienet vzw and Prevention of Allergies asbl, and the diffusion in the South of the country, in 2014, of circular 4888 dedicated to the care and administration of medication to pupils of kindergarten to secondary school. Hardly have these initiatives been used by school principals or school doctors, thereby not bearing fruit. From a legal standpoint, in order for a community staff member to be able to perform an act reserved for nurses or doctors, qualification is needed which is synonymous with being able to identify the urgency of the situation and receiving training in the performance of the act ; otherwise neither they nor their organization could be liable for duty to rescue charges (12).

Given that the nursery and the school are the places where our young allergic patients spend the majority of their time, the organization by the public authorities of a simple 2-hour information and training session for the staff would improve the management of allergic reactions, thereby reducing the psycho-social impact of FA on the child and his parents, with legal protection to boot.

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12. Belgisch Staatsblad Koninklijk besluit nr 78 betreffende de uitoefening van gezondheidszorgberoepen van 10 november 1967 and Article 422 bis du Code Pénal, de quelques abstentions coupables

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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]:** 25 microgram. • [1] Geproduceerd in *E. colicellen* door recombinantDNAtechnologie. [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}). [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de volledige SPK. **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 B stammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **Dosering en wijze van toediening:** Dosering: **Tabel 1. Samenvatting van de dosering: Leeftijd bij eerste dosis: Zuigelingen van 2 tot en met 5 maanden[a]:Primaire immunisatie:** Drie doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis [b c]. - **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis [b c]. • **Leeftijd bij eerste dosis: Zuigelingen van 6 tot en met 11 maanden: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis [c]. • **Leeftijd bij eerste dosis: Kinderen van 12 tot en met 23 maanden: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis [c]. • **Leeftijd bij eerste dosis: Kinderen van 2 tot en met 10 jaar: 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 (zie rubriek 5.1 van de volledige SPK). 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 (zie rubriek 5.1 van de volledige SPK). 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. Dit middel bevat minder dan 1 mmol natrium (23 mg) per dosis, dat wil zeggen dat het in wezen 'natriumvrij' is. 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, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventueele 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 vaccinatie reeks. Tabel met bijwerkingen: Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. **De frequentie is als volgt geclassificeerd:** Zeer vaak: (≥1/10) - Vaak: (≥1/100, <1/10) - Soms: (≥1/1.000, <1/100) - Zelden: (≥1/10.000, <1/1.000) - Zeer zelden: (<1/10.000) - Niet bekend: (kan met de beschikbare gegevens niet worden bepaald). De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar):** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Voedings en stofwisselingsstoornissen: Zeer vaak: eetstoornissen. Zenuwstelselaandoeningen: Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn. - Soms: insulten (inclusief febriele insulten) - Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen: Soms: bleekheid (zelden na booster) - Zelden: ziekte van Kawasaki. Maagdarmstelselaandoeningen: Zeer vaak: diarree, braken (soms na booster). Huid en onderhuidaandoeningen: Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster) - Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar) - Soms: eczeem - Zelden: urticaria. Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: koorts (≥38°C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid - Soms: koorts (≥40°C) - Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). **Adolescenten (van 11 jaar en ouder) en volwassenen:** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Zenuwstelselaandoeningen: Zeer vaak: hoofdpijn - Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen: Zeer vaak: misselijkheid. Huid en onderhuidaandoeningen: Niet bekend: huiduitslag. Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: myalgie, artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise - Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België:** Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Afdeling Vigilantie - Postbus 97 - B-1000 Brussel - Madou - Website: www.eenbijwerkingmelden.be - e-mail: adr@fagg.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 - e-mail: crpv@chru-nancy.fr ou Direction de la Santé - Division de la Pharmacie et des Médicaments - 20, rue de Bitbourg - L-1273 Luxembourg-Hamm - Tél.: (+352) 2478 5592 - e-mail: pharmacovigilance@ms.etat.lu - Link pour le formulaire : https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.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:** 25/02/2022 (v13). **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-ADVR-220001 - Augustus 2022

GSK

Health literacy among caregivers of children with IgE-mediated allergy at risk of anaphylaxis

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Keywords

Food allergy, health literacy, patient education, training session, venom allergy

Introduction

Anaphylaxis is an acute, life-threatening multi-systemic allergic reaction (1). The prevalence in children is increasing, resulting in more hospital admissions over the last decade (2). Some anaphylactic reactions may be fatal if not treated appropriately, but the fatality rate is low (<0.001%) (3). The most common trigger in children is food. The prevalence of food allergy in European schoolchildren is estimated to be 4-7% (4). The epidemiological data of anaphylaxis are probably underestimated due to under-diagnosis and underreporting (3). A European study identified peanuts as the most frequent trigger, followed by wheat, hen's egg and cow's milk (5). Under the age of 3 years anaphylaxis is mostly triggered by hen's egg and cow's milk. Most children acquire tolerance for the latter products with age. Therefore, the prevalence of anaphylaxis due to food is higher in young children (2).

Complete avoidance of the food allergen remains crucial, but accidental exposure is common (6). Caregivers of children with anaphylaxis therefore need an action plan to manage severe reactions. The adrenaline auto-injector is the first line therapy for all anaphylactic reactions and should be available for all patients at risk (6). Parents report a lack of information at diagnosis that increases both anxiety and uncertainty in managing an accidental ingestion (7). Several guidelines recommend the provision of comprehensive information on allergen avoidance, reading food labels, rapid recognition of symptoms and management of allergic reactions, with education on how and when to use the adrenaline auto-injector (4,8-11).

According to a recent study based on data of the Allergy Vigilance Network the prevalence of food-allergic anaphylactic reactions at school in France is 28% (12). Most fatal cases of anaphylaxis at school are attributed to a delay in the initial treatment due to lack of recognizing symptoms and/or delay in using the adrenaline auto-injector (10). Adequate education of family members and training in non-clinical settings such as schools, is advised to improve this lack of knowledge (6).

Health literacy is defined as people's knowledge, motivation and competencies to access, understand, appraise and apply health information in order to make judgments and decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during one's life course (13). The general level of health literacy is quite limited in Europe (13). A higher level of health literacy is necessary to optimize the management of anaphylaxis. To improve the caregivers' level of health literacy, their level of self-efficacy needs attention. Self-efficacy is defined as confidence and 'the belief in one's capabilities to organize and execute the courses of action required to manage prospective situations' (7). Improving self-efficacy through education has been shown to be effective in improving quality of life, self-management and coping with asthma and other long term conditions (7). Several previous studies about self-efficacy in the management of anaphylaxis at school have shown that the self-efficacy score improved by education (10, 14-16).

The goal of this study is to assess the effect of a training session on caregiver's knowledge and self-efficacy in managing children with IgE-mediated allergy at risk of anaphylaxis. We assumed that a group training session about anaphylaxis would improve the level of health literacy by increasing the level of knowledge and self-efficacy of the caregivers.

Materials and Methods

Study design

We conducted a prospective cohort study in a population of caregivers of children with IgE-mediated food or insect venom allergy at risk of anaphylaxis at a regional hospital in Belgium (AZ Maria Middelares Ghent). The protocol was approved by the institutional Ethics Committee (committee's reference number: MMS.2020.017) and was registered in clinicaltrials.gov (NCT04475003). A written informed consent was obtained from all participants. The data were collected and analyzed by the researchers (J.V., J.L. and D.B.), and an independent academic statistician.

Study population and procedure

The subjects enrolled in this study were caregivers (parents, grandparents, crèche supervisors and teachers) of children with IgE-mediated food or insect venom allergy at risk of anaphylaxis. Eligible caregivers were recruited during outpatient consultation from 30 July 2020 till September 2021. During consultation parent(s) were extensively informed by the pediatrician specialized in allergy. They received an information leaflet, were taught how to use the adrenaline auto-injector and - in case of food allergy - also visited a dietician specialized in allergy. All Dutch speaking parents and related caregivers were then invited for a training session 3-4 months after diagnosis. We invited all caregivers to participate the study, so there was no bias in favor of some profiles. The session was always given by the same pediatrician specialized in allergy. A maximum of four caregivers per patient were allowed to participate. All caregivers were informed about the purpose of the research and the voluntary nature of participation. The two hours training consisted of a theoretical and practical part, and ended with a Q&A session. During the practical part each caregiver learnt how to use the adrenaline auto-injector with a trainer pen and how to read food labels. Before the start of the session the caregivers filled in a paper questionnaire. During the Covid pandemic the sessions were digital, so the questionnaire

was sent online a few days before the training. One week after the training all caregivers received the same survey online. If the questionnaire was not completed, reminders were sent several times. Four training sessions were organized, two live and two digital, and each participant followed one session. All training sessions (digital, live) were given by one and the same pediatrician specialized in allergy. Two sessions were cancelled due to the pandemic. The digital session was a live, online non-recordable session. There was no possibility to obtain the PowerPoint slideshow afterwards and the participants were not allowed to take screen shots of the power point slides.

Questionnaire

The questionnaire was specially designed for this study and consisted of three parts: twelve multiple choice and true-false questions about anaphylaxis, a Dutch translation of a validated questionnaire with eight multiple choice questions (answering scores from one to five, one meaning 'I cannot do that at all' and five meaning 'I certainly can do this') about self-efficacy of caregivers in the management of anaphylaxis (S.PER.SE-FAAQ) and a section with demographic information (caregiver type, level of education, age and sex) and one final question 'To what extent did this training session make you feel more confident in taking care of a child at risk of anaphylaxis?', scoring zero to ten, zero meaning 'no added value', ten meaning 'absolutely of value' (10).

Statistics

The data were analyzed with the SPSS IBM version 26 using nonparametric statistics (Wilcoxon Signed Ranks Test). Univariate Regression analysis with knowledge/self-efficacy as dependent factor, and age, type of caregiver, education level and type of training session as independent factors, was performed. The primary outcomes were the effect of the training session on the total score of caregivers' knowledge and self-efficacy. P-values below 0.05 were considered statistically significant. Bonferroni adjustment was used when necessary.

For the power calculation we used the first part of the questionnaire (knowledge). In order to have a power of 90% (SD of 35% for an - = 0.025) we had to include at least 62 participants. Prior to the study, J.L, J.V. and B.D. agreed that the effect of the training session would be clinically relevant if the difference in total knowledge score was an improvement of two out of twelve questions (16 %). The secondary outcome was the subjective score on the question whether the session contributed in feeling more confident in taking care of a severe allergic child.

Results

Population description (table 1)

One-hundred-forty caregivers followed the training sessions and could be eligible for this prospective cohort study, 116 people agreed to participate and completed the first questionnaire. Forty-five out of 116 (39%) participants did not complete the questionnaire after the training (partial responders). Seventy-one participants completed the questionnaire twice (complete responders), of which 69% were below 55 years, the majority (70.4%) of them were female. Most caregivers (40.8%) were first-degree relatives (parent, sister), followed by second-degree relatives (grandparents, aunt, uncle) (33.8%) and school- and nursery caregivers (25.4%). The majority of school caregivers were teachers (19.7%), followed by one director (1.4%), one school manager (1.4%), one speech therapist (1.4%) and one childcare supervisor (1.4%). Most participants (85.9%) were higher educated (master's or bachelor's degree). Thirty-five caregivers (49.3%) followed the live training session, 36 (50.7%) the digital session.

Knowledge (figure 1)

The median total knowledge score before the training for both complete and partial responders was 66.7%, afterwards 83.3%. This was a significant improvement (p< 0.001). The difference in total score of knowledge was an improvement of two out of twelve questions (16.6%) which means a clinically relevant improvement in the complete responders group.

Subgroup analyses (table 2)

The younger participants (<55 years old; n=49/71) had a higher median score before (75% versus 58.3%; p=0.03) and after the training session (83% versus 75%; p= 0.005) in comparison to the older participants (≥55 years; n=22/71). In both age groups, the total knowledge percentage significantly increased. The caregivers who followed the live training session (n=35/71) had a higher median knowledge score before the training (75% versus 66.7%, p=0.024) in comparison to the caregivers who followed the digital session (n=36/71). After the training session the median knowledge score was equal in both groups. The total knowledge score significantly increased in both groups after the training session. No difference in baseline knowledge score was observed between the type of caregiver or their level of education. All caregiver groups however improved their total score on the knowledge percentage significantly. After the training session the scores differed significantly across the caregiver groups (p=0.003); post-hoc we saw a significantly lower knowledge score in the second degree caregivers compared to the other caregiver groups (p<0.001). The effect of training was not different between levels of education, but we observed that all groups improved their level of knowledge.

Correlations

In a stepwise, univariate regression analysis for the difference in knowledge before and after the training session as dependent variable age category, type of caregiver, education level and type of training session (live/digital) are not withheld as significant influencing factors.

Self-efficacy (figure 2)

The median total score of self-efficacy before the training session for both complete and partial responders was 80%, afterwards 85%. This was a significant improvement (p<0.001).

Subgroup analyses (table 3)

No difference in baseline median total self-efficacy score depending on age, caregiver type, degree of education and type of training session could be observed. All groups improved their score on self-efficacy significantly, no difference was seen after training amongst the different groups.

Additional information

Forty-six participants answered the additional question "To what extent did this training make you feel more confident in taking care of a child at risk of anaphylaxis? Only one participant felt that the training session had no added value at all. The others were more confident after the session, with scores of seven and higher out of ten.

When asked how they preferred to receive information, a significant number of caregivers (39.4%) chose the training session, followed by written information in a paper leaflet (23.9%), written information on a website (22.5%), an online group with peers (8.5%) and an information video on a website (5.6%).

Discussion and Conclusion

4.1 Discussion

This is the first Belgian study reporting the effect of an additional group training about anaphylaxis on knowledge and self-efficacy of caregivers of children at risk of anaphylaxis. Parents often are unable to inform other caregivers about the diagnosis of anaphylaxis. Therefore we decided not only to invite the parents, but also second-degree relatives and school caregivers. The training session consisted of a theoretical, a practical part and a discussion moment. We concluded that the training session resulted in a significant improvement of the knowledge score in the complete responders group (66.7% to 83.3%). This improvement was clinically relevant as we had agreed that there should be an improvement of at least 16%. Furthermore, the training resulted in a significant improvement of the median total score of self-efficacy (80% to 85%). The self-efficacy questionnaire had to be answered on a scale of one to five, so we could not define how much improvement there had to be in order to be clinically relevant. These results were consistent with previous studies on the effect of training session on self-efficacy (10, 14-16). The effect of a training

Table 1: population characteristics

Population characteristics		Complete responder group (n= 71)
Gender	Female	50/71 (70.4%)
	Male	20/71 (28.2%)
Age	Age <55 years	49/71 (69%)
	Age ≥55 years	22/71 (31%)
Type of caregiver	First-degree relatives	29/71 (40.8%)
	Second-degree relatives	24/71 (33.8%)
	School caregivers	18/71 (25.4%)
Level of education	Higher education	61/71 (85.9%)
	Secondary school	10/71 (14.1%)
Type of training session	Live	35/71 (49.3%)
	Digital	36/71 (50.7%)

Table 2: results total score of knowledge and subgroup analysis. All values are expressed as medians, with the interquartile range Q1 to Q3 in between brackets.

		Pre-training Knowledge median (Q1; Q3)%	Post-training Knowledge median (Q1; Q3)%	P-value
All participants (n = 71)		66.7 (58.3; 75)	83.3 (75; 91.7)	**P < 0.001**
Age	<55 years	75(66.7; 79.2)	83.3 (83.3; 91.7)	**P < 0.001**
	≥55 years	58.3 (58.3; 75)	75 (66.7; 83.3)	**P =0.004**
		P = 0.030	**P= 0.005**	
Type care giver	First-degree relatives	75 (58.3; 83.3)	83.3 (83.3; 100)	**P < 0.001**
	Second-degree relatives	62.5 (58.3; 75)	75 (66.7; 83.3)	**P = 0.003**
	School caregivers	66.7 (66.7; 75)	83.3 (75; 83.3)	**P = 0.004**
		P = 0.056	**P = 0.003** *POST hoc (2nd<other groups; p<0.001)*	
Level of education	Higher education (master's degree)	75 (58.3; 75)	83.3 (83.3; 91.7)	**P = 0.027**
	Higher education (bachelor's degree)	66.7 (58.3; 75)	83.3 (75; 83.3)	**P < 0.001**
	Secondary school	58.3 (50; 77.1)	79.2 (58; 91.7)	**P = 0.002**
		P = 0.355	P= 0.487	
Type of training session	Live training session	75 (66.7; 83.3)	83.3 (75; 91.7)	**P<0.001**
	Digital training session	66.7 (58.3; 75)	83.3 (75; 83.3)	**P<0.001**
		P=0.024	**P=0.013**	

session on knowledge level has been less well studied.

We noticed that every subgroup (age, education level, caregiver and session type) showed a significant amelioration in the total knowledge score and self-efficacy. Overall, this implies that the training is valuable for all kinds of caregivers, also for the parents who received information directly from the allergy pediatrician at time of diagnosis. This is in line with the EAACI Food Allergy and Anaphylaxis Guidelines in which repeated education is advised (8).

The high median total score of knowledge (66.7%) before the training of both partial and complete responders was in stark contrast to what one might expect. A previous study about knowledge on asthma, food allergy and anaphylaxis in a group of university students, school teachers and parents of asthmatic children, showed a low knowledge level on food allergy and anaphylaxis (17). The higher scores in our study can be attributed to the participants' level of education and the extensive information all parents received from the pediatrician and dietician at the time of diagnosis (max 3- 4 months before the training session). The significantly higher knowledge score in the younger group may be due to the large proportion of parents in this group.

The high median total score of self-efficacy (80%) before the training session in the partial and complete responder group corresponds to previously published studies showing a high level of health literacy within a population of caregivers of food-allergic children. Caregivers participating in these research studies are more college-educated, middle or higher socio-economic status caregivers, that are presumably less likely to have poor health literacy (18). In addition the high total score of self-efficacy before the training session might be as well explained by the short time between the individual and group training session. The high level of self-efficacy before the training session is in disagreement with the Belgian KCE study (13). The much higher self-efficacy score in our population may be due to the selected group of Dutch speaking, higher educated and predominantly first degree relatives who received extensive information at diagnosis.

The most important study limitations were the one center patient recruitment, the Dutch translation of a validated questionnaire, the fact that the self-efficacy questionnaire was designed for school caregivers only and the voluntary aspect.

In contrast to most European countries allergologists are not recognized nor have a specific title in Belgium (19). Therefore, funding of referring these patients for those time-consuming therapeutic educational sessions is also lacking. Given the here proven efficacy of these sessions, we would like to advocate for their reimbursement, which might be most efficient by introducing a recognition of (pediatric) allergologists in Belgium as (sub) specialty. By extension, it would even be potentially life-saving if we could initiate training in all schools and allow the use of auto-injectors to their personnel after training, even in children who have their first anaphylaxis attack at school.

4.2 Conclusion

We concluded that specialized group training on anaphylaxis prevention, recognition and treatment for all caregivers of children with IgE-mediated allergy at risk of anaphylaxis on top of standard care, significantly improves the total score of knowledge and self-efficacy of all the caregivers. This group training on anaphylaxis should become a part of standard of care. Investment in repeated education for all caregivers might improve both level of knowledge and self-efficacy and could prevent accidental exposures and severe anaphylactic reactions. This might reduce emergency care admissions and hospitalizations, which might result in lower medical costs.

Acknowledgments

We would like to thank Yves Vandekerckhove and Pieter Vandekerckhove for their comments and support and Koen Huysentruyt for his contribution in the statistical analysis of this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.. All caregivers in this research participated voluntary the training sessions and the training sessions were free of charge.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Table 3: results total score of self-efficacy and subgroup analysis. All values are expressed as medians, with the interquartile range Q1 to Q3 in between brackets.

		Pre-training Self-efficacy median (Q1;Q3)%	Post-training Self-efficacy median (Q1;Q3)%	P-value
All participants (n = 71)		80 (75; 87.5)	85 (80%;92.5%)	**P < 0.001**
Age	<55 years	80 (75; 90)	85 (80; 92.5)	**P<0.001**
	≥55 years	81.3 (64.4; 85)	83.8 (79.4; 92.5)	**P=0.006**
		P=0.471	P=0.878	
Type caregiver	First-degree relatives	82.5 (75; 93)	87.5 (80; 93.8)	**P=0.026**
	Second-degree relatives	80 (63.1; 85)	82.5 (77.5; 91.3)	**P=0.007**
	School caregivers	76.3 (72.5; 82.5)	82.5 (80, 88.1)	**P=0.001**
		P=0.098	P=0.275	
Level of education	Higher education (master's degree)	80 (67.5; 85)	87.5 (77.5; 92.5)	**P=0.005**
	Higher education (bachelor's degree)	80 (75; 90)	83.8 (80; 93.1)	**P=0.005**
	Secondary school	75 (46.9; 85.6)	82.5 (77.5; 90.6)	**P=0.024**
		P=0.265	P=0.153	
Type of training session	Live training session	80 (75; 92.5)	85 (80; 92.5)	**P=0.013**
	Digital training session	80 (73.1-85)	82.5 (80-91.9)	**P<0.001**
		P=0.730	P=0.560	

Figure 1: Total knowledge score (%) before vs. after training

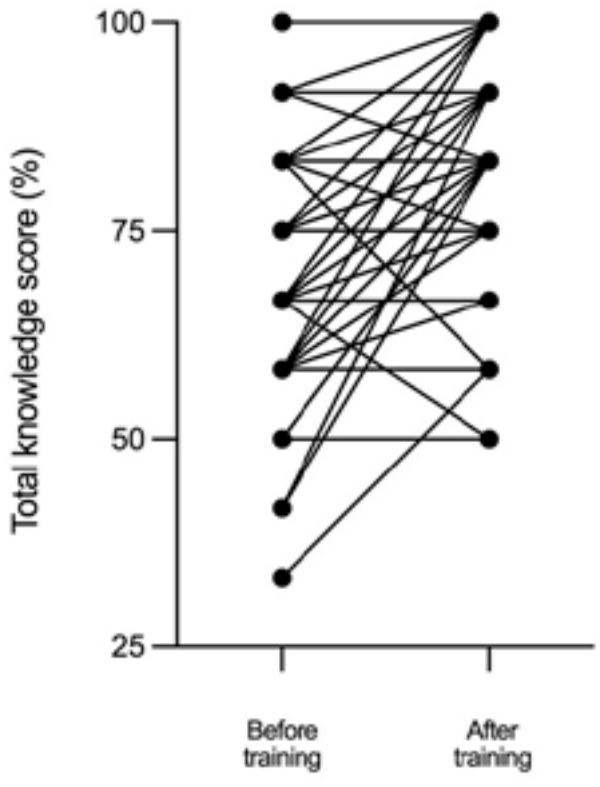
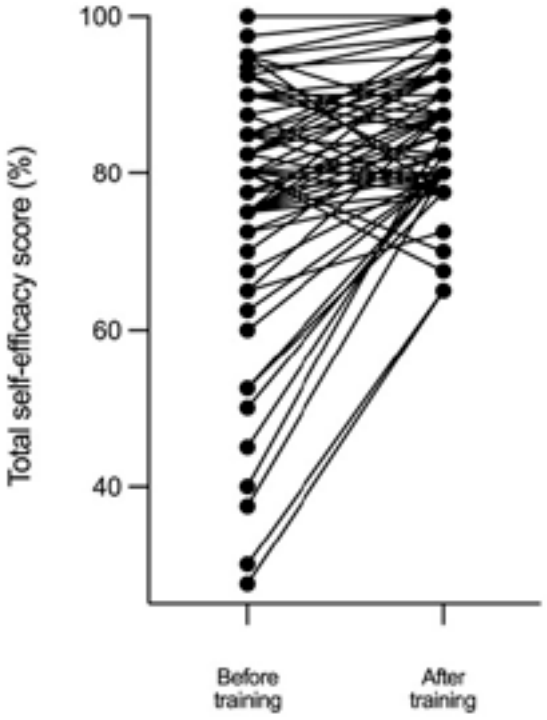


Figure 2: Total self-efficacy score (%) before vs. after training



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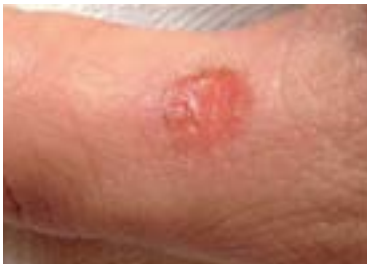
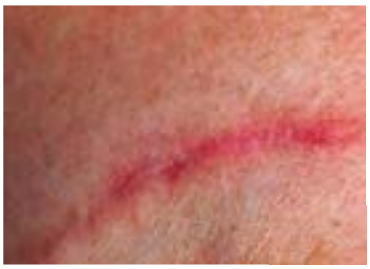

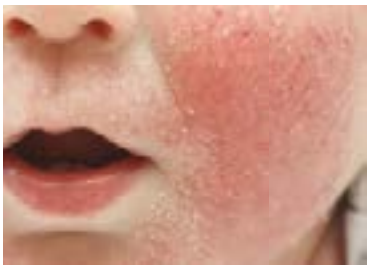
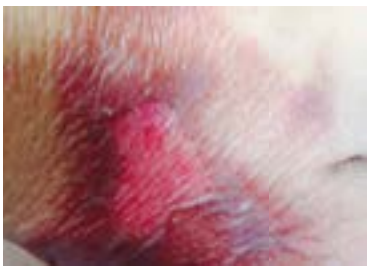


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Compounded hydrocortisone preparations for children with congenital adrenal hyperplasia: are they safe ?

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Keywords

Congenital adrenal hyperplasia, hydrocortisone, fludrocortisone, compounding, safety

Abstract

Children with congenital adrenal hyperplasia (CAH) or adrenal insufficiency (AI) need hydrocortisone and sometimes fludrocortisone in appropriate doses to survive. Low dose hydrocortisone preparations and fludrocortisone are not commercially available on the Belgian market so pediatricians have to rely on tablet splitting or crushing and pharmacy compounding. These methods can create substantial dosage errors with important clinical implications and are not subject to the quality controls and pharmacovigilance requirements that govern approved drug preparations. In addition, repeated supply shortages of the active pharmaceutical ingredients have occurred in the last years. Commercial low dose hydrocortisone and fludrocortisone products and modified-release hydrocortisone preparations, reliably produced under GMP regulations, could improve the safety risk associated with compounded medication but are not yet available in Belgium.

Classic congenital adrenal hyperplasia (CAH) is a rare (1:15000) hereditary autosomal recessive condition affecting adrenal steroidogenesis. Most of the cases (90–95%) are caused by mutations in the 21-hydroxylase gene (*CYP21A2*) leading to reduced cortisol synthesis. Additionally, aldosterone synthesis is impaired in about 75% of the patients resulting in salt-wasting CAH. The reduced feedback of cortisol causes a surge in ACTH which stimulates adrenal androgen production (1-3).

Hydrocortisone treatment in CAH substitutes the glucocorticoid deficiency and blunts the ACTH secretion. In addition, mineralocorticoid deficiency is treated with fludrocortisone.

Hydrocortisone treatment in classic CAH is a balance between overtreatment with multiple adverse side effects on growth and on metabolic, cardiovascular and bone health, and undertreatment, which carries risks for life-threatening adrenal crises, virilization and reduced adult height. Both over- and under treatment also affect reproductive function in both sexes.(2). The physiological production of hydrocortisone in humans is 6-8 mg/m^2/day and this quantity, divided in 3 or 4 doses, is used for patients with primary adrenal insufficiency. A higher dose is needed to suppress ACTH production in patients with CAH especially early in the morning. Consensus guidelines propose a dose of 10-15 mg/m^2/per day divided in 3 doses in children (3). This translates to doses of 1 and 2 mg hydrocortisone in toddlers and young children (e.g. 2-1-1 mg per day) (4). The recommended dose of fludrocortisone is 50-200 microgram in 1 or 2 doses (3).

Currently, only a 20 mg hydrocortisone tablet is available on the Belgian market and there is no commercially available form of oral fludrocortisone. A survey of pediatric endocrinologists from 16 countries in Europe revealed that 60% of them used divided adult hydrocortisone tablets and 55% used unlicensed individualized capsules, with the prescribed doses reported to be as small as 0.5 mg (5).

Dosage errors

Several methods are used to arrive at these low doses: tablet splitting, crushing and dissolving in liquids or individualized compounding in the pharmacy. European Pharmacopoeia guidelines on subdivision of tablets require that the parts meet the following criteria “at least 194 of 200 parts resp. 582 of 600 parts should be within 85–115% and all parts within 75–125% of the theoretical weight of a tablet part”(6). The accuracy of tablet splitting depends, among others, on the tablet type and size, the presence of a scoring line, the splitting device (by hand, kitchen knife or tablet splitter) (7,8).

Saimbi et al. measured the accuracy of splitting 2 types of 10 mg hydrocortisone tablets and found that the dose of halved tablets ranged from 41 to 55% for tablet A and 29- 70 % for tablet B .Quartering the tablets gave doses between 17-35% for tablet A and 12-42 % for tablet B instead of the 25% expected (9). In another experiment, more than 40% of the quartered tablets were outside the European Pharmacopoeia weight variation allowance when splitting a 10 mg hydrocortisone tablet in 4 with a standard pill splitter in lab conditions (10).

Thirty unexperienced participants were asked in a study to prepare a 2.5 mg hydrocortisone dose by splitting 10 mg tablets. When the tablet was scored, 70% of the doses ranged between 2,0 and 3,0 mg (20% variability of the intended dose). When unscored tablets were used, only 57 % of the doses were within this 2,0 – 3,0 mg dose range. Worrisome, more than 25% of the parents of children with CAH were not able to produce a dose within 20% of the theoretical value even after a training session(11).

Dispersion of tablets into liquid and withdrawal of the required volume is another popular method to prepare pediatric doses but it is also associated with large errors (7). Hydrocortisone is poorly soluble in water (0,28 mg/ml at 25°C) so most of the product is suspended or precipitates when caregivers prepare an aqueous solution. Saimbi et al crushed a 10 mg hydrocortisone tablet with a spoon, dissolved it in 10 ml of water and took 2 ml with a syringe. The mean actual dose ranged from 1,3 to 1,7 mg instead of 2,0 mg (9). In another study, only 67% and 87% of the liquid doses prepared using tablet A or tablet B respectively were within a ± 20% tolerance limit. (11).

A commercial oral suspension (Cortef suspension, Pfizer) was recalled from the market because it was not bioequivalent to tablets and failed to provide adequate control in children with CAH (12). Although an improved suspension has been proposed (13) the Endocrine Society Clinical Practice Guidelines on congenital adrenal hyperplasia (CAH) still recommend against using hydrocortisone suspensions (3).

To avoid these dosage errors, pediatricians often prescribe individualized doses of hydrocortisone for the pharmacist to prepare in capsules. Unfortunately, huge dose errors have also been described for this method. A group from Ghent University reported that a significant amount of the hydrocorti-

sone is lost during the preparation of the capsules and more than 1% remains in the capsule after emptying them (14). Neumann et al analyzed the hydrocortisone content of 1125 capsules sent in by 56 patients. In this real world analysis, more than 20 % of the batches revealed insufficiency in uniformity of net mass or drug content as defined by the European Pharmacopoeia and the capsules of 2 patients did not contain any hydrocortisone (15) (**Figure 1**).

Clinical implications of dosage errors

The extent of health problems related to the quality and safety of compounded drugs is unknown, as there is no requirement to report adverse effects of compounded drugs. However, regulatory agencies such as the FDA (Food and Drug Administration, USA) continuously receive reports of serious and sometimes deadly adverse events especially in children (16).

Overtreatment of CAH patients with hydrocortisone causes short stature, weight gain, decreased bone mineral density, hypertension and glucose intolerance . Undertreatment results in hyperandrogenism, low blood pressure and, in extreme cases, an adrenal crisis (1,2,3). Iatrogenic Cushing syndrome has been described in a child with congenital adrenal hyperplasia due to a hydrocortisone dose in the compounded medication that was 5 to 10 times the prescribed dose (17). Al Rayess et al described a 6 y old girl with CAH who became severely Cushingoid and developed gastric ulcers. The caregivers dissolved tablets in hot water and withdrew the desired volume from the bottom of the container. Due to the poor solubility of hydrocortisone the dose was much larger than expected (18). In the Netherlands, several cases of adrenal crisis have been reported by patients to the pharmacovigilance website LAREB (19).

Differences between approved and compounded medications

Approved drugs are manufactured under good manufacturing practice (GMP) regulations that govern the production and testing of pharmaceutical materials. The regulatory agencies regularly inspect pharmaceutical manufacturing facilities to ensure compliance with GMPs. Pharmacies are exempt from GMP regulations and are seldom inspected (20). **Table 1** lists other important differences in the requirements for approved drugs and compounded preparations.

Because there is less assurance that compounded products provide a constant product quality the rules stipulate that a compounded product cannot be prescribed when an approved product is available on the market.

Table 1: Regulatory differences between approved and compounded drugs

Approved drugs	Compounded drugs
Must follow GMP regulations	Exempt from GMP regulation
Efficacy (or bioequivalence) and safety tested	No testing
Retesting of bulk ingredients mandatory	Rely on Certificate of Analysis
Labeling and inserts required and approved	No labelling and information needed
Adverse events reporting mandatory	No adverse event reporting needed

Supply chain interruptions

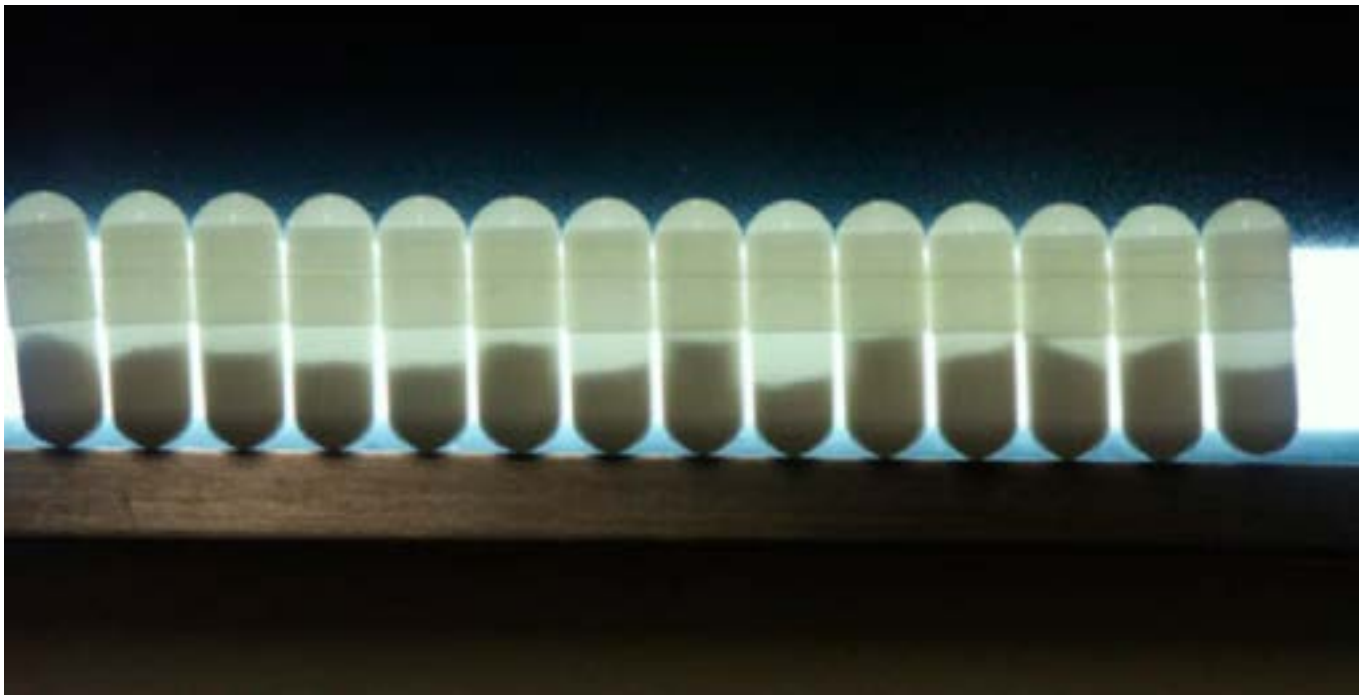
Hydrocortisone and fludrocortisone are essential and life-saving medications and their supply should be guaranteed for patients that need them. However, hydrocortisone and fludrocortisone used for compounding are often produced abroad and shortages have been reported in several countries in recent years (21-23). This brings an additional safety risk to patients with CAH and AI.

New treatment modalities on the horizon

The described safety issues with the current treatment modalities underscore the need for licensed pediatric hydrocortisone formulations. This is also endorsed by a 2017 European Commission report on pediatric medicines that states : "there is a broad consensus that children deserve access to medicines that have been specifically developed and researched for their use "and" crushing adult tablets and using only a portion comes with the risk of inefficacy and/or adverse reactions in children" (24).

At the request of the care platform BijnierNET/AdrenalNET, ACE Pharmaceuticals recently introduced hydrocortisone tablets (Acecort®) of 2, 3 and 10 mg, produced under GMP regulations on the Dutch market the 2 and 3 mg tablets have been registered in the meantime (25). Each tablet strength has a different color to minimize dosing errors and has a neutral taste. The same company also produces GMP fludrocortisone tablets (Fludrace®) of 62,5 microgram, from locally produced fludrocortisone (26). ACE Pharmaceuticals registered both products in Belgium and their market introduction awaits a viable price setting.

Figure 1: A "real world" batch of compounded hydrocortisone capsules dispensed for a child with CAH. Each capsule should contain the same dose, but it is clear that there is great variation in capsule content(13)(reproduced with permission from Uta Neumann).



Hydrocortisone granules (0.5mg, 1mg, 2mg and 5mg) with immediate release and taste masking (Infacort, Alkindi®, Diurnal Pharma) have been approved in Europe in 2018 but are not yet available in Belgium (27).The absorption of Infacort was studied in 24 neonates and small children age 1 day to 6 years with CAH replacing their usual morning dose of hydrocortisone. Serum cortisol levels measured 1hr after dose administration were more than 150 nmol/L in all children, with a geometric mean of 575.8 ± 299.5 nmol/L (28) . Neumann et al treated 18 children (17 with CAH and 1 with congenital hypopituitarism) with Alkindi for up to 2 years. The dose of hydrocortisone was titrated based on salivary 17-OH-progesterone levels as recommended. At the last visit, the hydrocortisone doses were at the lower end of the recommended dose range without any adrenal crises. There were no treatment related severe adverse events and the participants had normal growth trajectories (29). Biopredictive modeling demonstrated that the hydrocortisone granules can be mixed with fruit juices and yoghourt and a pharmacokinetic study in adults confirmed a similar bioavailability when administered either as dry granules or sprinkled on top of soft food such as yoghurt or apple sauce facilitating the administration to young children(30)(31). Alkindi is unfortunately not available in Belgium.

Modified release tablets have been developed to alter the absorption profile of hydrocortisone after administration. Duocort (Plenadren®, Shire/Takeda 5 and 20 mg tablets) combines a slow release core with an immediate release layer of hydrocortisone After ingestion in the morning serum cortisol peaks after 40-50 min and remains detectable during the afternoon and evening . The hydrocortisone profile more closely resembles the physiological profile and allows a once a day administration (32). The lower total cortisol exposure compared to 3 times daily immediate release hydrocortisone tablets, had a less adverse effect on blood pressure and body mass index and improved quality of life in adults (33). A major drawback is the very low hydrocortisone level during the night and early morning which makes it less suitable for patients with CAH.

Chronocort (Efmody®, Diurnal) is designed to have a delayed and sustained release of hydrocortisone (34). The peak levels occur 5 hours after ingestion (35). It is taken in two daily doses and the evening dose generates a hydrocortisone peak in the early morning. In clinical trials in adults, Efmody suppressed ACTH and 17-OH-progesterone levels at a lower daily dose than hydrocortisone (36). A physiologically based pharmacokinetic model showed that the profile in adults and adolescents is identical and the European Medicines Agency therefore licensed its use from age 12 onwards (37). However, Efmody is so far not available on the Belgian market.

Conclusion

The established practice to obtain small hydrocortisone doses for children with CAH by splitting, crushing, dissolving or compounding available tablets is fraud with errors that can result in serious complications. Commercial low dose hydrocortisone and fludrocortisone products, reliably produced under GMP regulations, are urgently needed.

Acknowledgements

I thank Alida Noordzij and Johan G. Beun (BijnierNET/AdrenalNET) for their support in the writing of this manuscript

Disclosure of potential conflicts of interest

Raoul Rooman received an honorarium from ACE Pharmaceuticals to write this manuscript

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Bénéfices des synbiotiques sur les symptômes gastro-intestinaux chez les nourrissons souffrant d'APLV

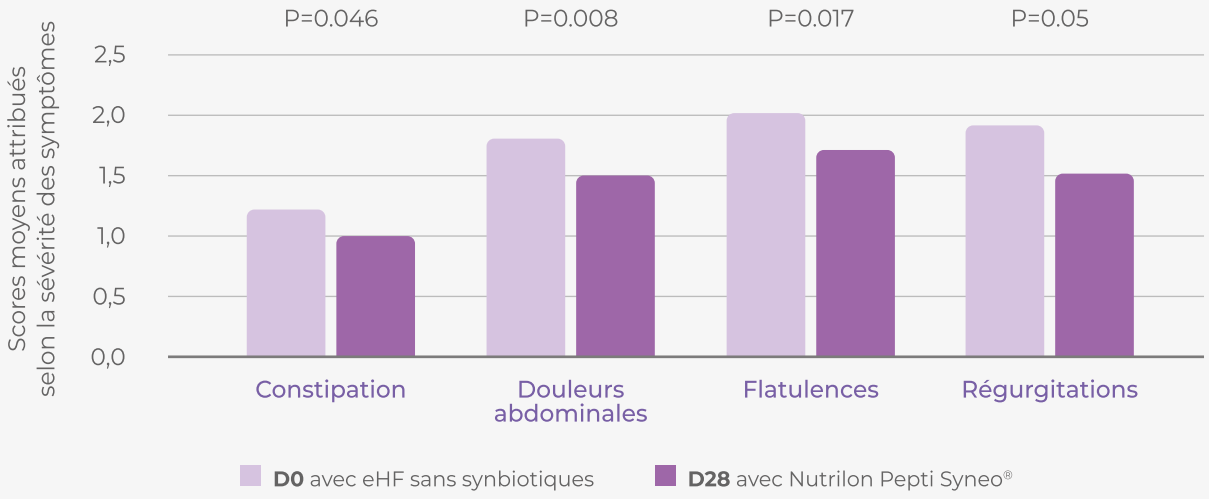
L'allergie aux protéines du lait de vache (APLV) est l'une des allergies alimentaires les plus courantes chez les enfants. Elle est généralement diagnostiquée au cours de la première année de vie. L'APLV est associée à une série de symptômes respiratoires, cutanés et gastro-intestinaux, tels que la constipation ou les douleurs abdominales.[1,2]

La dysbiose intestinale, étroitement liée à l'APLV

Le développement du microbiote intestinal des nourrissons représente une période cruciale, car il affecte la fonction immunitaire et la réponse inflammatoire. Ses altérations peuvent impacter la santé de l'enfant ainsi que sa prédisposition à certaines maladies, plus tard dans la vie. La dysbiose se définit par un déséquilibre du microbiote intestinal. Elle se caractérise par une diversité microbienne plus faible, une présence accrue d'espèces pathogènes (*Clostridia et Coliformes*) et une réduction du nombre d'espèces bénéfiques, telles que les *Bifidobacterium* (spécifiquement, *Bifidobacterium breve* et *Bifidobacterium bifidum*), au sein du microbiote intestinal.[1] Il est bien établi que les nourrissons souffrant d'APLV présentent une dysbiose. Par conséquent, la modification du microbiote intestinal mérite d'être étudiée en tant que stratégie potentielle de gestion de l'APLV.[2]

Figure 1 : Amélioration des scores moyens de sévérité des symptômes gastro-intestinaux au jour 28, comparativement au jour 0.[1,10]

Un effet supérieur dans le soulagement des symptômes gastro-intestinaux



NUTRILON PEPTI SYNEO® SOULAGE SIGNIFICATIVEMENT

✓ Constipation ✓ Douleurs abdominales ✓ Flatulences ✓ Régurgitations

chez les nourissons atteints d'APLV, déjà alimentés avec un eHF

Rééquilibrage du microbiote intestinal

De nombreuses preuves montrent que les composants alimentaires tels que les pré- et probiotiques modulent le microbiote intestinal. Or, le rééquilibrage du microbiote intestinal permet de soulager les symptômes associés à l'atopie.[1,3]

Des analyses récentes[4,5] ont conclu que l'utilisation d'une préparation à base d'acides aminés (AAF) contenant des synbiotiques (prébiotiques et *Bifidobacterium breve* M-16V) peut mener, à un rééquilibrage du microbiote intestinal, associé à une diminution du risque d'infections, d'hospitalisation et de la prise de médicaments.[1,2]

Le *Bifidobacterium breve* M-16V est considéré comme étant une des souches les plus efficaces pour réduire l'inflammation en cas d'allergie.[1,6,7,8] Le *Bifidobacterium breve* M-16V (probiotiques) fait partie d'un mélange synbiotique spécifique avec des galacto-oligosaccharides (scGOS) à chaîne courte et des fructo-oligosaccharides (lcFOS) à chaîne longue (prébiotiques). Ces composants pré- et probiotiques ont notamment été sélectionnées en raison de leur capacité synbiotique, c'est-à-dire leur capacité à amplifier les bénéfices observés séparément avec les pré- et probiotiques. Cette association a démontré une amélioration significative des espèces bénéfiques du microbiote intestinal et des biomarqueurs de la santé intestinale, une réduction du nombre d'infections, de la prise de médicaments anti-infectieux, et des problèmes gastro-intestinaux chez les nourrissons atteints d'APLV.[1,9]

Un hydrolysat extensif de protéines contenant un mélange de synbiotiques, une association efficace

Les avantages de cette association d'un hydrolysat extensif de protéines avec un mélange de synbiotiques ont été confirmés dans une étude publiée en 2022, prospective, longitudinale et multicentrique durant laquelle des nourrissons souffrant d'APLV ont reçu, pendant 28 jours, une eHF à base de lactosérum (SeHF) contenant des synbiotiques : des scGOS/lcFOS et du *Bifidobacterium breve* M-16V.[1]

Impact de la SeHF sur les symptômes gastro-intestinaux

L'évaluation des troubles gastro-intestinaux constituait le résultat primaire. À la fin de l'essai, des améliorations significatives de la gravité des douleurs abdominales, des éructations, des flatulences et de la constipation ont été observées (Figure 1).
Aucun symptôme grave n'a été enregistré (contre 27 % pour l'ensemble des symptômes, au départ). Les autres symptômes gastro-intestinaux (vomissements, nausées, ballonnements et diarrhée), étaient majoritairement absents/légers au départ et sont restés inchangés ($p > 0,05$, NS).[1]

En outre, en termes de résultats secondaires, une amélioration significative ($p < 0,05$) de la rhinite (41 %), des démangeaisons oculaires (73 %), ainsi que de la dermatite atopique chez les nourrissons souffrant de symptômes sévères à l'inclusion (réduction du PO- SCORAD© : 34,7- 18,2 ($p = 0,003$)) a été observée au fil du temps. L'analyse a également révélé une augmentation significative de toutes les mesures anthropométriques absolues et de la croissance relative pour les paramètres évalués (longueur, poids et circonférence de la tête). De même, une augmentation de la qualité de vie des soignants a été observée (score du questionnaire FAQL-PB : +26,7 %, $p < 0,05$). Les visites à l'hôpital et la prise de médicaments ont diminué de manière significative (-1,61 et -2,23, respectivement, $p < 0,005$) au cours des 6 mois après l'initiation de la SeHF.[1]

La dysbiose intestinale est fréquente dans l'APLV et constitue un enjeu majeur pour la prise en charge des nourrissons. La modulation du microbiote intestinal, notamment avec l'apport de pré- et probiotiques, s'inscrit dans une démarche de gestion active de l'APLV et se base sur des preuves solides. Les résultats de cette étude pilote démontrent que les SeHF contenant des synbiotiques améliorent significativement les symptômes gastro-intestinaux des nourrissons atteints d'APLV, et constituent une valeur ajoutée par rapport aux eHF sans synbiotiques. Cette étude s'ajoute aux preuves robustes soutenant les avantages de l'utilisation de formules hypoallergéniques contenant des synbiotiques pour la gestion de l'APLV.[1,2]

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Prophylactic azithromycin in pre-schoolers with chronic respiratory symptoms: a longitudinal survey

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Keywords

azithromycin: macrolide; child; respiratory exacerbations; disease progression

Abstract

Objectives: Long-term prophylactic azithromycin (AZM) is used in daily practice in children with chronic respiratory symptoms because of its immunomodulatory and anti-inflammatory properties. No substantial scientific evidence is available for the population without underlying condition. The objective of this study is to test if prophylactic azithromycin has an effect on respiratory outcomes in preschool non-cystic fibrosis (CF) children with chronic respiratory symptoms. As secondary outcomes the evolution of body mass index Z-scores, as a measure of overall health, and respiratory tract cultures were studied.

Study design: Non-CF-children between one and six years old with chronic respiratory symptoms, treated with prophylactic AZM were included in this retrospective analysis. The number of respiratory exacerbations and body mass index Z-scores one year before and one year after the start of AZM were compared. The nature of the respiratory disease, reason for discontinuing AZM and respiratory microbiological profiles were studied.

Results: 35 children were included. A significant reduction in the number of exacerbations was observed, both in the entire population (p=0.00004) and in the subgroup of children (n=14) without an underlying condition (p=0.002). No significant difference in body mass index Z-scores and respiratory microbiological profiles was seen. However, a non-significant increase (p=0.188) in macrolide-resistant bacterial infections was observed.

Conclusion: Prophylactic AZM may decrease the number of exacerbations in non-CF pre-schoolers with chronic respiratory symptoms. However, the increased bacterial macrolide-resistance requires further evaluation.

Introduction

The management of chronic respiratory symptoms, especially in young children, remains a challenge. Symptoms are often difficult to control and response to treatment varies from child to child. Chronic respiratory symptoms include recurrent wheeze and persistent productive and non-productive cough. They can occur after a single lower respiratory tract infection, after multiple viral infections, or present as result of an underlying asthma, Protracted Bacterial Bronchitis (PBB) or other chronic lung diseases such as cystic fibrosis (CF), primary ciliary dyskinesia (PCD) or immune deficiencies (1,2). If not treated properly, chronic inflammation and obstruction of the lower airways can cause destruction of the airway wall, resulting in irreversible dilated bronchi, better known as bronchiectasis (3). Conditions as CF, PCD, immune deficiency, but also recurrent PBB increase the risk of bronchiectasis in children (2).

In recent years, macrolides have been used, not only for their antimicrobial effects but also for their anti-inflammatory and immunomodulatory properties. Macrolides reduce airway mucus secretion and viscosity, downregulate the inflammatory cascade and reduce pro-inflammatory cytokine production (4,5). In vitro, broad-spectrum anti-viral properties have been demonstrated. Azithromycin (AZM) in particular shows promising results for clinical efficacy (5).

The purpose of this survey is to investigate if prophylactic AZM in preschool children with chronic respiratory symptoms has an effect on: the number of respiratory exacerbations, the body mass index (BMI) Z-score (standard deviation scores) which is an indicator of the general health status of the child, and the microbiological profile of the respiratory cultures.

Methods

Study design

This retrospective, longitudinal, single-centre, observational cohort study was conducted in the KidZ Health Castle of the UZ Brussel. Approval of the ethics committee of our institution was obtained on the 8th of November 2017 (reference number 2017-321).

Study population

Children from one to six years old treated for minimal 3 months with prophylactic AZM for chronic respiratory symptoms (between January 2011 and November 2016) were included in the analysis. These children were followed at the paediatric pulmonology department at least every three months and more frequently if needed.

Chronic respiratory symptoms were defined as wheezing, dyspnoea, cough or bronchorrhea over a period of minimum three months in one year, despite maximal conventional therapy (inhaled corticosteroids, bronchodilators, antibiotic courses, physiotherapy) (6). Prophylactic AZM treatment was defined as the administration of AZM during at least a period of three entire months with a dosage of 10mg/kg/day three consecutive days a week.

Exclusion criteria were: AZM treatment with the intention to cure an acute infection such as whooping cough or Mycoplasma infections and children with CF or an immunodeficiency in whom treatment with IV or SC immunoglobulins was started during the year before or the year after the start of prophylactic AZM therapy.

Children without CF but with an underlying condition such as PCD, bronchopulmonary dysplasia, significant anatomical abnormalities, immune deficiencies or with proven structural lung damage as for example non-CF bronchiectasis were not excluded from analysis.

Patients who met the inclusion criteria were identified by electronic and manual searches in the electronic medical records of the years 2011 until 2016. They were divided in two groups: children with chronic respiratory symptoms/unremitting wheeze without a known underlying aetiology and children with a known underlying condition as described earlier.

The duration of the AZM treatment and the reason for discontinuing AZM were included in the analysis. Analysis occurred for a one-year period before and a one-year period after prophylactic AZM therapy.

As primary outcome, the number of respiratory exacerbations during the year before (Y-1) and the year after (Y+1) the start of AZM were determined.

An exacerbation was defined as an increase in signs and symptoms (wheezing, dyspnoea, cough, bronchorrhea) with, according to the treating physician, need for oral antibiotics or need for hospitalisation.

As secondary outcome, the BMI Z-score was recorded just before and one year after the start of AZM. BMI Z-scores were calculated using the software WHO Anthro and WHO Anthro Plus (7,8).

Fungal and bacterial cultures of respiratory tract secretions were performed on an occasional basis: cough swab performed by the physiotherapist (9), sputum if possible and bronchoalveolar lavage (BAL) in case a bronchoscopy was required for diagnostic or therapeutic purpose (atelectasis). The microbiological profile from the respiratory cultures were compared between Y-1 and Y+1.

Statistical analyses were performed using IBM SPSS Statistics version 23. The number of respiratory exacerbations were analysed using a Wilcoxon signed rank test. Fisher's exact test was applied for the results of cultures for respiratory tract secretions. BMI Z-scores were analysed using a paired t-test. A p-value <0.05 was accepted as statistically significant.

Results

Study population (Table 1)

Thirty-five patients (54% males mean age: four years) met the inclusion criteria. Of these, 14 (40%) had chronic respiratory symptoms or unremitting wheeze without an underlying condition whereas 21 (60%) had a known underlying condition (bronchiectasis 6/21, PCD 7/21, immune deficiency 6/21, bronchopulmonary dysplasia 1/21, anatomical abnormality 1/21).

Treatment duration with prophylactic AZM varies between three months and 12 months, with an The main reason for discontinuing AZM was a favourable clinical course (12/35; 34%). AZM was discontinued during the summer period in 6/35 patients (17%) and was not restarted after the summer or because the summer period concurred with the 12 month follow-up after the start of AZM. In 2/35 (6%) patients AZM was stopped because of insufficient clinical benefit. Only one patient had therapy related adverse events (gastrointestinal complaints), requiring discontinuation of AZM. In one patient, AZM was stopped because of refusal by the child (taste problem). (Table 2)

Respiratory exacerbations (Table 3, Figure 1, Figure 2)

In Y-1, the cohort had a median of three respiratory exacerbations (p25=2; p75=5). Of the 124 respiratory exacerbations for the whole group, 82 (66%) were treated at home with antibiotics and 42 (34%) required hospitalization.

In Y+1, a median of one respiratory exacerbation (p25=0; p75=2) was found. Of the 53 respiratory exacerbations found, 36 (68%) were treated at home with antibiotics and 17 (32%) required hospitalization.

In Y+1 significantly fewer respiratory exacerbations were observed (p=0.00004) compared to Y-1, with a median difference of two exacerbations. In Y+1, 26 patients (74%) had fewer respiratory exacerbations than in Y-1. In five patients (14%) the number of respiratory exacerbations did not change and in four patients (11%) more respiratory exacerbations were noted in Y+1 compared to Y-1.

A significant decrease (p=0.007) in de number of hospitalisations was noted with a median of one hospitalization in Y-1 compared to a median of zero hospitalizations in Y+1.

In the subgroup without an underlying condition (n:14) a decrease in the median number of exacerbations (p=0.002) was seen, with a median of 3.5 exacerbations in Y-1 and a median of 0.5 exacerbations in Y+1. The number of hospitalizations in this subgroup decreased by approximately one hospitalization a year (p=0.007).

In the subgroup with a known underlying condition (n:21), a significant decrease in the total number of exacerbations was seen (from median 3 exacerbations per year to two exacerbations per year, p=0.007). However, no difference in the number of hospitalizations (p=0.231) was noted. (Table 3)

BMI Z-scores

Before the start of AZM, the average BMI Z-score was 0.38. One year later, the average BMI Z-score remained unchanged (0.40)(p=0.873).

Respiratory microbiological profile (Figure 3)

Twenty patients (54%) had cultures from respiratory tract secretions taken the year before as well as during the year after the start of AZM. Only these patients were used for further analyses. The number of cultures taken in Y-1 (n=80) did not significantly differ from Y+1 (n=71) (p=0.450).

The most common pathogen in Y-1 was Haemophilus influenzae, which was found in 26 of the 80 cultures (32.5%). In Y+1, H. influenzae was cultured 16 times (22.5%) (p = 0.205). Moraxella catarrhalis was isolated in Y-1 in 5% of the cultures. In Y+1, M. catarrhalis was no longer found (p = 0.123). No significant difference was found in any of the other most frequent respiratory (bacterial et fungal) pathogens.

In the total study population, only one macrolide resistant bacterium (Streptococcus pneumonia) was cultured in Y-1. In Y+1, an increase in macrolide resistance to four isolates was observed, two macrolide-resistant Staphylococcus aureus and two macrolide-resistant S. pneumoniae strains, however these are considered non-significant (p = 0.188).

Discussion

This longitudinal retrospective analysis shows that prophylactic AZM in non-CF preschool children with chronic respiratory symptoms results in a significant reduction of respiratory exacerbations. Our data also show a significant decrease in the number of hospitalizations after prophylactic AZM.

Similar results on pulmonary exacerbations in different patient populations were reported.

One randomized controlled trial (RCT) on long-term AZM use in preschool children with non-CF bronchiectasis, aged one to eight years old, showed a decrease of exacerbations in the AZM group compared to placebo (10). Comparable results were seen in adults with bronchiectasis (11, 12).

Long-term AZM use in patients, aged 7 to 50 years old, with PCD showed a 50% reduction in pulmonary exacerbations (13). Also in CF patients prophylactic AZM use demonstrated a decrease in pulmonary exacerbations (14-16).

Abovementioned studies report all similar findings regarding pulmonary exacerbations. It is important to notice that these studies only included patients with an underlying condition. Our analysis is therefore unique as it also includes preschool children without an underlying condition. Subanalysis of our data showed that in otherwise healthy children, AZM could also reduce the number of hospitalisations. Earlier studies did not support this finding. A possible explanation for this discrepancy is that children with an underlying disease may be hospitalised more frequently as a preventive measure.

Long-term AZM therapy is in most of the cases well tolerated, which is in line with previous publications (10, 11, 16, 17).

Despite its positive effect on pulmonary exacerbations, no change in BMI Z-scores was observed before and during/after AZM treatment. Importantly, mean BMI Z-scores before treatment were not so poor in our cohort. Only a study in CF-children could demonstrate an increase in weight and BMI in the AZM group compared to placebo (16).

Respiratory microbiological profiles showed no difference in the respiratory pathogens nor in the number of positive cultures before and after prophylactic AZM use. An increase, though non-significant, in macrolide-resistant S. aureus and S. pneumoniae isolates was seen. Isolation of an increased number of macrolide-resistant strains, especially S. aureus, has also been observed in CF-children under prophylactic AZM. (14,18)

In areas where prophylactic AZM is widely used, such as East Asia, bacterial resistance is dramatically high (19). This possible risk of antibiotic resistance shows that long-term prophylactic AZM use is not without risks and needs to be limited. New non-antibiotic macrolides, with immunomod-

Table 1: Clinical characteristics before the start of azithromycin

	Patients (n=35)
Age (mean ± SD) (years)	3.95 ± 1.73
Male (n, %)	19 (54%)
Female (n, %)	16 (46%)
Nature of the respiratory condition (n, %)	
1. Chronic respiratory symptoms/unremitting wheeze	14 (40%)
2. Known underlying condition	21 (60%)
BMI Z-score (mean ± SD)	0.38 ± 1.18
Median number of exacerbations the previous year	3

Abbreviations: SD: standard deviation; BMI: body mass index

Table 2: Duration and reason for discontinuing azithromycin

Duration of azithromycin (mean ± SD) (months)	9 ± 2.9
Reason for discontinuing azithromycin (n, %)	
No discontinuation within 12 months	13 (37%)
Favorable evolution	12 (34%)
Summer months	6 (17%)
Insufficient effect	2 (6%)
Refusal by child	1 (3%)
Side effects	1 (3%)

Abbreviations: SD: standard deviation

Table 3: Exacerbations (median, [p25;p75])

	Y-1	Y+1	p-value
Total study population (n=35)			
Total number of exacerbations	3 [2;5]	1 [0;2]	0.00004
At home oral antibiotics	2 [1;3]	1 [0;1]	0.0003
Hospitalization intravenous antibiotics	1 [0;1]	0 [0;0]	0.008
Hospitalization oral antibiotics	0 [0;0]	0 [0;0]	0.317
Hospitalization without antibiotics	0 [0;0]	0 [0;0]	0.595
Total number of hospitalizations	1 [0;2]	0 [0;1]	0.007
Chronic respiratory symptoms (n=14)			
Total number of exacerbations	3.5 [2.75;5.25]	0.5 [0;1]	0.002
At home oral antibiotics	2 [1;4.25]	0 [0;1]	0.012
Hospitalization intravenous antibiotics	1 [0;2]	0 [0;0.25]	0.030
Hospitalization oral antibiotics	0 [0;0]	0 [0;0]	1.000
Hospitalization without antibiotics	0 [0;0]	0 [0;0]	0.157
Total number of hospitalizations	1 [0.75;2]	0 [0;0.25]	0.007
Known underlying condition (n=21)			
Total number of exacerbations	3 [1;5]	2 [0.5;2.5]	0.007
At home oral antibiotics	2 [1;3]	1 [0;2]	0.011
Hospitalization intravenous antibiotics	1 [0;1]	0 [0;0.5]	0.128
Hospitalization oral antibiotics	0 [0;0]	0 [0;0]	0.317
Hospitalization without antibiotics	0 [0;0]	0 [0;0]	1.000
Total number of hospitalizations	1 [0;1]	0 [0;1]	0.231

Figure 1: Respiratory exacerbations in total study population
Boxplot with median, p25, p75 and outliners of the total number of exacerbations, the total number of hospitalizations and the exacerbations treated by oral antibiotics at home, Y-1 compared to Y+1. A significant reduction in the total number of exacerbations (p=0.00004), in the total number of hospitalizations (p=0.007) and in the exacerbations treated at home with oral antibiotics (p=0.0003) is seen.

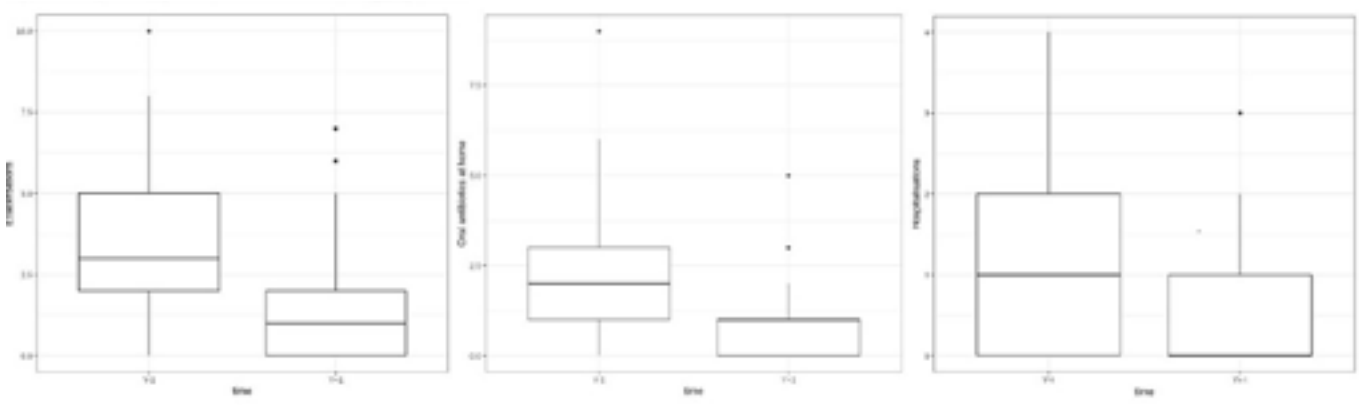


Figure 2: Exacerbations per subject
Difference in the number of exacerbations per subject, Y-1 (begin of arrow) compared to Y+1 (end of arrow).

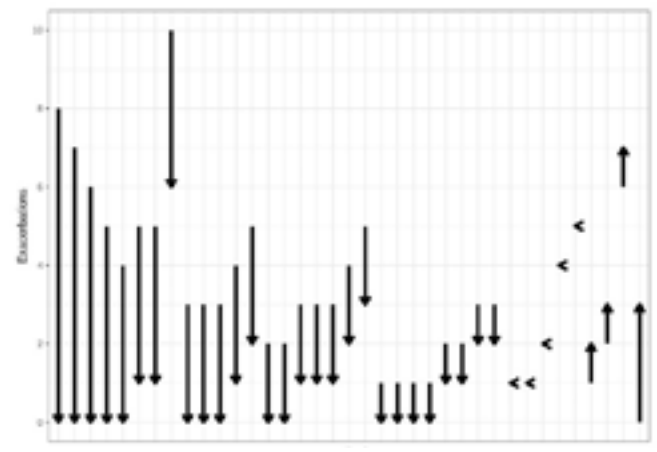
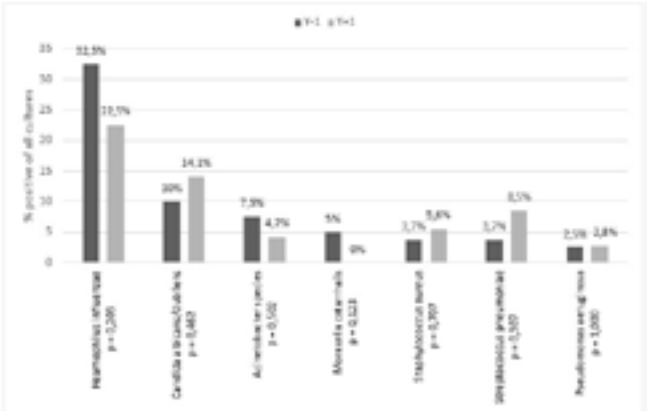


Figure 3: Respiratory microbiological profile
Respiratory microbiological profile of the study population, Y-1 compared to Y+1. The percentage of positive cultures of the total number of respiratory cultures is shown for the most frequent pathogens.



ulatory and anti-inflammatory properties, but without antibacterial activity are likely to gain more attention in the future (20). Studies to determine whether these non-antibiotic macrolides have an equal benefit as prophylactic AZM for chronic respiratory symptoms have not yet been undertaken.

Despite some original findings, limitations of our analysis must be quoted as the study design (retrospective study), the small study population and the age category of the population. As we did not perform a case-control study we could not demonstrate that the reduction in the number of exacerbations is not related to the normal evolution of respiratory infections in the child at this age. This is particularly important in children with persistent wheezing, since it is a condition characterized by a spontaneous resolution with age. Another bias due to the unstandardized (retrospective) follow-up of the patients may have had an effect on the results. Also due to the retrospective nature of our study, the effect of AZM on daily chronic symptoms and quality of life could not be investigated.

Additionally, we could not use a better outcome measure than 'respiratory exacerbation'. The age group of the study population limits the use of more objective parameters like spirometry. In preschool children with CF the use of lung clearance index (LCI) has shown to be a good parameter to measure exacerbations and its effect on treatment (21). However, LCI measurements are not routinely performed in this age group. A prospective double-blind RCT using LCI as an outcome could overcome some limitations in this report.

Conclusion

We demonstrate a beneficial effect of the prophylactic use of AZM in preschool children with chronic respiratory symptoms irresponsive to conventional treatment. A clinically relevant and significant decrease in the number of respiratory exacerbations is observed, as well as a reduction in the hospitalizations related to these exacerbations. This finding may be of interest for paediatricians who are facing therapeutic dilemma's in treating pre-schoolers with recurrent respiratory symptoms. However, the increased bacterial macrolide-resistance requires further evaluation. Before concluding that long-term AZM in children with recurrent respiratory symptoms should become a standard of care, larger and placebo-controlled studies will have to be conducted. Meanwhile, starting prophylactic AZM in a child with chronic respiratory symptoms should be a well-considered decision, after a thorough evaluation including diagnostics for underlying conditions and taking in account possible side effects.

Disclosure

The authors declare that there is no conflict of interest.

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

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

PID2942 – September 2022. / Septembre 2022. V.U./R.E. : S. Alexander, Nestlé Belgilux SA/NV, Rue de Birminghamstraat 221 - 1070 Bruxelles/Brussel, BCE/KBO 0402.231.383.

Presentation, diagnosis and management of congenital long-segment tracheal stenosis: a single-centre experience.

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Keywords

congenital tracheal stenosis, long-segment tracheal stenosis, optical coherence tomography, slide tracheoplasty

Abstract

Congenital long-segment tracheal stenosis (CLSTS) is a rare airway malformation, caused by absence of the pars membranacea in part of the trachea.

The aim of this study is to provide our single-centre experience with CLSTS and a literature review on clinical presentation, diagnostic workup, treatment methods and outcome. Special attention will be given to the relatively new technique for anatomic visualisation, using anatomic optical coherence tomography (aOCT).

Methods: Single-centre retrospective cohort study of children diagnosed with CLSTS and treated at the University Hospital of Leuven between January 2010 and July 2021. A literature review was performed using PubMed.

Results: Six children were included, age at diagnosis between 11 days and 12 years. Three children had associated pulmonary artery sling and one had unilateral agenesis of the lung, both requiring additional surgery. Presenting symptoms were mainly stridor and respiratory insufficiency during lower airway infections. Diagnosis was made by a combination of bronchoscopy, chest CT, bronchography and aOCT. Four patients have been treated surgically and one is awaiting surgery; one was treated conservatively. One patient suffered from important cardiac ischemia postoperatively. Three patients required balloon dilation and one required additional pericardial patch tracheoplasty. Follow-up after diagnosis ranged between two and eight years. One patient still has stridor with exercise, two still have intermittent stridor with respiratory tract infections after surgery.

Interpretation: Outcome in our study population was consistent with data from the literature. CLSTS requires a dedicated and multidisciplinary approach to obtain optimal results. aOCT has proven its added value for diagnosis.

Introduction

Congenital tracheal stenosis is a rare type of airway malformation in children, occurring in one in 64500 live births and is caused by absence of the pars membranacea of one or more tracheal rings resulting in complete cartilaginous rings (1). Depending on the percentage of trachea involved, it is classified as congenital short-segment (< 30-50% of tracheal length) or congenital long-segment tracheal stenosis (CLSTS) (> 30-50% of tracheal length) (1,2,3). The presence and severity of symptoms is dependent on the diameter of the lumen: symptoms are often only present when there is more than 50% narrowing of the lumen, and symptoms at rest when there is more than 75% narrowing (1,4). Stenosis is generally considered severe when the diameter of the lumen is ≤ 3 mm, and in that situation surgical intervention is required in most cases (5). Resection with an end-to-end anastomosis of the trachea is not advisable if more than 30% of the trachea is affected, as the risk for dehiscence becomes too high due to traction on the anastomosis (2,6,7).

For surgical treatment of CLSTS slide tracheoplasty is the preferred technique. After sternotomy, the anterior trachea is denuded to identify the entire length of the stenosis by inspection and placement of markers visualised by combined bronchoscopy. The trachea is then completely mobilised until normal trachea and/or bronchi are seen. In the absence of combined cardiovascular repairs, normothermic cardiopulmonary bypass is started and the trachea is transected halfway through the stenotic part, in combination with a posterior vertical incision in the proximal part of the stenotic trachea and an anterior vertical incision in the distal part. Subsequently, an oblique sliding anastomosis is performed with interrupted mattress polydioxanone (PDS) sutures, resulting in a doubling of the diameter of the lumen and a shortening of the trachea by half the length of the stenotic part (3).

This technique remains a challenging intervention with need for cardiopulmonary bypass, high morbidity and a mortality rate between 5% and 12% in larger studies (1,3,4,8). Therefore, this treatment should be performed by an experienced multidisciplinary team through centralisation of care. For countries with a smaller population, collaboration with an experienced foreign team can be an added value.

Materials and methods

All patients under the age of 18 years diagnosed with and/or treated for CLSTS at the University Hospital of Leuven between January 2010 and July 2021 were included and data were collected retrospectively from their medical files and pseudonymized. The study was approved by the local ethics committee (MP016961).

A literature review was conducted using PubMed with search terms 'congenital tracheal stenosis', 'slide tracheoplasty' and 'optical coherence tomography', reviewing relevant articles written in English from the year 2000 onwards and their most important references.

Results

Literature review

Clinical presentation

The clinical presentation of CLSTS is variable: some children present with severe neonatal respiratory distress, stridor and/or cyanotic spells, others develop symptoms of stridor and respiratory insufficiency at the time of an airway infection during infancy. Some present in adolescence or adulthood with exercise-induced stridor, respiratory distress or cyanosis (1,4).

A high proportion (70-90%) of patients have associated congenital malformations: cardiovascular anomalies in 70% of the cases and other congenital malformations such as respiratory and gastro-intestinal tract, anorectal, renal and skeletal abnormalities in 40% (1,3,4,8). In around 6% of cases, these malformations are part of a VACTERL/VATER association (1). The most frequently associated malformation is a pulmonary artery sling (abnormal position of the left pulmonary artery arising from the right pulmonary artery and going to the left lung between the trachea and oesophagus), present in 50% of patients (1,3,8). Important are also additional respiratory tract malformations such as abnormal bronchial arborisation (30-35%) and unilateral agenesis of the lung (7-9%) (1,3,7).

Diagnostic workup

It is suggested in the literature that diagnostic workup for CLSTS should include contrast computed tomography (CT) of the thorax as well as bronchoscopy with bronchography and anatomic optical coherence tomography (aOCT) (1,3). Which of these investigations is performed first, depends on the presenting symptoms and the availability of the techniques.

However, both CT and bronchoscopy have important limitations. Due to the dynamic nature of the stenosis and the difficulties getting detailed images in young dyspnoeic children, CT may underestimate the degree of luminal narrowing and does not allow a proper evaluation of the tracheobronchial cartilaginous structures (4). Bronchoscopy on the other hand provides limited possibilities for obtaining quantitative measurements and the distal airways can be inaccessible with the bronchoscope when severe proximal stenosis is present. The addition of bronchography to the evaluation will accommodate to some of these limitations (1). It can visualize the anatomy of the respiratory tract distal to the stenosis even if the bronchoscope cannot pass it, which is especially useful to map the anatomy of the main stem bronchi to detect possible involvement in the stenotic disease. While ventilated using a laryngeal mask, a guide wire is placed through the vocal cords by bronchoscopy guidance. Then, a small catheter is placed over the wire and the wire is removed. Contrast is injected through the catheter and fluoroscopy images are made in 2 planes.

aOCT is a more recently implemented light-based imaging modality, using a technique similar to ultrasound, but overcoming several limitations of a soundwave-based method such as its inability to image through air-filled spaces and its suboptimal spatial resolution (9). The minuscule probe (as small as 0.36 mm) can be inserted through the bronchoscope to acquire a series of real-time ultra-high detail (spatial resolution 20 µm) cross-sectional and longitudinal images of the airway and the tracheobronchial wall with the possibility of quantitative measurement of the luminal diameter and characterisation of surrounding tissue, and allowing three-dimensional reconstruction of the images (fly-through) (3). In addition to bronchoscopy and bronchography, aOCT thus provides more information about the degree and characteristics of the stenosis and the airways distal to the stenosis and can confirm the presence of complete cartilaginous rings (see figure 1b) (3,7).

Finally, to screen for associated anomalies, a thorough history and physical examination as well as a cardiac ultrasound are indispensable to detect associated abnormalities (4).

Treatment and outcome

The treatment strategy is highly dependent on the severity of symptoms, individual patient characteristics and associated malformations and should therefore always be discussed multidisciplinary (1,4). Patients with mild symptoms, mostly presenting at a later age, can sometimes be treated conservatively (4).

In the past, several treatment options have been used when surgery is needed. Insertion of a cartilaginous, pericardial or donor homograft and tracheal stenting resulted in major complications including increased risk of granulation tissue formation, restenosis, anastomotic leakage and graft necrosis, and are therefore only recommended as a salvage technique (1,2,4,7).

Slide tracheoplasty is currently the method of choice, as the risk of complications is significantly lower than with other methods (1,4). The technique can be adapted in case of abnormal arborization or bronchial stenotic disease, although some complex cases will require a different technique, and can be combined with cardiovascular surgery (4,7). Tracheal growth after tracheoplasty was found to be satisfactory (4,8,10). Still, it remains a complex and invasive procedure with need for cardiopulmonary bypass and mortality rates between 5 and 12% in larger studies (1,3,4,8).

The optimal age for surgery is thought to be between 10 and 24 months (8). Patients presenting in the neonatal period are often the most difficult to treat, sometimes even requiring extracorporeal membrane oxygenation prior to surgery, and have a significantly higher risk of mortality (4,8). From a surgical point of view, older children and adolescents also pose an important challenge: mobilization of the trachea becomes more difficult, the stenotic part is longer with more risk of traction on the suture, shortening of the trachea caused by the slide tracheoplasty causes more anatomic and functional issues and operation time is longer (8).

Restenosis with need for balloon dilation and/or CO_2 lasering occurs in 33-48% of children after slide tracheoplasty, need for additional stenting or pericardial patch insertion in around 21% (1,3,4). Other frequent postoperative complications are residual tracheomalacia in 20-25% and granulation tissue formation (1,3). One study showed an overall incidence of granulation tissue formation of 13.6% in their study population, with a significant decrease from 31.6% in the first three years to 8.1% in the following three years. It also demonstrated an age-related difference with significantly less granulation tissue formation when surgery was performed between 10 and 24 months of age (5.7%) compared to surgery before 10 months (45.5%) or after 24 months (17.6%) (8).

Less frequent complications include anastomotic dehiscence resulting in mediastinitis or pneumothorax, -mediastinum or -pericardium, laryngeal nerve paralysis, chylothorax, pulmonary hypertension and swallowing difficulties, occurring in 2-4% of patients each (1,3,4,8).

Patient characteristics

Five patients were diagnosed with CLSTS at our institution during the inclusion period and one was referred after diagnosis elsewhere. The patient characteristics, treatment and outcome were summarized in table 1 and 2.

Clinical presentation and diagnosis

The age at diagnosis ranged from 11 days to 12 years and was mostly dependent on the severity of symptoms. One patient presented in the neonatal period with recurrent episodes of severe desaturation, four patients presented during infancy or early childhood with respiratory insufficiency during viral airway infections, and one had similar but less severe symptomatology in childhood, but was only diagnosed during adolescence because of exercise-induced stridor.

Four patients had associated congenital malformations. Three patients had a pulmonary artery sling, one of which had several other cardiovascular anomalies. One patient had an atrial septal defect. Two patients had skeletal anomalies, one had a unilateral agenesis of the lung and one patient was born with an imperforate anus.

Diagnostic workup

Diagnosis was made in all patients by a combination of contrast chest CT and bronchoscopy with bronchography. The added value of bronchography was illustrated in several cases, providing better visualization of the respiratory tract anatomy distal to a particularly narrow stenosis and getting more detailed information about the anatomy of the left main stem bronchus in the patient with unilateral agenesis of the lung. The two most recently diagnosed patients were also examined with aOCT during diagnostic

Table 1: Patient characteristics and treatment method (M= male, F= female)

Patient	Sex	Age at diagnosis (days or months)	Presenting symptoms	Associated congenital malformations	Minimal luminal diameter (mm)	Treatment method	Age at surgical intervention (months)
1	M	34 months	Persistent stridor, respiratory insufficiency with airway infections	Pulmonary artery sling, persistent left vena cava superior Dysmorphism Skeletal anomalies	2.9-3.5	Slide tracheoplasty and pulmonary artery reimplantation	52 months
2	F	11 days	Neonatal severe desaturations Respiratory insufficiency with airway infections	Agenesis left lung Skeletal anomalies Accessory spleen ASD	1.7	Tissue expander Awaiting slide tracheoplasty	Tissue expander at 12 months
3	F	60 days	Respiratory insufficiency with infections	Pulmonary artery sling Anal imperforation	3	Slide tracheoplasty and pulmonary artery reimplantation	18 months
4	F	4 months	Respiratory insufficiency with infections	Pulmonary artery sling	1.3	Slide tracheoplasty and pulmonary artery reimplantation	7 months
5	F	73 months	Almost constant stridor, exercise-induced dyspnoea, frequent lower airway infections, feeding difficulties	/	3	Slide tracheoplasty Pericardial patch tracheoplasty Awaiting correction of a tracheal wall dehiscence	117 months 123 months
6	F	148 months	Respiratory distress with infections Exercise-induced stridor and respiratory distress	/	9	Conservative Avoid intense physical activity	/

Table 2: Postoperative course, need for additional interventions and outcome (ETT = endotracheal tube; ECMO = extracorporeal membrane oxygenation; ASD = atrial septal defect)

Patient	Age at surgery (months)	Treatment method	Days of invasive airway management (ETT)	Days of hospitalization at paediatric ICU postoperatively including day of surgery	Need for additional interventions after surgical repair	Morbidity and outcome after surgery
1	52	Slide tracheoplasty and pulmonary artery re-implantation	19	68	3 balloon dilations	Severe cardiac ischemia with impaired cardiac function requiring ECMO, partially recovered over time Mild dyspnoea with exercise No hospitalizations for respiratory tract infections
2	12	Insertion tissue expander	1	6	Awaits slide tracheoplasty	8 days after surgery reduction of volume of tissue expander because of suspicion of compression on surrounding tissues Since diagnosis 3 hospitalizations because of respiratory insufficiency during airway infections
3	18	Slide tracheoplasty and pulmonary artery re-implantation	4	11	/	Residual tracheo/bronchomalacia Recurrent episodes of respiratory distress/insufficiency with respiratory infections, factor asthma Need for maintenance treatment with azithromycin and inhaled corticosteroids during winter months 1 hospitalization because of respiratory insufficiency
4	7	Slide tracheoplasty and pulmonary artery re-implantation	1	11	2 balloon dilations	Mild residual tracheo- and bronchomalacia with residual stridor mostly with exercise and infections Need for maintenance therapy with azithromycin prophylaxis and inhaled corticosteroids during winter months 3 hospitalizations because of respiratory insufficiency
5	117	Slide tracheoplasty	4	5	16 balloon dilations 2x CO_2 lasering Patch tracheoplasty 6 months after slide tracheoplasty	Residual severe stenosis with tracheal wall dehiscence Dyspnoea and stridor with moderate exercise Intermittent dysphagia and subjective swallowing difficulties
6	/	No surgical intervention	/	/	/	/

bronchoscopy, which provided important additional information about the degree and length of stenosis in both cases.

Figure 1a shows the round aspect of the trachea during bronchoscopy. Figure 1b-e show aOCT images of the same patient. Figure 2A shows a CT reconstruction of the trachea of patient 3 before tracheoplasty.

Treatment and outcome

Four patients have been treated surgically with slide tracheoplasty, three of them combined with pulmonary artery reimplantation. Table 2 shows treatment and outcome results of our study population. Age at surgical repair ranged between 7 and 117 months. Need for ventilatory support varied between 24 hours and 19 days, including the day of surgery. The patients were discharged from the paediatric ICU after 5 to 68 days. One patient was readmitted to the paediatric ICU shortly after discharge because of acute deterioration caused by restenosis. One patient with combined CLSTS and pulmonary agenesis was still awaiting slide tracheoplasty after initial insertion of a tissue expander in the left thoracic cage at the end of the study period. One patient was not treated surgically because of limited symptoms at the age of 12 years. All treatment strategies were discussed multidisciplinary between the paediatric pulmonologists and cardiothoracic surgeons of our institution, with additional advice of other health care professionals depending on the individual characteristics of the cases, as well as consultation of highly experienced international colleagues.

Figure 3 shows the evolution of the tracheal diameter in patient 3 on bronchography before and after tracheoplasty.

One patient suffered from severe perioperative cardiac ischemia, with prolonged need for extracorporeal membrane oxygenation and residual left ventricular dysfunction. Three patients required postoperative balloon dilations because of restenosis or excessive granuloma formation. One of these patients required additional CO_2 lasering and a pericardial patch tracheoplasty because of insufficient effect of minimally invasive treatment of the restenosis. Follow-up investigations showed tracheal wall dehiscence with the formation of a fibrotic band, for which redo surgery will be planned.

Three patients had residual tracheo- and/or bronchomalacia. One patient suffered from intermittent dysphagia and subjective swallowing difficulties. Two patients experience intermittent respiratory distress or stridor with respiratory tract infections. No other complications were observed in the study population, nor was there any mortality perioperatively or during follow-up. In July 2021, the length of follow-up after surgery ranged between 34 months and 6 years. For privacy reasons in this small patient population, the length of follow-up is not reported for each individual case.

Discussion

Our patient series, albeit small, illustrates the broad range of signs and symptoms that can be caused by CLSTS, and therefore the different ways these patients present in clinical practice. Some children were referred because of unexplained respiratory symptoms, some already with a tentative diagnosis of tracheal stenosis elsewhere, others after diagnosis of a pulmonary artery sling, and one child because of difficult intubation. Also the broad range of age at diagnosis and presenting symptoms is consistent with data from the literature, as is the rate of associated congenital anomalies (1,3,4,8). In our population, four out of six patients (66%) had associated congenital anomalies, three of which (50%) had a pulmonary artery sling and three of which had involvement of other organ systems: two (33%) had skeletal abnormalities, one (16%) had unilateral agenesis of the lung and one (16%) had an anal imperforation. These rates correlate well with the results from literature.

Most frequently, the diagnosis of CLSTS is made unsuspectedly when investigations are issued because of respiratory symptoms. When stridor is a prominent symptom, laryngotracheobronchoscopy is often the investigation of choice, as it can identify a wide variety of possible causes, like laryngo- and tracheomalacia, subglottic stenosis, airway haemangiomas, foreign body aspiration and vocal cord paralysis. When investigations are issued because of recurrent or persistent respiratory infections or when a vascular ring is suspected, a tentative diagnosis is often made by contrast enhanced chest CT.

In our study, all patients underwent a contrast enhanced chest CT as well as a bronchoscopy with bronchography. The two most recently diagnosed patients were also examined with aOCT during diagnostic bronchoscopy. As the measurement is three-dimensional and real-time, both longitudinal and transverse measurements can be performed. It also has the best resolution to evaluate the presence of complete cartilaginous tracheal rings compared to bronchoscopy or CT, as it can differentiate between different types of tissue underneath the surface of the respiratory epithelium. Additional advantages are the lack of radiation exposure and the possibility to use it during diagnostic bronchoscopy.

When decisions are made concerning surgical intervention, several factors must be taken into account. The surgery is complex, needs cardiopulmonary bypass and has a mortality rate between 5 and 12% (1,3,4,8). Therefore, only patients with severe symptoms are eligible for tracheoplasty and the decision should always be made by a multidisciplinary team. The ideal age for surgical repair is estimated between 10 and 24 months of age (8). When surgery is deemed necessary, slide tracheoplasty is the best technique available, as it has several advantages compared to other surgical strategies and a lower risk of complications like restenosis and excessive granulation tissue formation (1,4). The original blood supply to the tracheal wall is preserved, the doubling of the diameter of the trachea leads to quadrupling of the cross-sectional area and the suture is not circular, thereby decreasing the risk of restenosis. Also, the length of the trachea is only diminished by half the length of the stenosis, which makes it possible to correct even very long segments of diseased trachea, with sufficient tracheal growth afterwards (8).

The decision to treat conservatively should also be discussed multidisciplinarily and close follow-up with the possibility of reconsideration of surgical treatment should be organized if needed.

The most frequently occurring complications after surgery are restenosis and granulation tissue formation, which we encountered in three out of four operated patients, with one patient suffering from persistent granulation tissue formation requiring more than three interventions. A large single-centre study showed a need for additional endoscopic interventions of 48% (3). This high rate of reintervention is an important aspect to keep in mind, both to give patients and parents realistic expectations and to understand the need for intensive follow-up, especially in the first weeks to months after surgery. Whether reintervention is necessary or not, many children have residual symptoms after surgery. Three out of four operated patients had some degree of postoperative airway malacia, compared to 20-25% in larger studies, possibly partially because of different definitions of the degree of airway collapse needed for the diagnosis (1,3). Our patient with recurrent need for endoscopic interventions was known to develop excessive granulation tissue formation and keloid formation on her skin after surgery, possibly illustrating an underlying vulnerability to complications due to improper healing of damaged tissues. It could therefore partially explain her complicated postoperative course. Another possible explanation for the increased need for additional endoscopic interventions when comparing to the literature is the small size of the study population, making it more prone to skewing of results.

Our patients are currently 34 months, 46 months, 47 months, and 6 years in follow-up after slide tracheoplasty and all but one experience none to mild symptoms in daily life. One patient suffers from recurrent granulation tissue formation and still experiences respiratory distress with exercise and intermittent swallowing difficulties. Two patients experience respiratory distress and more frequent need of antibiotic treatment with respiratory tract infections, for which they are treated with inhaled corticosteroids, prophylactic antibiotics and respiratory physiotherapy during winter months. The larger studies available in literature do not clearly describe the frequency of this symptom in their population.

The patient who was treated conservatively, was referred to her own primary care physician for follow-up, with no new referrals to a paediatric pulmonologist or hospitalisations since diagnosis. One patient was still awaiting further treatment at the end of the study period and has been hospitalized

Figure 1a: shows the round aspect of the trachea during bronchoscopy, resulting from the absence of the pars membranacea, in patient 5.

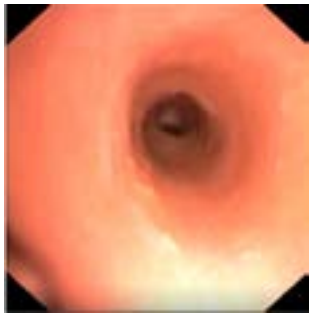
Figure 1b: shows an aOCT image of the same patient, with transverse imaging of the trachea in the top half of the figure and the longitudinal image in the lower half. Note the black circle on the transverse image (yellow arrow) illustrating how aOCT confirmed the presence and extent of complete tracheal rings. The green arrow shows at which point the transverse image was made. Moreover, the diameter and minimal cross-sectional area can be measured along the entire length of the trachea.

Figure 1c: shows the same image as figure 1b, with the gray circles visualising the edges of the cartilaginous ring.

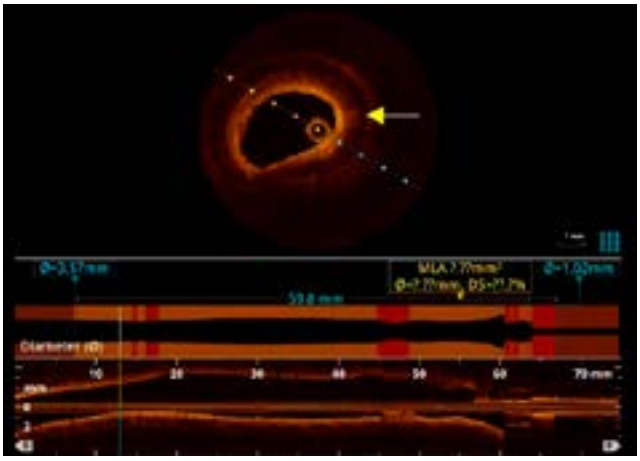
Figure 1d shows a normal part of the trachea with incomplete cartilaginous ring.

Figure 1e: shows a transverse image of the trachea in between two cartilaginous rings.

1a



1a



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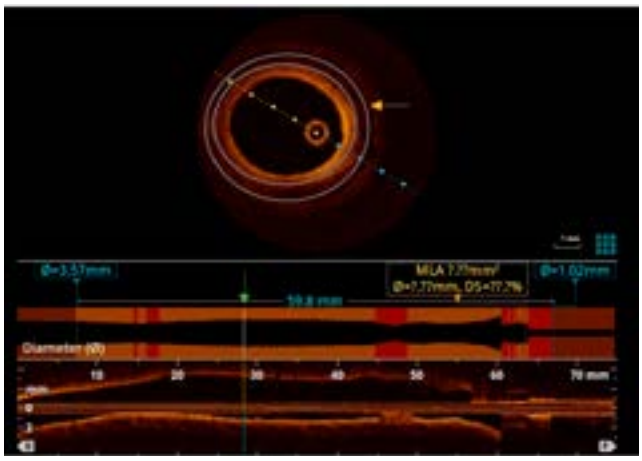
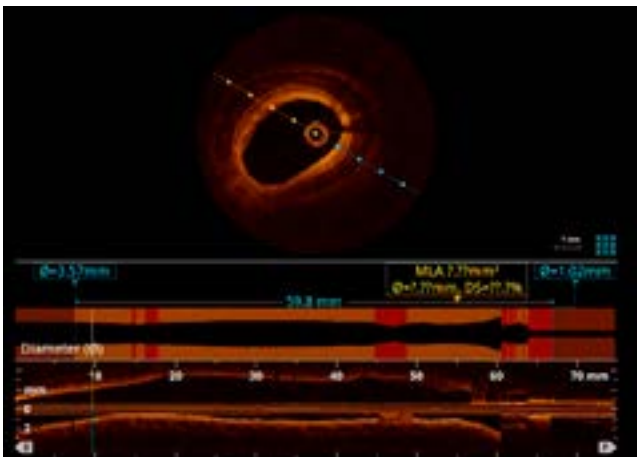


1c



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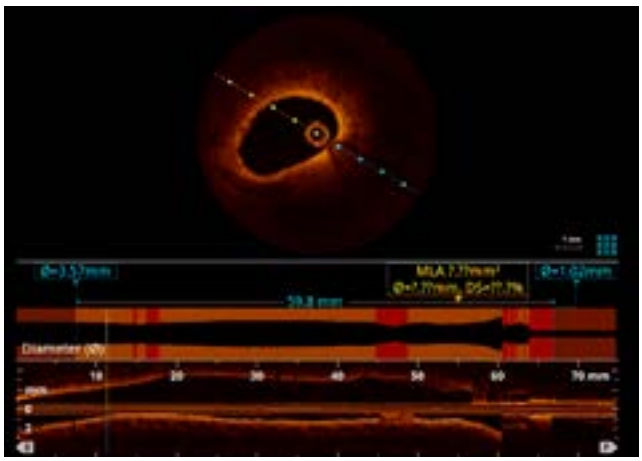
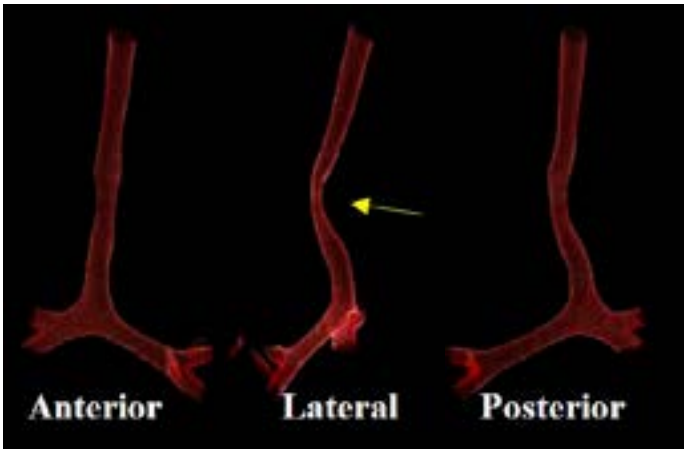


Figure 2a: shows a CT reconstruction of the trachea of patient 3 before tracheoplasty. The lateral view (middle panel) shows the external compression on the trachea from a pulmonary artery sling (yellow arrow).

Figure 2b: shows a transverse CT image showing both the narrow trachea (yellow arrow) and the presence of the pulmonary artery sling (red arrow) crossing the distal trachea posteriorly.

2a



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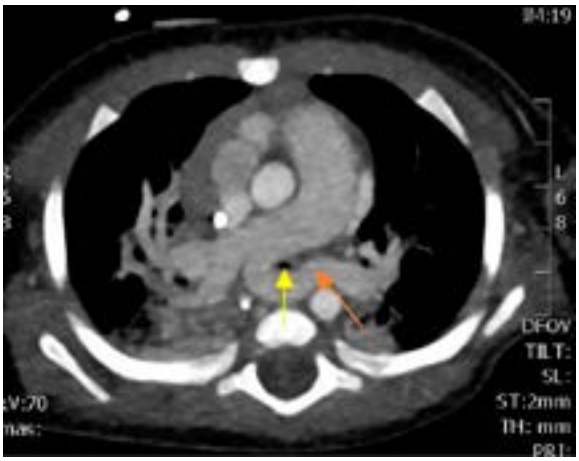
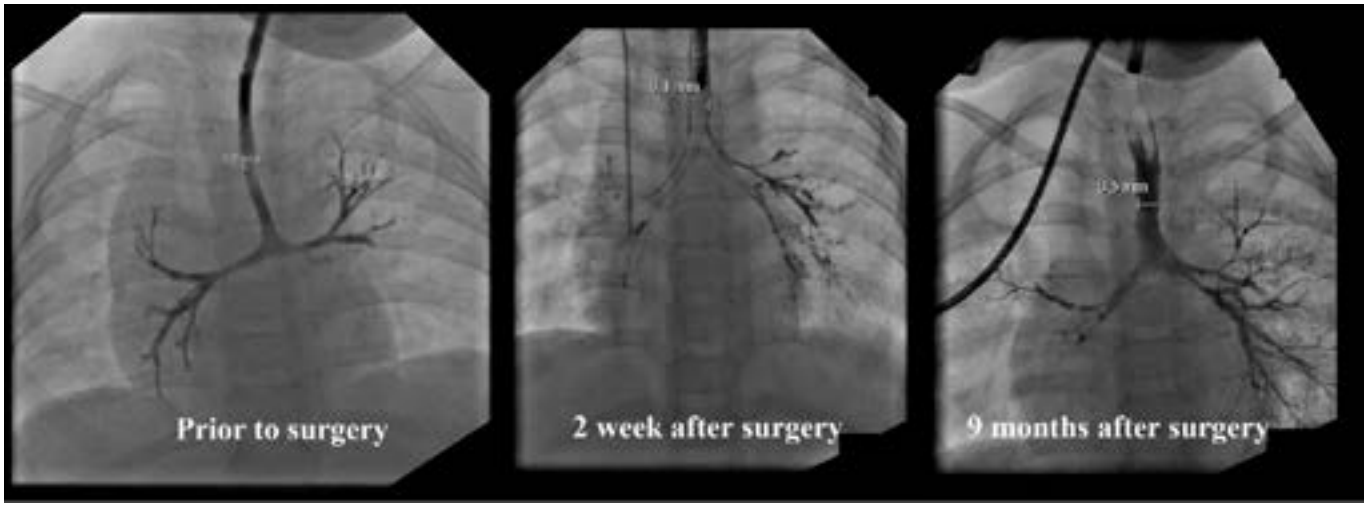


Figure 3: shows the evolution of the tracheal diameter in patient 3 on bronchography before (3.5 mm), 2 weeks after (8.1 mm) and 9 months after tracheoplasty (8.5 mm).



three times because of respiratory insufficiency with respiratory infections since diagnosis. During follow-up, some tracheal growth was seen with the narrowest luminal diameter of 3 mm at 32 months of age. Her slide tracheoplasty was eventually performed at the age of 41 months and was successful without perioperative complications. She was extubated the day after surgery and was hospitalized at the paediatric ICU for 8 days including day of surgery. So far, one bronchoscopic dilatation was performed during follow-up.

Strengths and limitations

Limitations of the study are the retrospective nature of the data collection and the small patient population. On the other hand, this is the first Belgian study about this topic and includes all patients with CLSTS diagnosed and/or treated at our hospital. Follow-up data are available for all but one patient. Another asset of the study is the use of aOCT in the most recently diagnosed patients, an investigational tool that allows more detailed visualisation of the stenosis when added to the diagnostic workup.

Conclusion

CLSTS is a rare but potentially life-threatening condition requiring an experienced multidisciplinary team of paediatric pulmonologists, cardiologists, cardiothoracic surgeons, ear-nose-throat surgeons, intensive care specialists and specialized paramedic healthcare professionals for diagnosis, treatment and follow-up. Dedicated care for these patients is important to optimize quality of care. Diagnosis is made by CT and bronchoscopy, with additional information gathered by bronchography and aOCT. Treatment with slide tracheoplasty is the method of choice when conservative treatment is insufficient. The most frequent complications are restenosis, granuloma formation and residual airway malacia.

This study displays our experience with the diagnosis and treatment of CLSTS, with no mortality, perioperative cardiac ischemia in one patient and need for postoperative interventions because of restenosis in three patients, of which one needed redo tracheoplasty with a pericardial patch.

Acknowledgements

The authors thank the Great Ormond Street Hospital tracheal team for their dedicated support, in particular doctor Nagarajan Muthialu.

Conflicts of Interest

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

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Consensus recommendations for pediatric fluid resuscitation in Belgium

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Keywords

children, resuscitation, fluid bolus, isotonic fluid, balanced fluid.

Abstract

Fluid resuscitation is an important part of pediatric critical care therapy and shock treatment. To date, there are no Belgian guidelines on this topic. As children's (patho) physiology differs from adults, existing recommendations for adults should not be carelessly adapted. Although no superiority has been found for a specific type of fluid, strong recommendations against dextrose-containing fluids, hypotonic fluids and starch-based colloids have been uniformly accepted due to their safety profile and/or cost. There is also considerable debate about rate and volume of fluid boluses needed during resuscitation where a distinction is often made based on access to pediatric critical care units. As these are widely accessible in Belgium, we do not make this distinction but advocate early contact or transfer.

If a child requires fluid resuscitation, we recommend using boluses of 10 ml/kg balanced crystalloids with careful reassessment after each bolus to assess fluid responsiveness as well as signs of fluid overload. The choice should be tailored to the child´s underlying illness since specific situations may necessitate specific treatment, as is shown in the proposed algorithm.

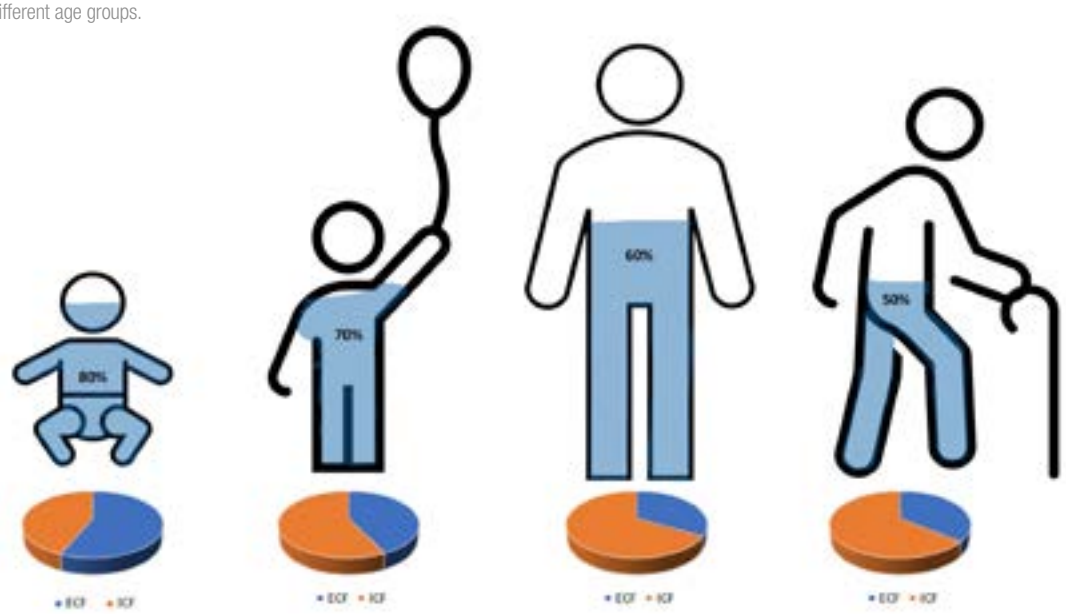
Introduction

Resuscitation is described as supporting or taking over the vital functions in a critically ill patient. One of the most important examples in the acute medical management of critically ill children is fluid resuscitation. Fluid deficit may be elicited by excessive fluid loss, insufficient fluid intake, a combination of both, or fluid redistribution. The most common cause in children is hypovolemia due to gastro-enteritis, but also sepsis, where shock can be multifactorial in etiology. Quick fluid resuscitation remains a key component in both children and adults although the pediatric recommendations were attenuated after publication of the FEAST trial reporting increased mortality (1, 2).

For fluid resuscitation three types of fluids can be used: crystalloids, colloids or blood products. Besides in the setting of trauma, there is no conclusive evidence on superiority of one type of fluid, although there seems to be increasing data in favor of using balanced crystalloids (3). A lot of ambiguity remains regarding the desired quantity or speed of infusion as well.

No guidelines exist on this topic in Belgium. In this narrative review, we give an overview of existing literature and guide the Belgian pediatrician through the plethora of fluids by means of a simple algorithm. We aim to harmonize the quality of fluid resuscitation in children in accordance with the current state of the art.

Figure 1: Percentage of total body water (number) changes with development. The pie charts at the bottom show the variation in extracellular fluid (ECF) and intracellular fluid (ICF) in different age groups.



Background

Essential physiological concepts

Children are not just small adults, a mantra that is also reflected when it comes to fluids. On average, water represents >80% of the body mass in newborns. It decreases during the first two years of life and at a slower rate during childhood to reach an adult level of 60-65% by the age of puberty (figure 1). In adults up to 70% of total body water (TBW) is intracellular fluid (ICF), the remaining being extracellular fluid (ECF), composed of interstitial fluid and plasma. In children these percentages vary with age, e.g., newborns have relatively more ECF (45% of their weight) which has implications in the dosage of water-soluble drugs.

Body water balance is defined as the equilibrium between body water gains and body water losses. In normal conditions, water is mostly lost through urine at a rate of at least 2 ml/kg/hr in neonates and 1-2 ml/kg/hr in children, as opposed to 0.5-1 ml/kg/hr in adults. Water is excreted through other routes as well, such as the skin, respiratory tract and stool. These losses, difficult to quantify, are bundled under the name insensible losses (ISL). Children's ISL are higher than those of adults since their respiratory rate is higher as is their body surface area to body mass ratio. In children up to 2 years of age, ISL can even be twice as high.

Thirst and hormonal mechanisms are both responsible for maintaining a proper water balance, where kidneys play a pivotal role in regulating both volume and composition of the ECF. To achieve this function, they are influenced by several hormones, especially anti-diuretic hormone (ADH), but also aldosterone and natriuretic factor. In normal circumstances, a water deficit increases plasma osmolality which stimulates the osmo-receptors in the hypothalamus. Drinking is stimulated and release of ADH increases, promoting water-reabsorption at the distal part of the nephron, leading to smaller volumes of concentrated urine. In the event of a water excess, the opposite effect will result in a decrease in intake and the production of larger volumes of diluted urine.

Fluid dysregulation during illness

Young children are more susceptible to dehydration due to a relatively larger TBW, renal immaturity, and inability to meet their needs independently. As dehydration progresses, hypovolemia ensues. If not corrected in a timely fashion, inadequate tissue perfusion and ischemic end-organ damage, the hallmark of shock, follow.

Shock can generally be defined as an acute dysfunction in which the circulatory system fails to provide adequate oxygen and nutrients to meet the metabolic demands of vital organs. Shock can and does exist without hypotension, especially in children. Although all types of shock encompass some degree of absolute or relative hypovolemia, they can be classified according to their underlying pathophysiological mechanism (Table 1). Nevertheless, the cause of shock can be multifactorial, e.g., in septic shock, hypovolemia, cardiac dysfunction and abnormal vascular tone frequently occur simultaneously. The most common cause of shock in children remains hypovolemia.

Table 1: Types and causes of shock.

Categories	Aetiology	Cause
Hypovolaemic	Loss of fluid	Haemorrhage, gastroenteritis, volvulus, burns, peritonitis, diabetic ketoacidosis
Distributive	Vessel abnormality	Septicaemia, anaphylaxis, vasodilating drugs, spinal cord injury
Cardiogenic	Pump failure	Arrhythmias, cardiomyopathy, myocarditis, valvular disease, myocardial contusion
Obstructive	Flow restriction	Tension-pneumothorax, cardiac tamponade, pulmonary embolism

Without prompt intervention, shock inevitably leads to multi-organ failure and ultimately death, making early recognition and appropriate therapy vital. A developing shock can clinically present with altered mental status, tachypnea, tachycardia, delayed capillary refill time (CRT), cool or sometimes warm extremities and clammy mottled skin. The variety and combination of symptoms, or the lack thereof, can be misleading and a high level of suspicion should be maintained during assessment. The World Health Organization defines pediatric shock when the following criteria are met: cold extremities with CRT greater than 3 seconds and weak, fast pulse (4).

Tonicity and balance

Tonicity details the concentration of non-penetrating solutes as compared to plasma and describes the effect intravenous (IV) fluids have on the osmolality of the ECF (table 2). Administration of hypotonic fluids decreases it, causing an influx of water into the cells. Hypertonic fluids such as NaCl 3%, force water out of the cells. Isotonic fluids will cause no osmotic driving force, cells will neither shrink nor swell. Although Dextrose 5% is an iso-osmolar solution, once infused its sugar breaks down and is transported intracellularly, leading to an in vivo hypotonic solution.

Table 2: Tonicity and its effect on extracellular fluid (ECF).

Type of fluid	Effect on extracellular fluid
Hypotonic · Dextrose 5-10% · Glucion 5-10%® · Glu 2,5%/ NaCl 0,45% (1/2-1/2) · Glu 3.3%/ NaCl 0,3% (2/3-1/3)	Decreases osmolality and ECF
Isotonic · NaCl 0,9% · Plasma-Lyte® · Hartmann's solution®	No effect
Hypertonic · NaCl 3% · NaCl 5%	Increases osmolality and ECF

Different fluids have different therapeutic targets.

- Isotonic fluids are typically employed both for *fluid resuscitation* (to correct an acute intravascular fluid deficit), and for *fluid replacement* of extracellular losses which cannot be compensated by oral fluid intake alone.
- Hypotonic fluids were historically used as *maintenance fluids* since they generate an osmotic driving force allowing water to move intracellularly, intended to replace water and electrolyte needs due to ISL and diuresis. Their use recently became the topic of intense debate.
- Hypertonic fluids are specifically used to decrease intracranial pressure (ICP) in children with impending herniation, or to correct severe hyponatremia.

Balanced solutions are isotonic fluids with an electrolyte composition which closely mimics plasma levels. Consequently, they maintain electrical neutrality with a total amount of free dissolved cations equal to that of free dissolved anions (figure 2). Most available fluids achieve electrical neutrality through added organic anions such as acetate or lactate (which rapidly metabolize to the anion bicarbonate) (table 3). In contrast, NaCl 0.9% contains a supra-physiological concentration of Cl^-, leading to a strong ion difference (SID or the difference between the cations (mainly Na^+) and anions (mainly Cl^-)) of zero, far beyond normal values (25-35 mEq/L). Addition of NaCl 0.9% to plasma will decrease plasma SID and therefore directly and independently decrease plasma pH leading to a hyperchloremic metabolic acidosis. In addition to acidosis, hyperchloremia alone is linked to renal injury: it reduces renal blood flow, causes renal vasoconstriction and reduces the glomerular filtration rate. Although other mechanisms may exist, most studies suggest the use of chloride-rich fluids is related to worse renal outcomes (3, 5).

Crystalloid versus colloid, a dying debate?

Both crystalloids and colloids are plasma volume expanders aiming at re-

Table 3: Content of fluids used in resuscitation.

	Plasma (ECF)	Isotonic non-balanced crystalloid	Isotonic Balanced crystalloid		Colloid				
		NaCl 0.9%	**Hartmann's solution®**	**Plasma-Lyte®**	**Albumin 5%**	**Gelofusine®**	**Geloplasma®**	**Voluven®**	**Volulyte 6%®**
Osmolarity (mOsm/l)	291	308	273	296	255	308		308	286
Na^+ (mmol/l)	135-145	154	130-131	140	130-160	154	150	154	137
K^+ (mmol/l)	4-5	0	4-5	5	< 2	0	5	0/0	4
Cl^-(mmol/l)	94-111	154	109	98	105-137	120	100	154	110
Ca^{++}(mmol/l)	2.2-2.6	0	1.5	0					
Bicarbonate (mmol/l)	23-27	0	0	0	0	0	0	0	0
Lactate (mmol/l)	1-2	0	28-29	0	0	0	30	0	34
Acetate (mmol/l)	0	0	0	27	0	0	0	0	0
Gluconate (mmol/l)	0	0	0	23	0	0	0	0	0
Octanoate (mmol/l)	0	0	0	0	32	0	0	0	0
Na^+-caprylate (mmol/g alb)					0.08	0	0	0	0
SID	± 35	0	±22	±42	Variable	±34	±54	0	±34

solving a depleted circulating volume. *Crystalloids* contain water-soluble electrolytes and non-electrolytes (e.g., dextrose), and lack proteins and insoluble molecules. They are classified by tonicity and whether they are balanced or not. Examples of crystalloids often used during resuscitation are NaCl 0.9%, Plasma-Lyte® and Lactated Ringer's® or Hartmann's solution®. Ringer's original saline solution was invented in the early 1880's by Sydney Ringer. In the 1930's, Hartmann added lactate for the purpose of treating acidosis, since lactate mitigates changes in pH by acting as a buffer for acid: Ringer's lactate® or Hartmann's solution® was born. *Colloids* are heterogeneous mixtures where the dispersed particles are intermediate in size between those of a solution (very small particles) and a suspension (large non-dissolving particles). Examples of colloids are 5-20% Albumin, gelatin-based fluids (Gelofuscine®, Geloplasma®), dextran or hydroxyethyl starch-based fluids (Volulyte®, Voluven® or HAES-steril®).

Since crystalloids contain small particles, they diffuse more readily into the interstitial space, thus greater volumes might be needed to expand the vascular space with a risk of edema. The bigger molecules of colloids remain in the intravascular space longer, which could theoretically favor fluid reabsorption into the plasma, reducing the risk of volume overload. Also, colloids could hypothetically account for less pulmonary edema by keeping a higher plasma oncotic pressure through creating less dilutional hyponatremia. Extensive research has been done to support this theoretical advantage of colloids during resuscitation, but literature remains inconclusive. Notably, a Cochrane review in 2018 showed no difference in survival or hospitalization (6). When using higher volumes of colloids (>15 ml/kg) in patients with severe sepsis, mortality was even increased. Also the renewed model of the endothelial glycocalyx has provided us with a better understanding of endothelial permeability, disproving the theoretical advantage of colloids (7).

In addition, colloids are more expensive, have a risk of anaphylaxis and some are unsuitable for vegetarian patients. Crystalloids are inexpensive and non-allergenic.

Fluid resuscitation 2.0

What?

A general advice advocating isotonic crystalloids was issued by the National Institute for Health and Care Excellence (NICE), the American Academy of Pediatrics (AAP) and the European Resuscitation Council (ERC) (3, 8, 9). We follow their advice.

Shock is not one entity but the end stage of many different pathologies. Hence, treatment should be based on the underlying etiology, pathophysiology, age, context, comorbidities and available resources. Nevertheless, some general remarks and a practical approach regarding fluid resuscitation can be advocated (Figure 3).

Figure 2: Plasma electro-neutrality with strong anions left and strong cations right. (SID = Strong ion difference, composed of weaker anions, meanly bicarbonate, albumin and phosphates).

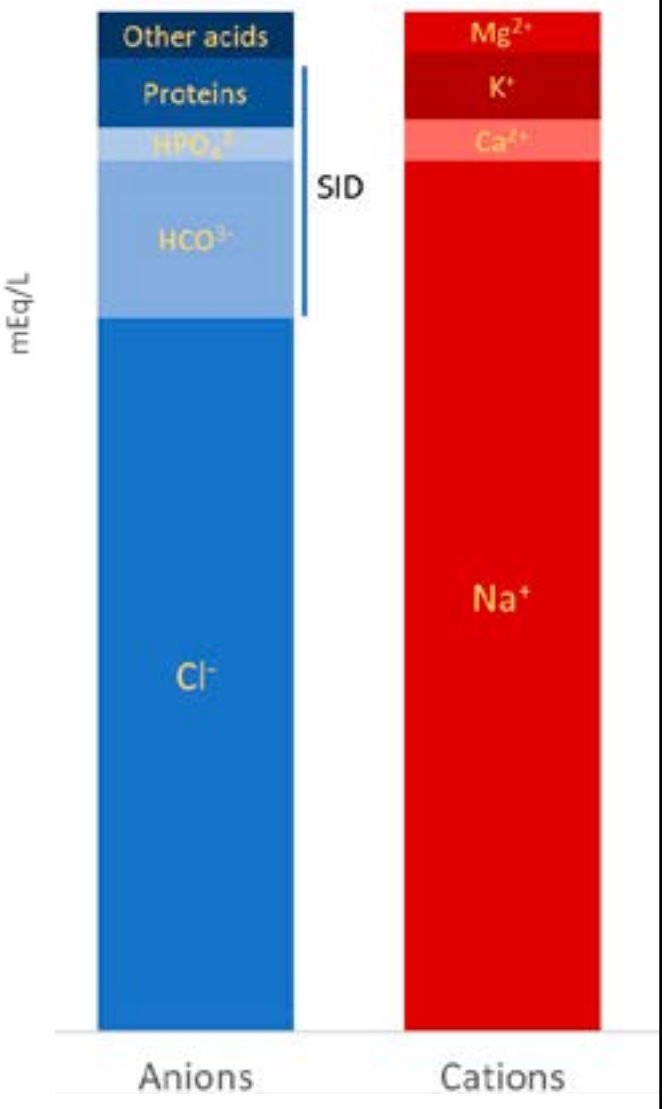
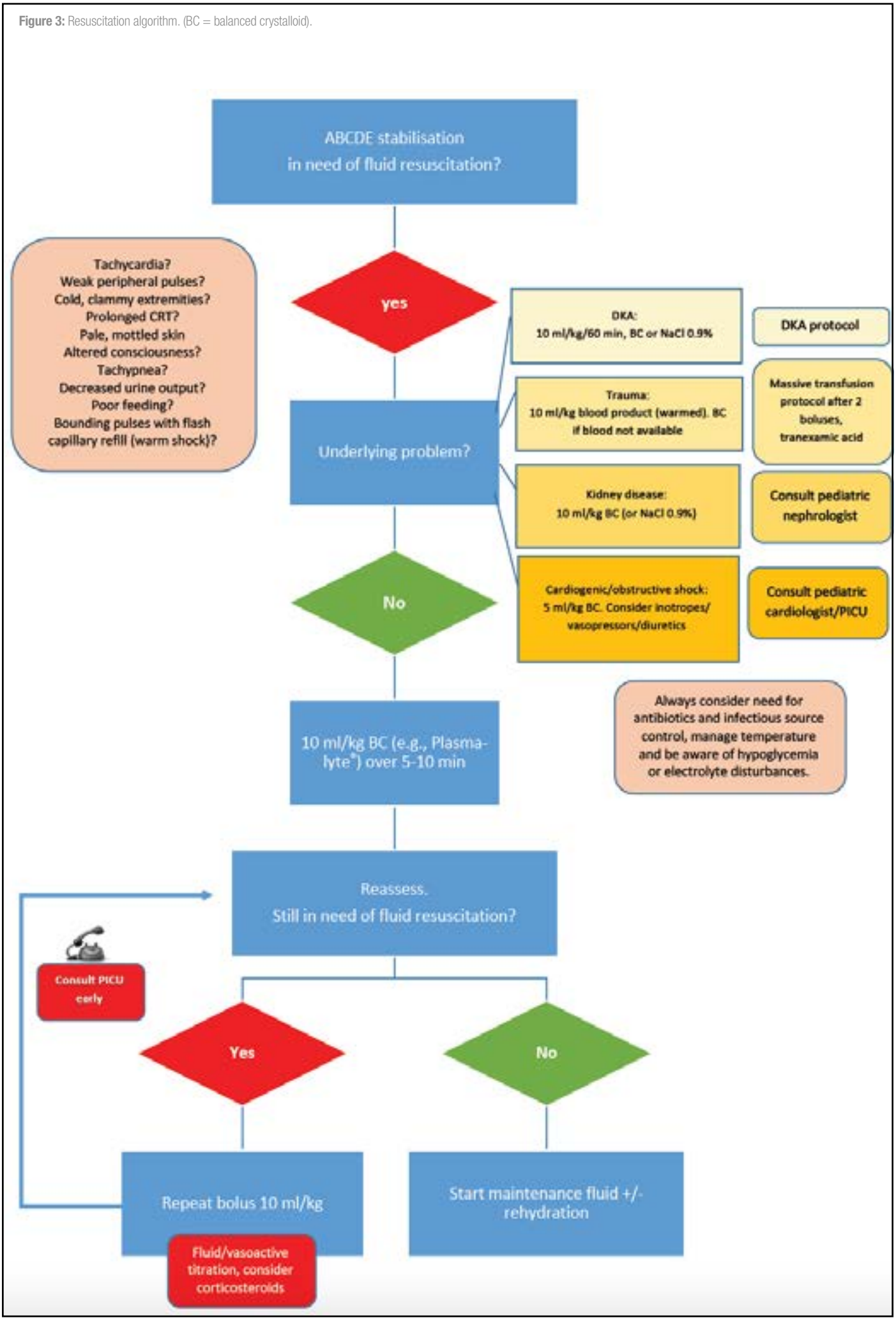


Figure 3: Resuscitation algorithm. (BC = balanced crystalloid).



In general, *crystalloids* are often preferred because they are effective, safer, cheaper and widely available. However, a few exceptions exist: dengue or cerebral malaria might benefit from early use of albumin as a resuscitation fluid, and albumin can be used as a second line option following crystalloids during pediatric shock (8, 10). Other *colloids* no longer have a place in resuscitation due to their safety profile and cost (6).

Dextrose-containing crystalloids are also not to be used during resuscitation, as they greatly worsen the neurologic outcome due to hyperglycemia (11). The dangers of *hypotonic fluids* in resuscitation are as well known, although unfortunately resuscitation with these fluids still occurs (12). A rapid fall in serum sodium level reduces plasma osmolality which causes water to shift intracellularly in the brain parenchyma leading to edema and hyponatremic encephalopathy associated with a mortality of 34% (13). Children are at higher risk than adults as they develop hyponatremic encephalopathy on higher plasma sodium levels. Moreover, due to a high brain/skull ratio and because children's brains contain more water, there is a greater risk of brain herniation. Hypotonic solutions should thus be avoided. Current data on *hypertonic solutions* in resuscitation are limited but they could cause pontine demyelination due to a risk of rapid increase in plasma osmolality (6, 14).

The next question that needs to be addressed is whether to use *balanced* or *unbalanced* solutions. The differences between balanced isotonic fluids and NaCl 0.9% are widely investigated, although mainly in adult patients. Historically, NaCl 0.9% is used the most, it is also the cheapest product. Some studies in adults reported an increased mortality and need for renal replacement therapy, or an increased incidence of persistent renal dysfunction with the use of NaCl 0.9% (5). This was most noticeable in very ill patients resuscitated with large volumes of fluids, or in sepsis with shock. A meta-analysis however, found no evidence that the risk of death or acute kidney injury among critically ill adults in the ICU was lower with the use of balanced fluids than with saline (15). In children, evidence is limited and no more than a trend towards better outcome is observed in reviews (16, 17).

Balanced fluids do not cause hyperchloremia or acidosis. Another theoretical benefit is the buffering effect of the added anions: e.g., Ringer's lactate® alkalinizes via its consumption in the citric acid cycle in the liver to bicarbonate. Some use Ringer's acetate, which has similar properties but no lactate. This was thought to be helpful when analyzing blood-lactate in shock. Later, it was shown that lactate is metabolized much faster than infused, so Ringer's lactate® does not cause hyperlactatemia except possibly in severe liver-failure (18).

Although the superiority of balanced isotonic fluids to NaCl 0.9% is still debated, many physiologic advantages hence exist. Considering the limited extra cost and potential benefits, we recommend their use in children, as do others (3, 8, 9, 19). Effects will be most profound when substantial volumes are needed — the choice of fluid in those receiving a one-time bolus is unlikely to matter.

NaCl 0.9% is still a good choice in patients who developed hypovolemia with a chloride responsive metabolic alkalosis (e.g., from vomiting). It can be advantageous when administering blood or certain medications (e.g., ceftriaxone) because it does not contain calcium, but neither does Plasma-Lyte®.

How fast and how much?

Until recently, early aggressive fluid resuscitation was recommended in children with septic shock, but the FEAST-trial challenged this (2). Most protocols however still recommend multiple boluses during the first hour to reverse shock although cautiously and with continuous assessment after each bolus (1, 3, 9, 14). The recently updated ERC-guidelines advocate 10 ml/kg boluses, up to 40-60 ml/kg might be needed in the first hour (8). The Society of Critical Care Medicine follows the same approach for sepsis when there is (pediatric) intensive care (PICU) availability (1). If not, fluid boluses are still advised but only in the case of hypotension and with a maximum of 40 ml/kg in the first hour. For children with septic shock without hypotension in low-resource settings, they recommend against bolus fluid administration while starting maintenance fluids (2). This restrictive approach seems to be at least as effective and reduces the incidence of mainly respiratory side effects necessitating PICU.

A bolus of 10 ml/kg is thus given in a timeframe of 5-15 minutes, with the severity of shock determining the speed. The bolus should be repeated in case of insufficient improvement and if there are no signs of fluid overload (deterioration of respiratory distress, increasing oxygen need, gallop rhythm, hepatomegaly, bradycardia). Following every bolus, reassessment should occur to identify those who are fluid responsive. This can be very challenging: clinical signs (heart rhythm, breathing frequency, CRT, consciousness, diuresis) and laboratory values (lactate, pH) could be helpful when combined, since one good parameter can be misleading. If experienced, the use of echocardiography or Point-Of-Care Ultrasound to recognize myocardial dysfunction or persistent hypovolemia can guide fluid administration (8). If more than 3-4 boluses are needed rapidly and the child is still shocked, or shows signs of cardiac decompensation, vasoactive/inotropic drugs are needed. Since fluid resuscitation is only one part of a much broader treatment plan in shocked children, PICU must be involved early in these patients to give advice and retrieve the patient.

Comparable to other guidelines, we recommend rehydration of severely dehydrated children who are not shocked to be done more gradually and preferably enterally (1, 20).

Special circumstances

Trauma

In trauma, active bleeding must be looked for and stopped via direct pressure or damage control surgery to avoid or reverse shock. Hemorrhagic shock not only generates fluid loss but also loss of blood components, thus blood products should be given as soon as possible, and crystalloids kept to a minimum (8). In general, there seems to be a tendency to over-resuscitate in pediatric trauma with higher risk of complications such as ascites, pleural effusion, increased need of ventilation and prolonged ICU stay attributable to excess fluid (21, 22).

In adults, permissive hypotension (maintaining a blood pressure lower than physiological levels) during trauma is aimed at limiting blood loss and avoid overly aggressive fluid resuscitation until definitive surgical control of bleeding occurs. There is no evidence to support permissive hypotension in children (mean arterial pressure at 5th percentile for age). Most children with trauma have associated brain injury. In these cases, permissive hypotension will be detrimental for cerebral perfusion. Excessive fluid administration on the other hand, may worsen cerebral edema. Hence fluids should be given stepwise aiming at maintaining a normal circulation (8, 23). Permissive hypotension could only be considered in children with hemorrhagic shock due to torso injuries from gunshots or stab wounds, without any suspicion of head trauma.

Major hemorrhage following injury is uncommon in children. Concepts that became standard in adult trauma care, e.g., the use of tranexamic acid, the avoidance of hypothermia and balanced resuscitation with plasma, platelets and packed cells in optimal ratio, are hence poorly studied in children. Retrospective analyses are the best to support using at least as much plasma as red blood cells and considering platelets early in pediatric massive transfusion protocols (22, 24). Tranexamic acid should be used in all requiring transfusion within the first three hours after injury, and/or (suspected) significant hemorrhage (8).

In burn victims, shock generally does not occur acutely. If so, other causes should be actively looked for. Fluid formulas correct fluid losses immediately after the initial approach but are outside the scope of this article.

Cardiogenic shock

Cardiogenic shock is a state of circulatory failure due to impairment of myocardial contractility, a less common entity in children. Possible causes are congenital cardiopathy, cardiomyopathy, myocarditis and arrhythmia. Extra-cardiac comorbidities exist as well, e.g., sepsis, leading to increased mortality.

In general, fluid resuscitation should be avoided in cardiogenic shock to avoid further decompensation. Some children may still benefit from a ju-

dicious fluid bolus (5 ml/kg) to optimize preload, while others will benefit from diuretics, ventilation or inotropes. All patients with cardiogenic shock should be transferred to a PICU and urgent advice of a pediatric cardiologist should be sought for further diagnostics and tailored treatment (25).

Kidney failure and/or hyperkalemia

Historically, balanced crystalloids were avoided in patients with kidney failure due to the risk of hyperkalemia. However, recent data suggest it might be safe and even preferable. The serum potassium concentration in a hyperkalemic patient is often higher than the potassium concentration in most balanced crystalloids. Moreover, NaCl 0.9% causes a hyperchloremic metabolic acidosis, which shifts potassium out of cells, increasing the hyperkalemia. Potassium shifts have a greater effect on the serum potassium than the actual concentration of potassium in the infused solution. Studies in renal transplant patients reported indeed higher potassium levels when using NaCl 0.9% as compared to balanced fluids (26). For most patients (with or without hyperkalemia) the effect of the potassium present in balanced solutions is minimal. Their use might even be beneficial in patients with concomitant metabolic acidosis.

Diabetic keto-acidosis (DKA)

Although most children with DKA are volume depleted, shock is rare (27). The range of ECF-deficit is usually in the range of 5-8% of bodyweight. Volume expansion starts with 10 mL/kg crystalloids infused over 60 minutes, although when signs of shock are present, this should be done faster. The remaining fluid deficit is corrected at a slower pace, usually over 48 hours. A second fluid bolus is rarely needed.

DKA often presents with acute kidney failure. Usually this resolves quickly with appropriate fluid therapy, confirming its prerenal etiology.

Mental status abnormalities occur in 4-15% of children treated for DKA; cerebral edema, rarely seen after adolescence, occurs in less than 1% but with a mortality rate of > 20%. It was initially attributed to rapid fluid administration causing abrupt changes in serum osmolality. More recently, an alternative hypothesis suggest intrinsic factors to DKA may be the cause of blood-brain-barrier disruption, which could be worsened during treatment. This is supported by the fact that cerebral edema correlates to the degree of initial hyperventilation and dehydration. No such link was found with the osmolality at presentation, nor with the osmotic changes caused by fluid resuscitation (27). Nevertheless, resuscitation in DKA must be monitored closely to avoid excessive fluid administration.

The Spink trial compared 0.9% saline with Plasma-Lyte® as initial fluid in pediatric DKA: Plasma-Lyte® was similar to 0.9% saline in time to resolution of DKA, need for renal replacement therapy, mortality, and length of PICU or hospital stay (28). Plasma-Lyte® does contain potassium, but studies suggest the serum potassium is unchanged or even higher with NaCl 0.9% because of the abovementioned shifts related to the metabolic acidosis caused by NaCl 0.9% (27). A recent meta-analysis showed that the use of NaCl 0.9% may be associated with longer time to DKA resolution, higher plasma chloride levels and lower plasma bicarbonate levels post resuscitation, and longer hospital stay (29). Although the International Society for Pediatric and Adolescent Diabetes recommends the use NaCl 0.9% the first hour, more and more data support the use of balanced crystalloids.

Conclusion

The most important in treating shock in children is to recognize the need for resuscitation in a timely fashion. The quest for the optimal resuscitation fluid is still ongoing, but there is growing evidence to recommend against using colloids, dextrose containing solutions and hypotonic fluids as a first choice. Even though NaCl 0.9% is historically the most widely used fluid during resuscitation, there is no physiologic reason we should still recommend it. Based on the available evidence and international guidelines, we recommend isotonic balanced crystalloids during fluid resuscitation in children in most cases. Therapy should start with a bolus of 10 ml/kg in 5-15 minutes depending on the clinical situation, with careful evaluation during and after each bolus.

Acknowledgements

We thank the Be-PIV-group (Belgian Pediatric Task force on IV fluids) for critical reading and approving the final draft of the manuscript. Be-PIV members:

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Disclosure of potential conflicts of interest: None of the authors has a conflict of interest to declare.

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Neonatal acute myeloid leukemia with KMT2A/MLLT3 rearrangement revealed by a Blueberry Muffin syndrome

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Keywords

Blueberry Muffin syndrome, neonatal leukemia, leukemia cutis, KMT2A rearrangement, case report.

Abstract

Blueberry Muffin syndrome is a rare skin manifestation that can be observed during neonatal period. It should make pediatricians explore the differential diagnosis of extramedullary hematopoiesis, including congenital infections, intrauterine anemias and, more rarely, neoplastic pathologies.

We report the case of a late term newborn showing birth lesions suggestive of this syndrome. In the absence of other associated clinical signs and abnormalities in the blood count, diagnostic investigations were completed by a skin biopsy and a bone marrow aspiration which led to the diagnosis of acute myeloid leukemia with a KMT2A/MLLT3 rearrangement. As leukemic burden was low, a watch-and-wait approach was chosen, until chemotherapy needed to be initiated at eight weeks of life.

Introduction

Blueberry Muffin syndrome (BMS) is the clinical manifestation in a newborn of a cutaneous extramedullary hematopoiesis that persists or reappears after the physiological embryological one. Its causes include congenital infections, hemolytic anemias, twin-to-twin transfusion syndromes, Langerhans histiocytosis and neoplastic causes such as neuroblastoma and acute leukemia. We report the case of a newborn with Blueberry Muffin syndrome without any associated clinical signs nor blood count abnormalities. The diagnosis of myeloid leukemia cutis could be made with a biopsy of the skin lesions and was then confirmed by a bone marrow aspiration. The KMT2A/MLLT3 rearrangement present in our patient made the management and prognosis singular.

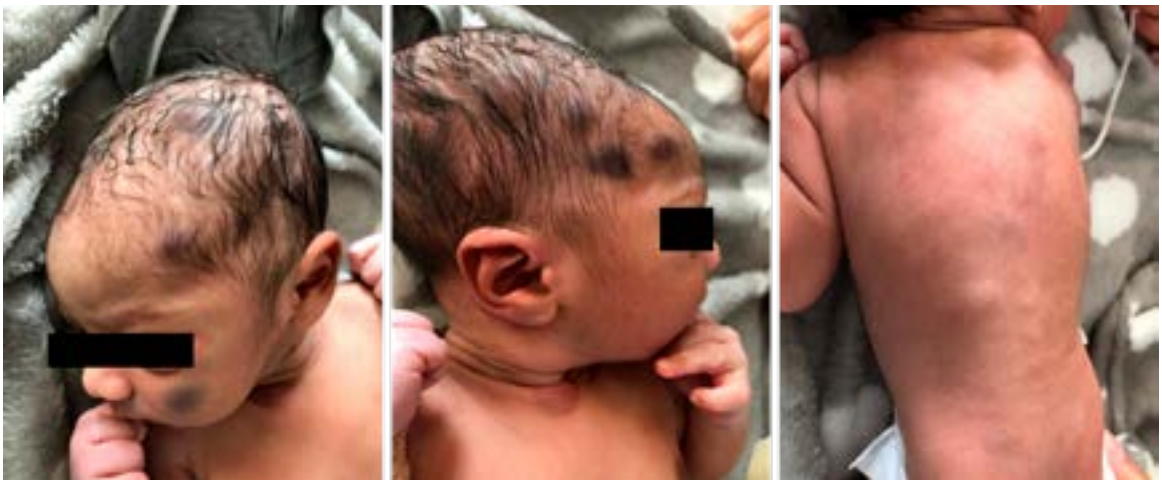
Case presentation

A male newborn, born at 41 weeks 2/7, eutrophic, presented himself at birth with erythematous-violaceous inflammatory macular, papular and nodular lesions of 1 to 1.5cm in diameter on the scalp, face, neck, trunk and limbs (Figure 1).

The pregnancy was triggered by artificial insemination and went without particularities. Family history was unremarkable, with non-consanguineous parents from Bangladesh. The mother was immune to rubella and cytomegalovirus (CMV) but not to toxoplasmosis. Prenatal ultrasounds were normal. The maternal screen for group B Streptococcus was negative. The delivery was induced for late-term pregnancy and was performed vaginally with vacuum instrumentation. The newborn presented a good adaptation to life and subsequently had cardiorespiratory parameters within standards and no fever. Apart from the skin lesions, his clinical examination was normal, with among others the absence of palpable intra-abdominal mass.

Because of the suspicion of BMS, an etiological workup was carried out. The blood tests showed a normal blood count without circulating blasts nor inflammatory syndrome. The infectious assessment was negative (toxoplasmosis, rubella, syphilis, herpes simplex, herpes zoster, parvovirus B19, Epstein-Barr virus, CMV, hepatitis B, and coxsackie serology and urinary CMV PCR). Hereditary spherocytosis and fetal-maternal incompatibility were also excluded. Lactate dehydrogenase and neuron-specific enolase were

Figure 1: Cutaneous erythematous-purplish infiltrated macules and papulonodules observed at birth.



normal. The abdominal ultrasound showed an absence of intra-abdominal mass and the chest X-ray showed no mediastinal enlargement.

In the absence of other etiological diagnosis, a skin biopsy was performed to exclude a tumoral etiology of the persistent skin lesions. This showed massive infiltration of the dermis by blast cells of the myeloid/monoblastic type, strongly positive for immunohistochemical labelling with CD33, CD68, CD123 and lysozyme, and weakly positive for CD56, CD43 and CD4, with a high index (>90%) of nuclear proliferation (Ki67) (Figure 2A-D). These results confirmed the diagnosis of myeloid leukemia cutis.

The bone marrow aspiration showed a moderate monocytoid-like blastosis consisting of monoblasts (12%) and promonocytes (10.5%) (Figure 2E). The immunological labeling was positive for CD45low, high SS, myeloperoxidase, HLA-DR, CD33, CD64, CD56, CD4 and negative for CD13, CD34, CD117 and CD11b. The cytogenetics study (FISH) revealed an abnormal clone characterized by a translocation involving part of the short arm of chromosome 9 and part of the long arm of chromosome 11 [t(9;11)(p21;q23)] leading to a KMT2A/MLLT3 rearrangement (formerly known as MLL-AF9). The lumbar puncture did not show any abnormal monoblastic population.

Because of the absence of peripheral blastosis, the low percentage of medullary blasts (< 30%) and the good general condition of the infant, a watch-and-wait approach was initially chosen in order to promote the growth of the infant and a better tolerance to chemotherapy.

Monitoring consisted of clinical and biological controls twice a week and a bone marrow aspiration every two weeks. The skin lesions involuted spontaneously after several weeks of life. The constitutional genetic workup for Down syndrome and Noonan syndrome then came back negative, when it would have modified the treatment if positive.

At eight weeks of life, the bone marrow aspiration showed an increase in the percentage of blasts (>30%), associated with neutropenia in the blood count, indicating the need to start chemotherapy for acute myeloid leukemia (AML) (following the NOPHO-DBH AML 2012 Protocol NCT01828489). The patient showed molecular remission 12 months after the end of treatment.

Discussion

Blueberry Muffin syndrome is the manifestation of a cutaneous extramedullary hematopoiesis. It presents as erythematous-purplish infiltrated macules or papulonodules (ranging from bright red to blue-grey), which are present at birth. It is often generalized but predominant in the trunk, head and neck (1).

The different etiologies are classified in table 1. Benign leukemoid reaction are due to the activation of the immune system in congenital infections or intrauterine anemias. Transient leukemoid reactions are due to constitutional chromosomic abnormalities responsible of an unstable hematopoiesis. They are associated with genetic syndromes or, more rarely, non-syndromic. Neoplastic causes are extremely rare and are due to an excessive production of immature or abnormal white blood cells (Table 1) (2).

In the case of skin nodules present during the neonatal period, clinicians have to look for malignancy characteristics such as the explosive nature (rapid multiplication) of the lesions, their indurated appearance and bluish color, an alteration of the general condition, and the presence of lymphadenopathies or hepatosplenomegaly (1).

Leukemia cutis or cutaneous leukemia is defined as the presence of leukemic cells in the dermis. It is the characteristic presentation of congenital leukemia, which is one of the causes of the so-called "Blueberry Muffin Syndrome. Around 2/3 of patients with neonatal leukemia have leukemic skin infiltration, and it is more often seen in acute myeloid leukemia (AML) than in acute lymphocytic leukemia (ALL).

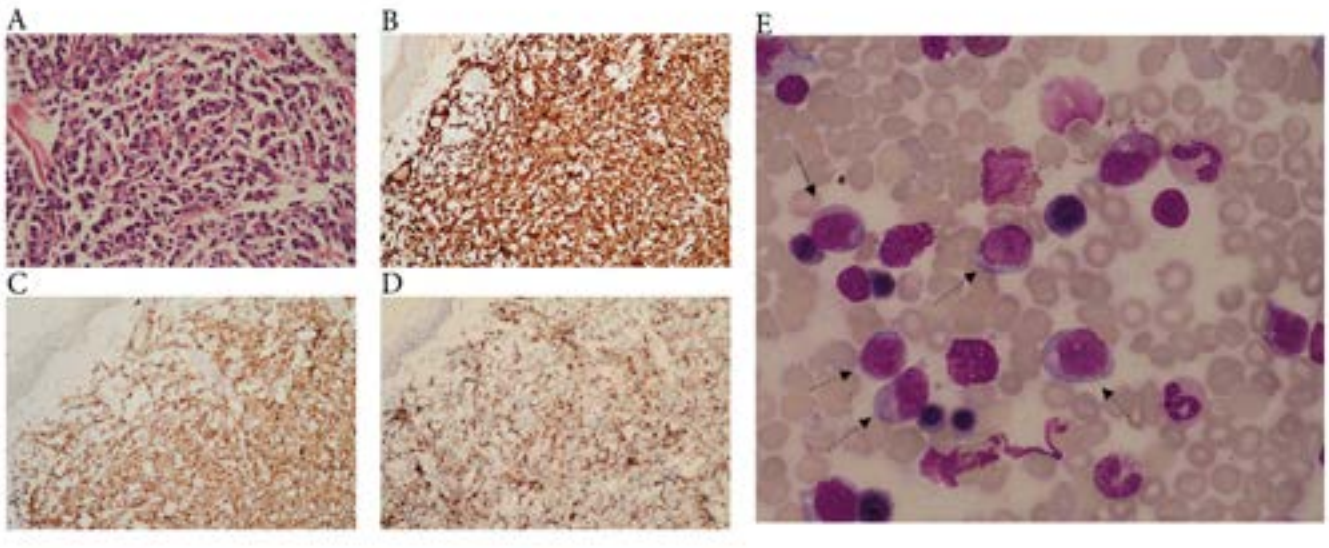
In 10% of newborns with leukemia cutis, no blasts are found at the bone marrow aspiration. In those cases, the term aleukemic leukemia cutis is used. A possible explanation for this phenomenon is the postnatal persistence of fetal physiological dermal hematopoiesis, which normally occurs during the first to fifth months of pregnancy but may be seen in cases of prematurity or intrauterine growth retardation, with a subsequent evolution to leukemic cells. Alternatively, leukemia cutis may represent skin metastases from unrecognized systemic leukemia (3).

Histologically, leukemia cutis classically appears as a dense and diffuse intra-dermal infiltrate of leukemic cells (as illustrated in our patient), of variable sizes and shapes. Their nuclei usually vary from an atypical aspect to a monomorphic appearance (3). In our patient, these cells presented a polymorphic appearance, showing either notches or a monocytoid appearance, sometimes accompanied by numerous nuclear debris.

A positive immunohistochemical labeling with CD68 and lysozyme has been described in 95% of adult cases of myeloid leukemia cutis regardless of the subtype of systemic leukemia (4). CD43 was found to be positive in 97% of patients with myeloid leukemia cutis in another study (4). These three markers were positive in our patient. In contrast, several studies which evaluated aleukemic myeloid leukemia cutis in adults and neonates showed no consistent markers (4).

Neonatal leukemia is defined by its onset within the first 28 days of life. It is a rare pathology (1 in 5 million births) which represents less than 1% of all pediatric

Figure 2: (A-D) Skin lesions biopsy on day 1. (A) Infiltration of the dermis and subcutaneous fat by blast cells. (B) Immunohistochemical labeling with lysozyme. (C) Immunohistochemical labeling with CD33. (D) Immunohistochemical labeling with CD68. (E) Bone marrow aspiration on day 7. Monocytoid-like blastosis consisting of monoblasts (dotted line arrows) and promonocytes (continuous arrow).



leukemias (3). It remains, however, the leading cause of neonatal death due to neoplasms. The majority of cases are congenital. In 66% of cases, neonatal leukemia is an AML with monocytic or monoblastic characteristics, while pediatric leukemias are mainly ALL (5).

Neonatal leukemia differs from pediatric leukemia by its clinical presentation (often presenting as a blueberry muffin appearance) and the frequency of associated cytogenetic abnormalities (such as KMT2A gene rearrangements) (6).

Clinically, neonatal leukemia can present with skin nodules (25-64% of cases), hepatomegaly (80% of cases), splenomegaly (75% of cases), lymphadenopathies (24% of cases) and central nervous system infiltration (50% of cases). Hyperleukocytosis is present in 49% of AML cases (7). Among these clinical and biological signs, only skin nodules were present in our patient.

The diagnosis was therefore made by the presence of medullary blastosis and skin infiltration in the absence of other causes of extramedullary hematopoiesis and genetic abnormalities.

Regarding the cytogenetics characteristics of neonatal leukemias, KMT2A gene rearrangements are found in 73-80% of neonatal ALL and in 32-50% of neonatal AML (8,9). The KMT2A gene is located at chromosome band 11q23 and encodes for the lysine-specific methyltransferase 2A that regulates gene expression (10). While wild-type KMT2A plays a major role in embryogenesis and maintenance of hematopoiesis, its rearrangements result in improper expression of genes involved in proliferation and lineage identity. Indeed, KMT2A rearrangements are acquired in hematopoietic precursors in utero and subsequently initiate a rapid progression to leukemia (9). There are currently approximately 100 different KMT2A fusion partner genes identified (9,10). The three most common partner genes in pediatric AML account for 66% of cases and are MLLT3 (22%), as seen in our patient, MLLT10 (27%) and ELL (17%) (9).

The prognosis for neonatal leukemia is poor. Moreover, KMT2A rearrangements are globally associated with inferior outcomes (10). In neonatal AML, the outcome significantly differs depending on the partner gene involved in the KMT2A rearrangements, unlike in neonatal ALL, in which KMT2A rearrangements are clearly associated with a poorer prognosis (9,11). Survival rates prior to 2000 were 23-26%, with a significantly better survival for AML (35%) than for ALL (9%) (5,7). In a more recent retrospective study of cases from 2001 to 2016, the two-year overall survival rate for congenital leukemia was 44.2%, and the two-years survival rate was 0% for patients with a KMT2A rearrangement and 69.5% for those without it (8). Recent multiomics analyses of KMT2A rearranged leukemia reveal higher lineage plasticity and stem-cell-like blasts in younger patients (12). These stem-cell-like blasts may contribute to the ability to evade chemotherapy and immune-mediated control, which explains the higher risk of relapse seen among younger patients with KMT2A ALL. As stated above, the outcome of pediatric AML with KMT2A rearrangements also differs according to the fusion partner genes. KMT2A/MLLT3 fusion is the most common rearrangement in children, but its prognosis remains controversial (10). Indeed, some reports have been able to demonstrate a better prognosis for AML associated with the KMT2A/MLLT3 rearrangement (11,13), while others have shown similar survival compared to the other KMT2A rearrangements (10,14). In many AML protocols, FISH screening for KMT2A rearrangements at diagnosis has thus become a standard approach (11). Finally, leukemia cutis, as described in our case, is also considered a factor of poor prognosis. Indeed, in the French ELAM02 cohort, they hypothesized that chemotherapy for AML may be sufficient to induce remission in bone marrow but not to penetrate the skin, thus leading to a higher risk of relapse (15).

Spontaneous remission is more likely to occur in neonates than in older infants and children, but it is unusual in neonates with KMT2A rearrangements (16,17). Nevertheless, due to its high toxicity during the first months of life and the possibility of spontaneous remission, the decision to initiate chemotherapy for the treatment of neonatal AML may be deferred in favor of a watch-and-wait attitude (16,17). Indeed, if the clinical and biological state of the patient allows it, a watch-and-wait attitude is advised until the potential remission or the progression to systemic leukemia (4). In this situation, regular clinical and biological (including bone marrow aspiration) follow-up is however essential for several years. Indeed, in the event of relapses during follow-up, some patients require chemotherapy as a second step. In two case reviews, Coenen et al. and Grundy et al. reported such relapses, respectively, in 4 out of 7 cases and in 10 out of 16 cases (16,18). The time to relapse was variable, ranging from several weeks to more than ten years. It is not clear which prognostic factors can predict these relapses, as the status of the bone marrow and the initial blood count cannot be used to predict a relapse or remission (18). In our patient, a watch-and-wait attitude was initially proposed to avoid the harmful impact of chemotherapy on the infant's growth. The decision to start chemotherapy was subsequently motivated in view of the progressive nature of the disease marked by the appearance of cervical, axillary and inguinal adenopathies, an increase in the percentage of bone marrow blasts (>30%), and the appearance of neutropenia and anemia. Besides, it would probably have been initiated anyways because of the KMT2A rearrangement present in our patient, as suggested by most authors (8-11).

In the latest published cases, chemotherapy usually associates cytarabine, etoposide, and an anthracycline, combined with intrathecal chemotherapy (in prophylaxis of an invasion of the central nervous system) (17). Our patient was treated with a similar protocol.

Table 1: Etiologies of Blueberry Muffin syndrome and associated diagnostic tests.

Etiologies	Diagnostic tests
Benign leukemoid reaction	
Congenital infections	
Toxoplasmosis, syphilis, herpes simplex, herpes zoster, rubella, CMV, parvovirus B19, EBV, coxsackies, hepatitis B, listeriosis	Serology or PCR
Intrauterine anemia	
Fetal-maternal incompatibility	Direct and indirect Coombs test, hemogram, reticulocytes, bilirubin, blood smear
Hereditary spherocytosis	MCHC/MCV rate, spherocytes at blood smear, osmotic fragility test, cryohemolysis test or 5'EMA test
Major anemia in twin-to-twin transfusion syndrome, fetal-maternal hemorrhage, intracranial perinatal bleeding	Hemogram
Transient leukemoid reactions due to chromosomic abnormalities	
Down syndrome, Noonan syndrome	Constitutional genetic workup
Neoplastic causes	
Langerhans histiocytosis	Hemogram, liver function tests, bilirubin coagulation tests, biopsy of skin lesions, abdominal ultrasound, chest and skeleton X-rays
Neonatal leukemia (leukemia cutis)	Hemogram, biopsy of skin lesions, bone marrow aspiration
Neuroblastoma	Urinary catecholamines, ferritin, neuron specific enolase, bone marrow aspiration
Congenital rhabdomyosarcoma	Biopsy of lesions

CMV: Cytomegalovirus. EBV: Epstein Barr Virus. MCHC: Mean Corpuscular Hemoglobin Concentration. MCV: Mean Corpuscular Volume.

Conclusion

This case highlights the importance of considering the hypothesis of neonatal leukemia in front of a Blueberry Muffin syndrome, even in the absence of other clinical signs, peripheral blastosis or abnormalities in the blood count. If no obvious etiology is found, investigation must be further conducted by a skin biopsy, supplemented subsequently by a bone marrow aspiration. Some neonatal acute myeloid leukemias show spontaneous remission. Due to the significant toxicity of chemotherapy in the first

months of life, a watch-and-wait approach can therefore be proposed at first, if the patient's condition allows it. However, in case of poor prognosis factors, such as KMT2A rearrangements, earlier chemotherapy should be applied. For those without KMT2A rearrangements, close biological and clinical monitoring is required for several years, due to the possibility of relapses. Chemotherapy is thus needed in the event of progressive disease.

Acknowledgments

The authors thank the patient's parents for authorizing the publication of the pictures; Dr I. Theate for the analysis and description of the skin biopsy; and Dr O. Ketelslegers for the analysis and description of the bone marrow aspiration.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Fetal and neonatal ventricular arrhythmias in Long QT type 2 syndrome: a case report

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Keywords

Long QT Syndrome, fetal, arrhythmias, gene mutation, case report

Abstract

Congenital Long QT syndrome is a family of conditions that share ion channel disturbances that can lead to severe ventricular arrhythmias. This report describes a rare case of fetal presentation, as well as its subsequent perinatal management. The postnatal electrocardiogram revealed ex-treme prolongation of QT interval, ventricular arrhythmias, and atrioventricular block. Patient was treated postnatally using propranolol and mexiletine, with pacemaker implantation. Type 2 LQTS was genetically confirmed. At last follow-up the patient remains free of ventricular arrhythmia. Fetal ventricular arrhythmias must raise suspicion of LQTS. This article provides additionally some practi-cal consideration in regard to diagnosis and treatment of fetal arrhythmia.

Introduction

Congenital Long QT syndrome (LQTS) is characterized by a prolonged corrected QT (QTc) interval on electrocardiogram (ECG) that possibly leads to arrhythmia-related syncope and sudden death. Thus far, 17 gene mutations involving ion channel have been identified.

Its incidence, estimated at no less than 1 in 2500 births, is probably underestimated, given that some mutations possibly lead to non-penetrance, or result only in subtle clinical abnormalities (1-3).

Patients can experience abrupt symptoms of syncope, cardiac arrest, or even sudden death. The syndrome onset is reported to occur within the first three decades of life for most patients. Never-theless, in some cases, LQTS can be suspected antenatally. We here report a rare case of fetal and postnatal LQTS presentation with severe ventricular arrhythmias and attempt to guide clini-cians in the management of perinatal presentation through our mistakes.

Case Presentation

A 29- year- old Caucasian woman, G1P0, was referred to our tertiary center for fetal cardiologic evaluation at 34 weeks of gestation for frequent premature ventricular contractions (PVC) on routine fetal echography. Previous antenatal evaluations were normal. None of the parents displayed any relevant familial or personal medical history.

Fetal echocardiography demonstrated mild right ventricular dysfunction, moderate tricuspid regurgitation, and ventricular arrhythmias consisting of PVCs and short but frequent ventricular tachycardia (VT) bursts. Owing to the lack of familial history of LQTS, fetal atrio-ventricular block (AVB), and fetal bradycardia, a transplacental therapy with sotalol at 80mg three times per day was initiated under close fetal monitoring, enabling a decrease in cardiac arrhythmias and normalization of right ventricular function. A male baby of 3.41Kg was delivered by cesarean section for monitoring purposes at 38 weeks and 2 days. He was promptly admitted to the pediatric intensive care unit for surveillance. Two hours after birth, he displayed several bursts of VT with compromised hemodynamic parameters. A unique dose of amiodarone was administrated, in an attempt to decrease ventricular arrhythmias. The ECG that was performed in sinus rhythm revealed a significant QTc prolongation (680msec) and 2:1 functional AVB (Figure 1). As cardiac ultrasound demonstrated systolic dysfunction, the patient was intubated for 36 hours. A treatment with continuous intravenous lidocaine at 15 mcg/Kg/min was initiated, which decreased the burden of VT. At that moment, it was assumed that the QT interval was prolonged due to antenatal treatment with sotalol and postnatal administration of amiodarone. At 24 hours of life, a temporary epicardial pacemaker was inserted in order to ensure a good atrioventricular conduction. At Day 3, following amiodarone discontinuation, the ECG revealed persistent QTc prolongation despite normal electrolytes (Figure 2) and the diagnosis of LQTS was evoked; therefore, lidocaine infusion was ceased and oral propranolol and oral mexiletine were initiated. Due to persistent AV conduction troubles, a permanent epicardial double chamber pacemaker was implanted at Day 22. Six days later, the infant was discharged on propranolol 8mg/Kg/day and mexiletine 4mg/Kg/day, without any ventricular arrhythmia. The case's timeline is summarized in table 1.

Table 1: timeline

	Premature ventricular contractions on routine fetal echography. Mild right ventricular dilatation, mild left ventricular dysfunction, moderate tricuspid regurgitation, PVCs and VT bursts. Sotalol initiation.
38 weeks 2/7 GA	Cesarean section. Male newborn 3,41kg
H+2	Ventricular tachycardia bursts. Amiodarone ECG : QTc 680ms and 2:1 AVB Echocardiography : left ventricular dysfunction Intubation Persistence of severe ventricular arrhythmias : Lidocaine infusion
H+24	Temporary epicardial pacemaker implantation.
D3	ECG : QTc 620ms Propranolol and Mexiletin started
D22	Permanent pacemaker implantation
D28	Discharged with Propranolol and Mexiletin

Genetic testing identified a heterozygous mutation in exon 7 of *KCNH2* gene (c.1897A>G, p.(Asn633Asp)), classified as likely pathogenic. Segregation study targeted at *KCNH2* confirmed the "de novo" mutation. Given the clinical presentation and the mutation finding, diagnosis of Type 2 LQTS was retained.

The child remained free of ventricular arrhythmias on unchanged treatment administered for 19 months.

Discussion

LQTS can lead to life-threatening arrhythmias in form of VT, torsades de pointe (TdP), or ventricular fibrillation (VF), and this condition is a well-known cause of sudden cardiac death. LQTS has been strongly associated with sudden infant death syndrome (SIDS) and is hypothesized to be at the origin of sudden intrauterine death (4).

LQTS can be antenatally suspected when fetal ventricular arrhythmias are observed in the context of a LQTS familial history. When the familial history is unremarkable, the LQTS diagnosis is more challenging, as it requires recognition of specific fetal rhythm abnormalities.

In most centers fetal echocardiography remains the main diagnostic tool for assessing fetal arrhythmias. While it cannot measure the QT interval, several publications have suggested other means for establishing antenatal LQTS diagnosis, mostly based on doppler flux (5-7).

Typical manifestation of in utero LQTS are ventricular arrhythmias and 2:1 AVB, whereas these disturbances account for only 25% of fetuses with postnatally proven LQTS (1, 8, 9). Sinus bradycardia has also been described among the more common (76%) manifestations of LQTS. Nevertheless, fetal bradycardia is less specific, given that LQTS is diagnosed in only 15-17% of all fetal bradycardias <110bpm (2, 9). There seems to be a correlation between rhythm phenotype and genotype. *KCNQ1* gene mutation carriers (Type 1 LQTS) are more prone to develop sinus bradycardia, while *SCN5A* gene mutation carriers (Type 3 LQTS) are more susceptible to develop a more severe phenotype with ventricular arrhythmias and/or 2:1 AVB, whereas *KCNH2* gene mutation carriers (Type 2 LQTS) can develop both phenotypes (10).

As the association between AVB and ventricular arrythmias should be suggestive of LQTS diagnosis, differential diagnoses of « real » high-degree AVB (as opposed to functional 2:1 AVB) and ventricular arrhythmias must be kept in mind. High-degree AVB can be caused by congenital heart disease, presence of maternal SSA or SSB autoantibodies (isoimmune AVB), or LQTS. As fetal ventricular tachycardia is extremely rare, this condition should evoke the suspicion of in utero cardiomyopathy, myocarditis, ventricular tumor, or LQTS.

Early recognition of this syndrome is imperative for several reasons: it permits to avoid the administration of some QT-prolonging maternal medications; right transplacental therapy can be promptly initiated; close monitoring of fetal distress signs can be scheduled, and postnatal care can be properly anticipated; and there is a higher risk of pre- or postnatal death if not recognized.

Currently, no guidelines for in utero management exist. In many cases, the LQTS fetus with a bradycardia or 2:1 AVB just needs to be observed (11). Intervention is indicated for hydrops fetalis or cardiac dysfunction attributable to ventricular arrhythmias or severe bradycardia. Fetal treatment should be considered if non-sustained ventricular tachycardia occurs, yet without any fetal distress signs.

If management is needed, immediate delivery or initiation of transplacental therapy must be discussed. As prematurity can cause additional morbidity, preterm delivery must be avoided as far as possible. Moreover, pacemaker insertion is often needed in the LQTS newborn and is more easily performed with a higher weight. Those considerations must outbalance the risks and the side-effects of giving pro-arrhythmogenic drugs in a healthy pregnant woman.

Severe ventricular arrhythmias, whether sustained VT and TdP, are most likely to be successfully treated using magnesium sulfate and lidocaine as it has been suggested in few reports.

Magnesium sulfate has been shown to successfully restore sinus rhythm pertaining to severe ventricular arrhythmias, including high burden of VT, VF or TdP (12).

Intravenous lidocaine has also been proposed as transplacental therapy for severe ventricular arrhythmias (13). Nevertheless, lidocaine has been shown to increase in utero ventricular arrhythmias, probably due to sodium channel modifications in *SCN5A* mutation cases (14).

Chronic treatment is often based on beta-blockers, yet other treatments have similarly been investigated.

Beta-blockers are likely the keystone of suspected fetal LQTS. Propranolol is the most frequently used beta-blocker because of its favorable transplacental transfer characteristics. While beta-blockers decrease the fetal VT burden, they appear to be less effective in TdP or VF cases. In addition, beta-blockers decrease fetal heart rate, enabling a 1:1 conduction if a 2:1 AVB is present.

Mexiletine, a class Ib antiarrhythmic drug, has also been tried in some cases, exhibiting variable effects on fetal ventricular arrhythmias (15, 16).

Flecainide has been the topic of several publications, yet it appears unable to decrease ventricular arrhythmias (12).

Sotalol and amiodarone may successfully treat some types of fetal VTs (17); however, in LQTS cases, these drugs often worsen the symptoms, potentially leading to TdP and fetal demise. Retrospectively, sotalol was not a good choice in our case.

Both the efficacy and doses of all those treatments have not yet been investigated in randomized controlled trials; thus, these drugs are all used off-label. Nevertheless, we suggest using beta-blockers in a first attempt to treat in utero ventricular arrhythmias, while avoiding QT interval prolonging drugs like amiodarone or sotalol.

At birth, medication prolonging QT interval should be avoided as well as electrolytic disturbances. First-line treatment includes beta-blocker therapy in all LQTS patients, whether symptomatic or not. Literature shows a preference for propranolol or nadolol, reporting a reduction in both syncope and sudden cardiac death.

In LQTS3 patients, in addition to beta-blocker therapy, mexiletine is recommended, given that it slows Na channel recovery (18). Recent data seem to confirm its efficacy to shorten QT interval in some LQTS2 cases (19). QT prolonging drugs should be avoided in neonatal patient exhibiting ventricular arrhythmias

Conclusion

By the recognition of some rhythmic patterns, cardiotocogram and fetal echocardiography can help the physician to suspect fetal LQTS. Antenatal sinus bradycardia should raise the possibility of Type 1 LQTS. More severe phenotypes, including 2:1 AVB and ventricular arrhythmias, are often due to Type 2 or Type 3 LQTS. Ventricular arrhythmias need a close follow-up and an aggressive treatment given the high risk of fetal complications (ventricular dysfunction, hydrops fetalis) or sudden intrauterine death. Antenatal therapy of congenital LQTS consists mostly in administrating beta-blockers. Severe fetal ventricular arrhythmias seem to be well treated with magnesium sulfate or lidocaine infusion. Those therapies are nevertheless empirical and need further studies to confirm the efficacy of such treatment. With improved knowledge in the genetical field, it is likely that individualized therapy based on genotype could optimize the patient care.

Consent for publication

Written informed consent was obtained from the legal guardians for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

Figure 1: Patient 1: ECG at Day 1 of life showing 2:1 atrioventricular block (Stars : p-wave, Arrows : QRS) due to extreme prolongation of QT interval (600msec)

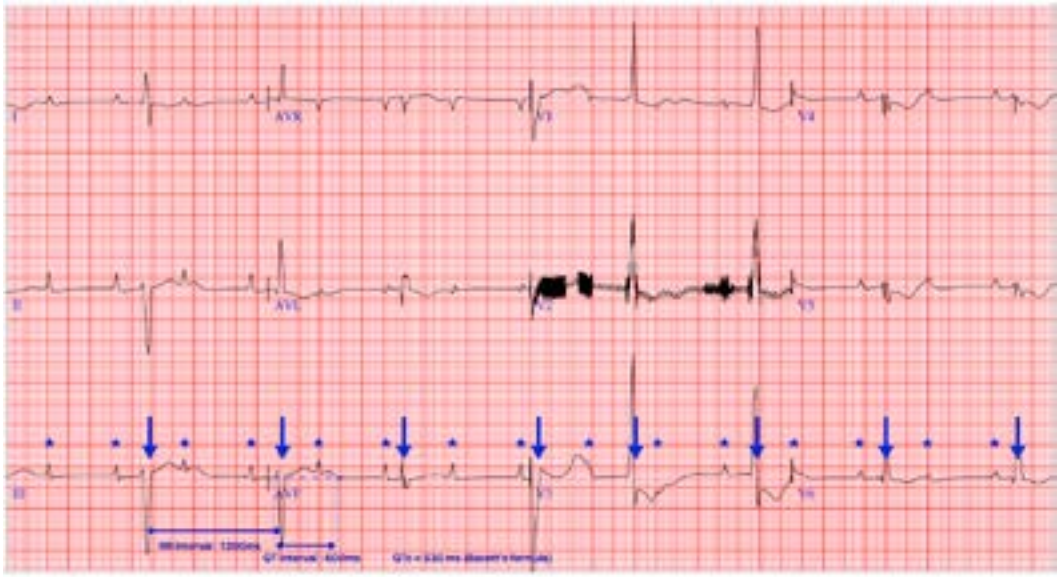
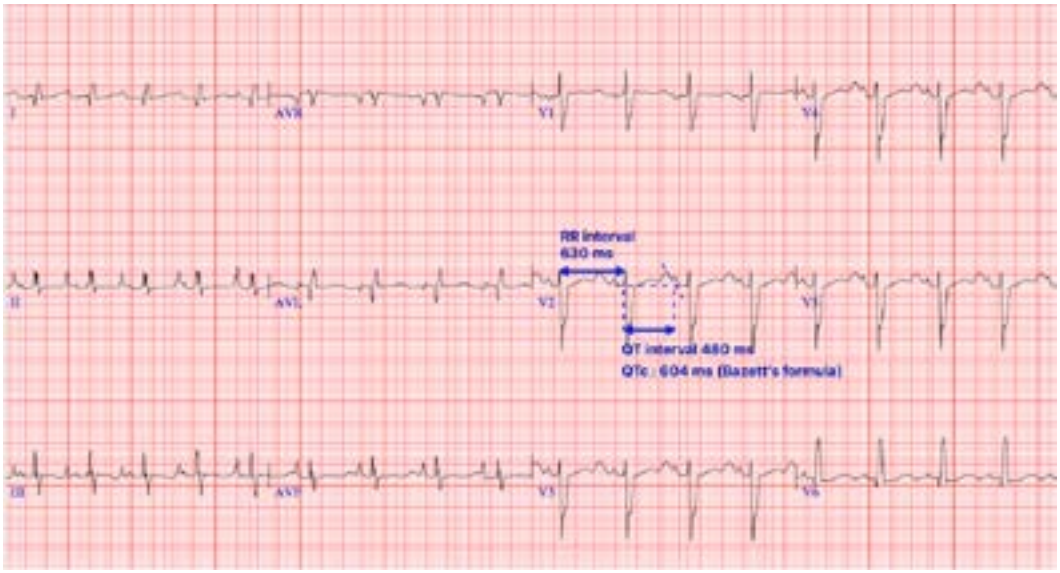


Figure 2: Patient 1: ECG at Day 3 of life after amiodarone discontinuation showing an incomplete left bun-dle branch block and confirming a prolonged QTc interval evaluated at 604msec



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Dit materiaal werd opgemaakt op 25 juli 2022 - LAC/22/005/NL

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Erythromelalgia in a young adolescent male

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Keywords

erythromelalgia, differential diagnosis, Fabry disease

Abstract

Erythromelalgia (EM) is a rare condition which is characterized by burning pain, warmth and redness of the limbs. Several cases of secondary EM have already been described. We report a 13-year-old boy who presented with burning pain in his hands and feet, which turned out to be secondary to Fabry disease. This case highlights the need for pediatricians and general practitioners to be aware of children who present with acute, unexplained pain episodes. When Fabry disease is diagnosed early and treated adequately this has a major impact on the associated morbidity and mortality.

Introduction

Erythromelalgia (EM), first described in 1878 by Weir Mitchell, is characterized by a triad of redness, warmth, and pain, usually of the extremities (1). Primary EM is a rare disease with an estimated incidence of 1,3/100.000 (2). In the largest retrospective study of EM, all 168 patients were white, the male-to-female ratio was 1 to 3, and the mean age was 55.8 years (3). The largest pediatric EM case series showed it to be more common in females and with a mean age of 14 years (4). During an attack of EM, the feet -or hands in 25%- become red, hot, and painful ('burning sensation') (5). The symptoms are intermittent in nearly all patients and episodes can last from minutes to hours and may be triggered by precipitating factors, usually by an increase in temperature of the affected acral area (e.g., increase in ambient temperature or exercise). Conversely, relief is achieved by the cooling of the affected extremity (5). EM is classified into primary and secondary disease. Primary EM (PE) is mainly caused by gain-of-function mutations in the *SCN9A* gene, encoding a voltage-gated sodium channel alpha subunit (Nav1.7) in sensory and sympathetic neurons (7). EM can be secondary in several diseases, such as hemorheological, metabolic, connective tissue, musculoskeletal, or infectious diseases, or it can be induced by drugs, or it can be a paraneoplastic phenomenon (8). Despite the fact that EM has been known for more than 140 years its pathophysiology and treatment remain elusive. And in children the demographic features, natural history, characteristics, prognosis, and pathogenesis of EM are even more poorly characterized. In this report, we present a case of secondary EM in a 13-year-old boy with burning pain in his hands and feet.

Case report

Approval from the Research Ethics Committee UZ/KU Leuven for this study was received (MP016948). A 13-year-old Syrian boy presented to his pediatrician with a 2-year history of intermittent severe pain in both feet and toes. The pain was accompanied by numbness, prickling sensation, erythema, and swelling of the affected extremities. Sometimes his hands and fingers could also be involved. An attack could be triggered by physical exercise. The pain was worst during the night, disturbing his sleep, with a pain score of 9 out of 10. The pain could be reduced by cold application and raising his feet. The symptoms had a major impact on his quality of life as he was unable to play sports for fear that the pain would increase. An episode passed spontaneously after a few hours. There was no medication intake and no relevant medical or surgical history. Immunizations were administered based on the standard schedule. There had been no recent trauma or illness before the first episode. His maternal grandmother was hard of hearing, his maternal grandfather had a stroke and died of an acute myocardial infarction, and one maternal uncle had a transient ischemic attack at the age of 48. His parents were distantly related. Clinical and neurological examinations were normal at the time of presentation. An initial blood test 'with full blood count, liver and kidney function and inflammatory markers) and an X-ray of both feet revealed no abnormalities. Musculoskeletal pains were first suspected. Therapeutic insoles were recommended, initially showing only a small improvement. Subsequently, Mediterranean fever was considered, but prophylactic analgesics proved ineffective. Consequently, he was referred to the University Hospitals Leuven, for further diagnostic work up in search for an etiology of his pain pattern as the pediatrician suspected a somatic origin.

During the initial assessment at our department the history was repeated and the absence of abnormal sweating, hearing and vision problems was also assessed. Clinical examination was normal, except for pressure pain of metacarpophalangeal joints 3 and 4 on the right and joint 1 on the left. No cutaneous lesions, especially no angiokeratomas, were observed. The additional laboratory work up included blood tests for thyroid function, immunity, and infection (Lyme borreliosis, Syphilis, Cytomegalovirus, Epstein Barr, and HIV), as well as a chest X-ray and a tuberculin skin test. The only abnormal result was the blood test for Fabry disease, which showed a significant decrease (<0.8 µmol/L/h, REF ≥15.3 µmol/L/h) in the enzyme activity of alpha-galactosidase A (alfa-gal A). A tentative diagnosis of secondary EM in the context of Fabry disease (FD) was made. Genetic testing was also done to exclude false low enzyme activity and showed a hemizygous mutation (c.1226C>T, p.Pro409Leu) of the galactosidase alfa (*GLA*) gene, coding for alfa-gal A. In addition, there was a significant increase (52.1 ng/ml, REF ≤1.8 ng/ml) in plasma globotriaosylsphingosine (lyso-Gb3), a storage product in this disease. Based on the presence of acroparesthesias, an undetectable low activity of alfa-gal A, the hemizygous mutation of the *GLA* gene, and a significantly elevated lyso-Gb3, secondary EM due to FD was definitively diagnosed.

Further follow-up and treatment was required in the context of this diagnosis. A 24-hour urine collection showed no proteinuria. His audiometry was normal. A cardiac ultrasound there was a mild thickening and hypertrophy

Table 1: Cases of Pediatric Erythromelalgia with Onset up to the age of 18 years (published since 1979 in chronological order)

First author, publication year	No	Sex (M/F)	Age at onset of symptoms vs. at diagnosis (y)	Major somatic symptoms	Dysautonomia signs	Illness, vaccination, a trauma in preceding weeks	Pathological confirmation of SFN	Autonomic function testing	Electrodiagnostic testing	Capillary microscopy	Blood test	Genetic testing	Outcome of immunotherapy	Diagnosis
Ozsoylu, 1979	1	F	9 vs. 9	Burning pain, warmth, swelling, and erythema in hands and feet	AHT	No data	No data	No data	No data	No data	Normal	No data	None administered	HAE
Cimaz, 2001	1	M	3 vs. 10	Burning pain, swelling, and ulceration in lower limbs and hands	AHT	No data	No (SB)	No data	No data	No data	Low GH, low IGF-1	No data	MR (systemic CS)	EM due to GH deficiency
Chan, 2002	1	M	no data vs. 11	Burning pain, warmth, and erythema with hyperkeratosis, maceration, and ulceration in hands and feet	AHT	No data	No data	No data	Abnormal NCS	Abnormal	No data	No data	None administered	HAE
Pfund, 2009	1	F	12 vs. 12	Burning pain, warmth, swelling, and erythema in hands and feet; muscle weakness in knees and feet	AHT	No data	Not performed	Abnormal QST	Abnormal ENG, NCS	Normal	Normal	No data	GR (systemic CS)	EM due to LFA
Firinci, 2010	1	F	11 vs. 11	Burning pain, warmth, and erythema in hands and right arm; arthralgia in hands and feet	No data	No data	No data	No data	Normal	No data	Hypocomplementia, high ESR, positive ANA, and positive dsDNA	No data	GR (systemic CS)	EM due to SLE
Morales, 2012	1	M	No data vs. 9	Burning pain, warmth, swelling, and erythema in hands and feet	AHT	No data	No (SB)	No data	Normal	No data	Normal	Normal	CR (systemic CS)	HAE
Wu, 2013	1	M	11 vs. 11	Burning pain, swelling, and erythema in the left medial thigh	No data	Trauma 8 weeks before	No (SB)	No data	No data	No data	Normal	No data	GR (systemic CS)	EM due to trauma
Duchatelet, 2014 (b)	2	M	4-9 vs. 11-14	Pain, swelling, and erythema in ears, hands, legs, and feet; plantar keratoderma	No data	No data	1/2 no (SB), 1/2 no data	No data	No data	No data	No data	2/2 TRPV3 mutations	No data	EM due to OS
Duchatelet, 2014 (a)	1	F	3 vs. 3	Pain, swelling, and erythema in ears, hands, and feet; plantar keratoderma	No data	No data	No (SB)	No data	No data	No data	No data	TRPV3 mutation	GR (systemic + topical CS)	EM due to OS
Huh, 2015	1	F	12 vs. 12	Burning pain and erythema in ears, hands, central body, and feet	No	No data	Not performed	No data	No data	No data	Normal	No testing	MR (systemic CS)	EM due to vasculitis
Hobson-Webb, 2015	1	M	7 vs. 7 (Pompe disease), 11 (SFN)	Burning pain and tingling in fingers and toes; muscle weakness	Bradycardia, gastrointestinal dysfunction, and urinary incontinence	No data	Yes (SB)	Abnormal QSART	Normal	No data	Normal	GAA mutations	None administered	EM due to SFN due to Pompe disease
Faignart, 2020	5	3M/2F	6-11 vs. 10-15	Burning pain in hands and feet	4/5 AHT, 3/5 tachycardia, 2/5 hyperthermia	3/5 preceding or concomitant infection	3/4 yes (SB)	1/1 abnormal ESC, 1/2 abnormal SSR	Normal	1/5 normal, 4/5 no data	2/5 positive ANA, 1/5 thrombocytosis, 1/5 low IgG	Normal	1/1 CR (CS), 1/1 CR (IVIg)	EM due to SFN
Fleitman, 2020	4	F	No data vs. 9-17	Burning pain, swelling, and erythema in lower limbs	No data	No data	Yes (SB)	No testing	Normal	No testing	1/4 low vitamin D, 1/4 low IgA and IgD, 1/4 positive ANA and HLA-B52	2/4 MEFV mutation (het), 1/4 MEFV mutation (hom)	1/1 GR (IVIg), 1/1 GR (anti-IL-1 agents + IVIg + CS), 1/1 MR (CS)	3/4 EM due to SFN, FMF; 1/4 EM due to SFN, Behçet's disease

Abbreviations: AHT = arterial hypertension, ANA = antinuclear antibodies , CR = complete remission, CS = corticosteroids, dsDNA = double-stranded DNA, EM = erythromelalgia, EMG = electromyography, ESC = electrochemical skin conductance, ESR = erythrocyte sedimentation rate, F = female, FMF = familial Mediterranean fever, GBS = Guillain-Barré syndrome, GH = growth hormone, GR = good response, HAE = hypertension-associated erythromelalgia, het = heterozygote, HLA = human leukocyte antigen, hom =homozygote, Ig = immunoglobulin, IGF-1 = insulin-like growth factor-1, IL = interleukin, IV = intravenous, LFA = large-fiber axonopathy, M = male, MR = mild response, NCS = nerve conduction studies, OS = Olmsted syndrome, PR = poor response, QSART = quantitative sudomotor axon reflex test, QST = quantitative sensory testing, SB = skin biopsy, SFN = small-fiber neuropathy, SLE = systemic lupus erythematosus, SSR = sympathetic skin response, TST = thermoregulatory sweat test, y = years

of the papillary muscles and the mitral valve. Electrocardiogram revealed the presence of rare isolated ventricular extrasystoles, which appeared benign on further assessment using a 24-hour Holter registration and ergospirometry. Magnetic resonance imaging of the brain showed a few nonspecific, subcentimetric lesions (para)median in the vermis, common to this disease. There were no white matter lesions. In addition, the ophthalmological examination showed normal vision and absence of cornea verticillata, but a mild tortuous retinal vasculature was seen.

Enzyme replacement therapy (ERT), using agalsidase beta (Fabrazyme°), a recombinant human alfa-gal A, was started every two weeks on the basis of the cardiac signs of end-organ damage and the neuropathic pain with important impact on quality of life. His neuropathic pain proved hard to treat and needed a multidisciplinary approach with specialists from the pain clinic. He is treated with a combination of morphine analogues and several pain modulators. Preventive measures, such as avoiding triggering factors, were also advised. With this combination moderate physical exercise is possible without invoking severe pain episodes.

Because FD is an X-linked inherited disease, further genetic screening was performed in other family members. This revealed that his mother and sister were heterozygous, and one younger brother was hemizygous for the familial mutation. The other family members were not affected.

Discussion

A patient with episodes of extremity pain, accompanied by erythema and warmth, should be suspected of EM. The five Thompson criteria are often used to make the clinical diagnosis: (a) burning extremity pain, pain (b) triggered by warming and (c) relieved by cooling, (d) erythema of the affected limb and (e) increase in temperature of the affected skin (10). All of these were observed in this 13-year-old boy, which led us to the diagnosis of EM. As this disease can be primary or secondary, we considered a broad array of underlying diseases. We performed a literature search that revealed 13 articles of secondary EM cases in children up to 18 years (Table 1). In these case reports, 11 girls and 10 boys aged from 3-17 years are described. A combination of the history, clinical examination and technical investigations led to the primary disease underlying EM in these 21 patients. These included diseases such as arterial hypertension (14.3%), growth hormone deficiency (4.8%), long-fiber axonopathy (4.8%), systemic lupus erythematosus (4.8%), trauma (4.8%), genetic diseases (33.3%), vasculitis (4.8%), small-fiber neuropathy (23.8%), and Behçet's disease (4.8%). No Fabry disease has been described in children, except in a genetic screening of three generations of a Chinese family (boy of 16yrs) (9).

Reported causes of secondary EM are presented in Table 2 (3). In our patient, secondary EM was mainly considered due to the absence of similar symptoms in other family members (as primary EM is an autosomal dominant condition). The investigations revealed that his condition was due to Fabry disease.

Fabry disease is an X - linked inherited disorder of glycosphingolipid metabolism caused by mutations of the gene encoding alfa-gal A (11, 12). Absent or deficient alfa-gal A results in an accumulation of lyso-Gb3 in a variety of different cell types (13). Therefore, this lysosomal storage disorder can cause multi-organ failure and premature death (14). Reported incidences, ranging from 1 in 476.000 to 1 in 117.000 may probably underestimate the true prevalence (15,16). A higher prevalence of the disease, about 1 in 3000, has recently been indicated with a newborn screening study (17). The clinical severity varies dependent on alpha-gal A activity and genotype (18, 19). Nevertheless, FD usually appears in childhood, and occurs in a predictable order in typically affected males. Early-onset signs include neuropathic pain, gastrointestinal symptoms, hypohidrosis, angiokeratoma, and corneal changes. Renal, cardiac, and cerebrovascular involvement increases with age (14). It is the neuropathic pain, sometimes in combination with the erythema, which leads to the clinical presentation of secondary EM. Treatment options for patients with FD include enzyme replacement therapy (ERT) and additional chaperone therapy (20, 21). Reimbursement criteria for ERT in FD in Belgium are a diagnosis of Fabry disease (both enzymatic and genetic) and a clinical presentation with either: kidney disease (decrease in glomerular filtration rate or microalbuminuria >30mg/24h); cardiac involvement (hypertrophic cardiomyopathy or valvulopathy); vascular disease (peripheral lymphoedema or CVA/TIA) or severe neuronopathic pain with impact on the quality of life, refractory to other treatments. Of note, current treatment guidelines advocate considering ERT even for asymptomatic boys from the age of 7 (22).

It may thus be able to halt the progression of this multisystemic disease before irreversible organ damage occurs, making it crucial to suspect FD as early as possible.

Conclusion

Even though EM is a very rare presentation in pediatrics, a thorough differential diagnosis is indicated. In our patient we diagnosed a disease with significant morbidity and mortality where appropriate treatment is available and were able to facilitate the diagnosis in other family members.

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Table 2: Reported Causes of "Secondary Erythromelalgia"

Myeloproliferative diseases and blood disorders	
	Myeloproliferative disorders
	Essential thrombocythemia
	Polycythemia vera
	Myelodysplastic syndrome
	Pernicious anemia
	Thrombotic and immunologic thrombocytopenic purpura
Drugs	
	Cyclosporine
	Norephedrine
	Verapamil
	Nicardipine
	Nifedipine
	Pergolide
	Bromocriptine
Infectious diseases	
	Human immunodeficiency virus
	Hepatitis B vaccine
	Influenza vaccine
	Infectious mononucleosis
	Poxvirus
Neoplastic	
	Paraneoplastic
	Astrocytoma
	Malignant thymoma
	Abdominal cancer
Connective tissue diseases	
	Systemic lupus erythematosus
	Vasculitis
Physiologic	
	Pregnancy
Neuropathic	
	Hereditary sensory neuropathy
	Neuropathy
	Polyneuropathy
	Riley-Day syndrome
	Multiple sclerosis
	Acute diabetic neuropathy
	Neurofibromatosis Fabry disease
Others	
	Mushroom ingestion (*Clitocybe acromelalga and Clitocybe amoenolens*) Mercury poisoning

(adapted from Davis *et al*, 2006)

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Pearson syndrome as a rare cause of liver dysfunction and malabsorption

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Keywords

Pearson syndrome; liver dysfunction; malabsorption; exocrine pancreatic dysfunction; lactic acidosis

Abstract

Pearson syndrome is a progressive multisystem disorder with sideroblastic anemia as its main feature. It is caused by single, large-scale deletions of the mitochondrial DNA. Most patients present in infancy with severe transfusion-dependent anemia and failure to thrive. Here, we describe a three-year-old girl with presumed liver failure during adenovirus gastroenteritis. The diagnosis of Pearson syndrome was suspected based on the co-occurrence of liver dysfunction, exocrine pancreatic insufficiency, megaloblastic anemia and lactic acidosis.This case report aims to increase general awareness for rare disorders, like Pearson syndrome, in the differential diagnosis of pediatric malabsorption and liver dysfunction.

Introduction

Acute liver failure (ALF) is a rare clinical condition in children, characterized by biochemical signs of acute hepatocellular injury and coagulopathy. The differential diagnosis of pediatric ALF is broad, including infectious and toxic etiologies, as well as underlying autoimmune or metabolic disorders (Table 1) (1). However, in the patient presenting raised transaminases, hypoalbuminemia and coagulopathy, ALF should be differentiated from a vitamin K-responsive elongation of the INR due to inadequate intake, drug interference or malabsorption (Table 2). For example severe gastrointestinal disease could also present with hypoalbuminemia, vitamin K malabsorption and elevated transaminases without ALF.

Here, we describe a three-year-old girl with presumed liver failure during adenovirus gastroenteritis. However, further investigations revealed severe malabsorption, megaloblastic anemia and lactic acidosis, fitting Pearson syndrome.

Pearson syndrome is a mitochondrial disorder caused by single, large scale mitochondrial DNA deletions (SLSMD). Sideroblastic anemia is considered to be the core feature of the disease. However, nowadays, Pearson syndrome is recognized as a multisystem disorder, demonstrating significant clinical overlap with other SLSMDs (2–4).

The aim of this case report is to increase the general awareness for rare disorders, like Pearson syndrome, in the differential diagnosis of malabsorption and liver dysfunction in the pediatric population.

Case report

A 3-year-old girl was referred to our center because of suspected nephrotic syndrome. She had been admitted for several days because of adenovirus gastroenteritis requiring intravenous rehydration. The clinical course was, complicated by hypokalemia, hypoalbuminemia, oedema of the lower extremities and episodes of somnolence.

She was the first child of non-consanguineous parents. Her medical history was unremarkable, apart from recurrent episodes of diarrhea, assumed to be due to lactose intolerance. Clinically, the patient presented a striking bronze skin tone, normal sclerae, brittle hair, a moon facies, protruding abdomen and oedema of the lower extremities. The liver was palpated 1 cm below the costal margin, there was no shifting dullness. The patient complained of persistent nausea and fatigue. Biochemically, she displayed a mild pancytopenia with macrocytic anemia and normal vitamin B12 and folate levels, normal renal function, increased transaminases (10-15 times the upper limit of normal) without cholestasis, hypoalbuminemia (23 g/L; nl: 35-52), a normal ammonia and a prolonged INR (2.1). Venous blood gas analyses revealed a normal glucose level and an increased lactate of 6 mmol/L (0,5-2,2). Screening for endocrine dysfunction was negative. Urinary analysis was normal. Abdominal ultrasound and CT of the brain were unsuspicious.

Biochemical screening and therapeutic measurements for suspected acute liver failure were initiated (1). Interestingly, coagulation normalized within 24 hours of intravenous administration of 10 mg vitamin K1, suggesting either nutritional deficiency or malabsorption. Factor V and VII were not measured prior to the administration of vitamin K. While factor V is vitamin K independent and could differentiate between ALF (decreased factor V) and vitamin K malabsorption (normal levels of factor V) turn-around-time for this test is longer than correcting with vitamin K and remeasuring INR.

The hypothesis of an underlying severe malabsorption was supported by the clinical presence of steatorrhea, faltering weight and growth (Figure 1) and by the biochemical evidence of decreased levels of total protein, essential amino acids, cholesterol and fat-soluble vitamins. Exocrine pancreatic insufficiency was evidenced by an undetectable fecal elastase level, proven steatorrhea on a 3-day stool collection and an abnormal 13C-triglyceride breath test indicating low pancreatic lipase activity. The malabsorptive state was initially managed by parenteral nutrition and subsequently by tube feeding supplemented with pancreatin and fat-soluble vitamins.

Lactate remained elevated over time (4-6 mmol/L; 0,5-2,2), despite substitution with high-dose thiamine. Additional metabolic testing revealed only a slight increase of some Krebs cycle intermediates on organic acid profile.

Due to the co-occurrence of megaloblastic anemia, malabsorption due to exocrine pancreatic insufficiency, liver dysfunction and lactic acidosis, Pearson syndrome was suspected early in the course of the hospitalization. A large scale mitochondrial DNA deletion (m.10759-13990del) was demonstrated in a heteroplasmic state in the patient, but could not be detected in the mother.

Discussion

Although ALF has a low prevalence in childhood, its differential diagnosis is broad, ranging from infectious and toxic causes to a myriad of inherited

Table 1: A non-exhaustive list for the differential diagnosis of pediatric and neonatal acute liver failure

Pediatric and Neonatal Acute Liver Failure – Differential Diagnosis *- Acute liver injury, i.e. elevated transaminases* *- INR ≥ 2 without encephalopathy or ≥1,5 with encephalopathy*	
Age group	**Etiology**
Neonatal ALF	Indeterminate liver failure
	Viral infection - *Herpes simplex virus* - *Enterovirus* - *Cytomegalovirus*
	Gestational alloimmune liver disease (GALD)
	Inborn errors of metabolism - *Galactosemia* - *Tyrosinemia type 1* - *Mitochondrial disorders* - *DLD (E3) deficiency* - *Fatty acid oxidation defects* - *Urea cycle disorders* - *Niemann Pick type C* - *Transaldolase deficiency* - *Adenosine kinase deficiency*
	Neonatal hemochromatosis
	Shock or sepsis
	Intoxication
Pediatric ALF	Indeterminate liver failure
	Intoxication - *Acetaminophen* - *Other drugs and herbal medication*
	Autoimmune hepatitis
	Viral infection - *HAV, HBV, HCV, HDV* - *Herpes simplex virus* - *Enterovirus* - *Adenovirus* - *HHV6, HHV7* - *Cytomegalovirus, Epstein-Barr virus*
	Inborn errors of metabolism - *Hereditary fructose intolerance* - *Tyrosinemia type 1* - *Mitochondrial disorders* - *DLD (E3) deficiency* - *Fatty acid oxidation defects* - *Urea cycle disorders* - *Glycogen storage disease type IV* - *Wilson disease* - *Congenital disorders of glycosylation* - *Transaldolase deficiency* - *Adenosine kinase deficiency*
	Shock or sepsis Hemophagocytic lymphohistiocytosis

Table 2: A non-exhaustive list for the differential diagnosis of pediatric malabsorption.

Pediatric malabsorption – Differential Diagnosis
Coeliac disease
Pancreatic disorders - *Cystic fibrosis* - *Exocrine pancreatic insufficiency* - *Chronic pancreatitis* - *Johanson-Blizzard syndrome* - *Schwachman-Diamond syndrome*
Crohn's disease
Infectious diarrhea - *Giardia lamblia* - *Cryptosporidium* - *Hookworm*
Hepatobiliary dysfunction with cholestasis
Short bowel syndrome
Congenital disorders of the brush border enzymes - *Glucose-galactose transporter deficiency* - *Sucrase-isomaltase deficiency* - *Microvillus inclusion disease* - *Trichohepatoenteric syndrome*
Inborn errors of metabolism - *Abetalipoproteinemia* - *Mitochondrial disorders, including MNGIE and Pearson syndrome* - *Congenital disorders of glycosylation*
Acrodermatitis enterohepatica
Intestinal lymphangiectasia

metabolic disorders (Table 1). Pediatric ALF is defined by the biochemical evidence of severe liver injury, i.e. increased transaminases and/or biliary dysfunction, and a vitamin K-unresponsive coagulopathy (INR ≥ 1,5 with encephalopathy or INR ≥ 2 without encephalopathy) (1). Important in this definition is the response to vitamin K, which will differentiate a tentative diagnosis of ALF from disorders associated with severe vitamin K deficiency such as inadequate intake, drug interference or malabsorption. Hence, intravenous administration of high dose vitamin K1 (1 mg for infants and 10 mg for children) should be pursued in any patient demonstrating new onset biochemical evidence of hepatocellular injury and coagulopathy (Figure 2) (1). In case of vitamin K deficiency, complete normalization of the coagulopathy is generally observed within hours of parenteral vitamin K administration. In liver failure, on the other hand, vitamin K will at best improve but never normalize the coagulopathy, making the resulting prothrombin time/INR a fairly good marker for the severity of liver damage. In addition, dosage of coagulation factors V and VII prior to vitamin K administration can further support the diagnosis, since the synthesis of factor V is independent of vitamin K.

Also in our case report, the presumed diagnosis of adenovirus-associated ALF was overruled by the prompt correction of the INR upon administration of vitamin K1. The alternative hypothesis of malabsorption was further supported by faltering weight and growth (Figure 1), as well as biochemical markers suggestive of both protein and fat malnutrition. In addition, steatorrhea was observed during hospitalization and also accounted in retrospect for the recurrent episodes of diarrhea in the last 1,5 year.

Pediatricians are regularly facing failure to thrive or malabsorption, and are therefore familiar with its differential diagnosis. Nevertheless, more rare disorders should also be considered, especially when biochemical or clinical findings are inconsistent with the usual suspects (Table 2) (5,6). Also in our case report, it were some peculiar lab results that directed us towards the final diagnosis. For example, a mild pancytopenia was observed that did not improve upon recovery from adenovirus gastroenteritis. In addition, red blood cells were macrocytic in the absence of vitamin B12 or folic acid deficiency or a high reticulocyte count. Also, lactic acid remained elevated despite thiamine substitution, and could thus not be accounted for by the malabsorption per se. Hence, the diagnosis of Pearson syndrome was already assumed early in the course of the hospitalization, based on

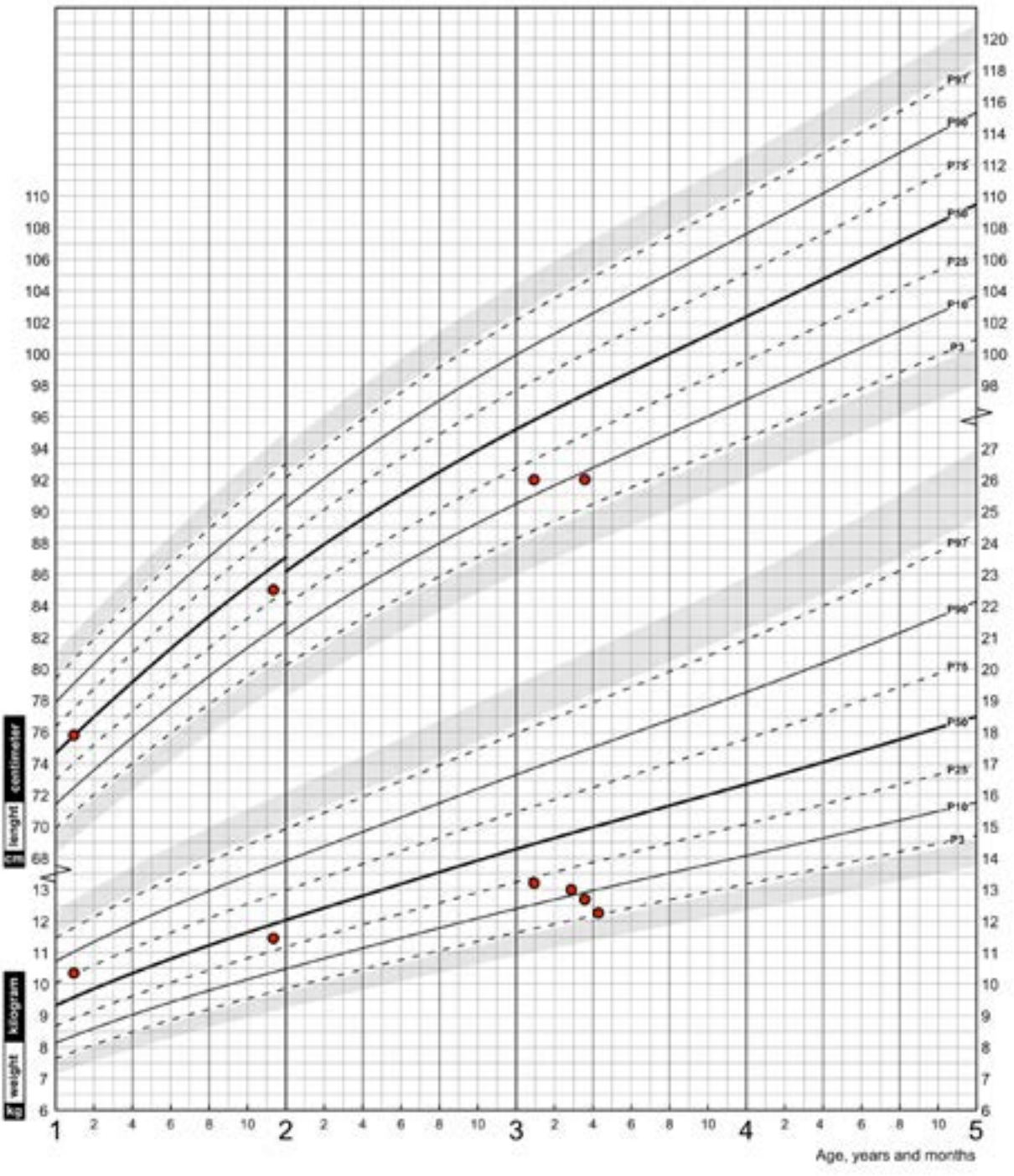
the co-occurrence of pancytopenia with macrocytosis, lactic acidosis, liver dysfunction and exocrine pancreatic insufficiency.

Pearson syndrome is a multisystem mitochondrial disorder originally defined by the presence of sideroblastic anemia and to a lesser extent exocrine pancreatic insufficiency. Together with Kearns-Sayre Syndrome (KSS) and Progressive External Ophthalmoplegia (PEO), Pearson syndrome constitutes one of the three overlapping phenotypes of SLSMDs (2). These large mitochondrial DNA (mtDNA) deletions usually occur spontaneously, either through improper mtDNA repair or replication. Therefore, germline transmission, i.e. inheritance through the maternal line, is only observed in a small proportion of patients with SLSMDs (7).

Classical Pearson syndrome presents in infancy with bone marrow failure and transfusion-dependent sideroblastic anemia. Exocrine pancreatic dysfunction is a variable finding, only seen in about 30% of patients (2,3,8). In addition, liver dysfunction, lactic acidosis and failure to thrive are some of the more prevalent clinical features. Pearson syndrome is often fatal at young age, due to septicemia, overwhelming lactic acidosis or hepatocellular insufficiency (9). Although patients surviving infancy typically demonstrate hematological improvement, they develop features compatible with KSS over time (2). This phenotypical shift is assumed to result from mitotic segregation with a gradual clearance of mtDNA deletions from rapidly dividing cells, and their accumulation in non-dividing tissues, e.g. the endocrinological organs and the central nervous system (7). As such, patients may develop pigmentary retinopathy, external ophthalmoplegia, progressive neurological impairment, sensorineural hearing loss, endocrinological issues (e.g. adrenal insufficiency and diabetes mellitus), renal tubulopathy and cardiac conduction defects (2,4).

Our case report relates to the phenotypic heterogeneity of Pearson syndrome. Although our patient demonstrated several features associated with

Figure 1: Growth charts (http://www.vub.ac.be/groeicurven) of the patient upon presentation, demonstrating a decline of both weight and height centiles with a more pronounced decline for weight compared to height.



Pearson syndrome, the hematological findings, which are considered as the chief hallmark, were only present to a limited extent.

At this point, no curative treatment exists for patients with Pearson syndrome. Therefore, symptomatic management and awareness of possible complications are critical to minimize disease-associated mortality and morbidity (7).

Conclusion

This case report highlights the importance of a comprehensive differential diagnosis in the patient with malabsorption and/or exocrine pancreatic insufficiency. Additional features such as liver dysfunction, elevated lactate or refractory megaloblastic anemia should trigger further genetic and metabolic investigations. Because of the phenotypic variability, Pearson syndrome should be considered in any patient with suggestive clinical features, even in the absence of the full clinical spectrum.

The authors have no conflict of interest to declare. Informed consent was obtained. This case report is approved by the ethical committee of University Hospitals of Leuven (S66706).

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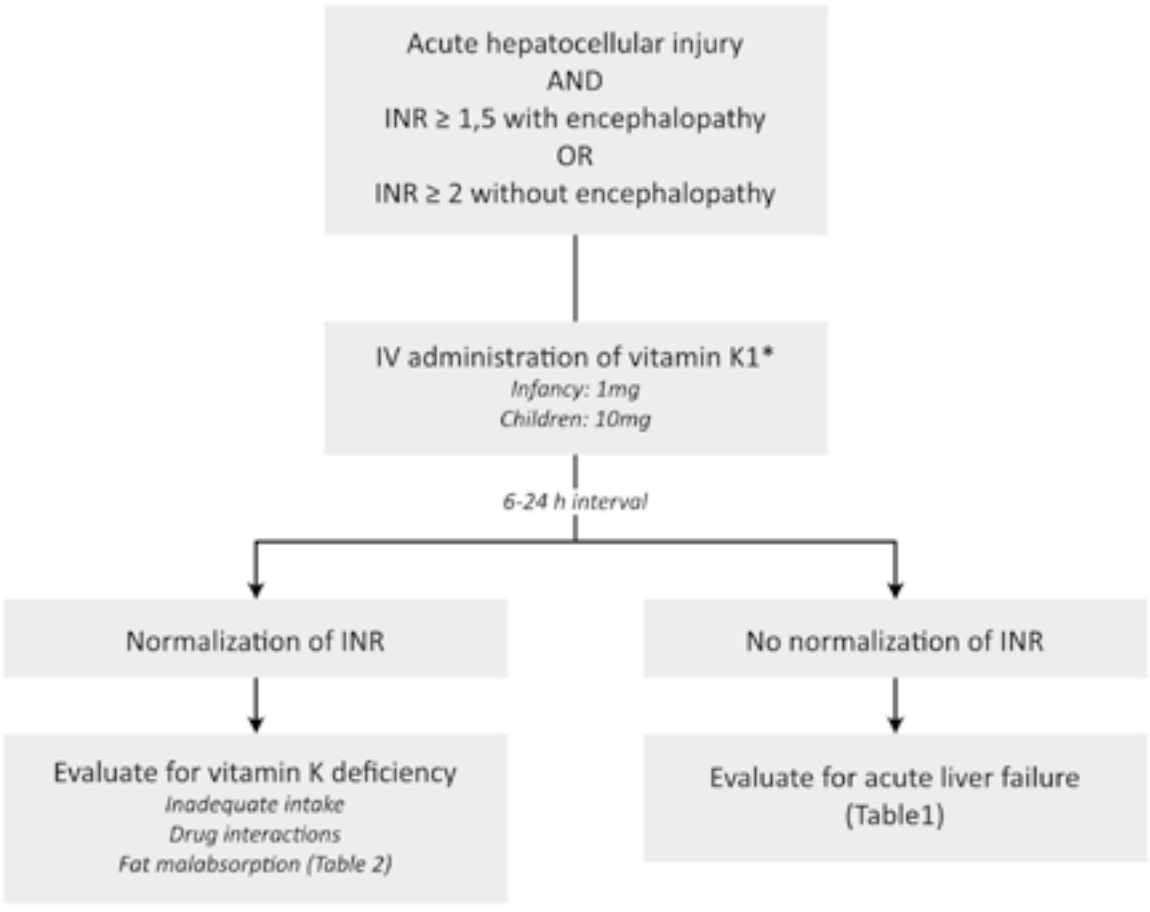
Figure 2: Administration of vitamin K in patients with hepatocellular injury and coagulopathy.
*In addition dosage of factor V and VII can be performed prior to the administration of vitamin K. Both factor V and VII will be decreased in case of acute liver failure, whereas only factor VII will be decreased in case of vitamin K deficiency.



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). Pour la liste complète des excipients, voir rubrique 6.1 du RCP complet. • **Indications thérapeutiques :** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration :** Posologie : **Tableau 1. Résumé de la posologie : Age lors de la première dose : Nourrissons de 2 à 5 mois[a] : Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c]. - **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c]. • **Age lors de la première dose : 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 avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 2 à 10 ans : 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'autres doses de rappel n'ont pas encore été déterminés. [d] Voir rubrique 5.1 du RCP complet. * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration : Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, souscutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6. **Contre-indications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1. **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 entrainer 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 (voir rubrique 5.1 du RCP complet). 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 (voir rubrique 5.1 du RCP complet). 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. Ce médicament contient moins de 1 mmol (23 mg) de sodium par dose, c'est-à-dire qu'il est essentiellement « sans sodium ». Tracabilité : Afin d'améliorer la tracabilité 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 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69 % à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et *Haemophilus influenzae* de type b), contre 44 % à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables : Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) - Fréquent : (≥ 1/100 à < 1/10) - Peu fréquent : (≥ 1/1 000 à < 1/100) - Rare : (≥ 1/10 000 à < 1/1 000) - Très rare : (< 1/10 000). Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles). Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans) :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Troubles du métabolisme et de la nutrition : Très fréquent : troubles alimentaires. Affections du système nerveux : Très fréquent : somnolence, pleurs inhabituels, céphalée. Peu fréquent : convulsions (y compris convulsions fébriles). Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des **méninges** (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections vasculaires : Peu fréquent : pâleur (rare après le rappel). Rare : syndrome de Kawasaki. Affections gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel). Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans) - Peu fréquent : eczéma - Rare : urticaire. Affections musculosquelettiques et systémiques : Très fréquent : arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité. - Peu fréquent : fièvre (≥ 40 °C). - Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois). **Adolescents (à partir de 11 ans) et adultes :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. - Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques et systémiques : Très fréquent : myalgies, arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise. - Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois). Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique :** Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance - Boîte Postale 97 - B-1000 Bruxelles - Madou - Site internet : www.notifieruneffetindesirable.be - e-mail: adr@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 - e-mail: crpv@chru-nancy.fr ou Direction de la Santé - Division de la Pharmacie et des Médicaments - 20, rue de Bitbourg - L-1273 Luxembourg-Hamm - Tél.: (+352) 2478 5592 - e-mail: pharmacovigilance@ms.etat.lu - Link pour le formulaire : https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.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:** 25/02/2022 (v13). **MODE DE DELIVRANCE:** Sur prescription médicale. **Référence :** SmPC Bexsero

PM-BE-BEX-ADVR-220002 - Août 2022 | E.R.: GlaxoSmithKline Pharmaceuticals s.a./n.v.
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GSK

Congenital Cytomegalovirus infection in Flanders: demography, management and outcome

PhD thesis presented on 16/2/2022 at Ghent University, Ghent, Belgium.

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Abstract

Congenital CMV is the most frequent congenital infection worldwide. Because of the major disease burden of cCMV, it is important to obtain data on congenital CMV infection as precisely as possible in order to optimize pre- and postnatal management and therapy. The Flemish cCMV registry collects data on diagnosis, management, treatment and follow-up of children with congenital CMV. It is, to our knowledge, the first time that outcome data are presented in such a large cohort of children with congenital CMV. Many of our data correspond well with what is known in literature or described in other cohorts.

Background

Congenital cytomegalovirus infection (cCMV) is the most common congenital infection affecting about 0,15-2% of all live births worldwide and 0,5% in Europe (1,2). In the United States (US), Canada, Western Europe, and Australia, cCMV occurs in about 5–7 per 1000 live births overall. In other parts of the world, such as Latin America, Africa, and most Asian countries, cCMV rates are higher at approximately 10–30 per 1000 live births (3).

Congenital CMV has a significant long-term impact on affected children, being the major cause of non-hereditary sensorineural hearing loss and the major infectious cause of neurodevelopmental abnormalities in infants born in developed countries. Despite this important disease burden, cCMV remains largely unrecognized and there is limited evidence on which to base management and therapy of children with cCMV infection. Since large-scale screening programs are not available to this point, we can only base our knowledge on data obtained by registries.

This PhD work is based on the Flemish CMV registry containing data on 1059 children with cCMV infection. In 2007 the registration of patients that presented with cCMV in the collaborating hospitals (Ghent University hospital, University hospital Leuven, University Hospital Antwerp, Middelheim Antwerp, Hospital Network Antwerp and AZ Sint Jan Bruges) was started.

Results

Conducting a registry for 14 years has shown us the possible limitations and shortcomings of a clinical registry and over the years we succeeded in addressing some of these shortcomings.

The development and introduction of the electronic version of the database was an important milestone which improved data gathering in a substantial way. In the electronic database, all data are reported in a uniform manner which makes it easier to describe the results. And, by making the database available online, more patients can be recruited, including from non-tertiary hospitals. To reduce the amount of missing data on neurological follow-up a patient-reported questionnaire was developed, based upon validated scoring systems for neurodevelopmental outcome, to evaluate the neurological development of children of 5-6 years of age. We have found that the use of questionnaires was most valuable and helped in filling the data gaps on long-term neurodevelopmental outcome. However, interventions to increase the response rate may enhance our data gathering even more (4).

During these 14 years of registration, data were collected on prenatal/neonatal management, treatment and follow-up of 1059 children with cCMV in Flanders. It is, to our knowledge, the first time that data are presented in such a large cohort of children with cCMV. Symptomatic disease was diagnosed in 319/1059 (30,5 %) children. Of those 13,5 % were classified as mild, 16 % as moderate and 70,5 % as severe infections. Antiviral therapy was given in 63,9 % of patients eligible for therapy. As for long-term follow-up, data show that both symptomatic and asymptomatic children can develop long-term sequelae, independent of the timing of seroconversion (5).

Hearing outcome in this population was described for the first time in 2016. Results from 123 children with a symptomatic and 256 children with an asymptomatic cCMV infection were analyzed. In children with symptomatic cCMV, 63% had hearing loss, in the group with asymptomatic cCMV this was only 8%. Delayed-onset hearing loss occurred in 10.6% of symptomatic cCMV children compared to 7.8% of children with asymptomatic cCMV. In symptomatic children 29.3% used some kind of hearing amplification, this was the case in 1.6% of asymptomatic children (6).

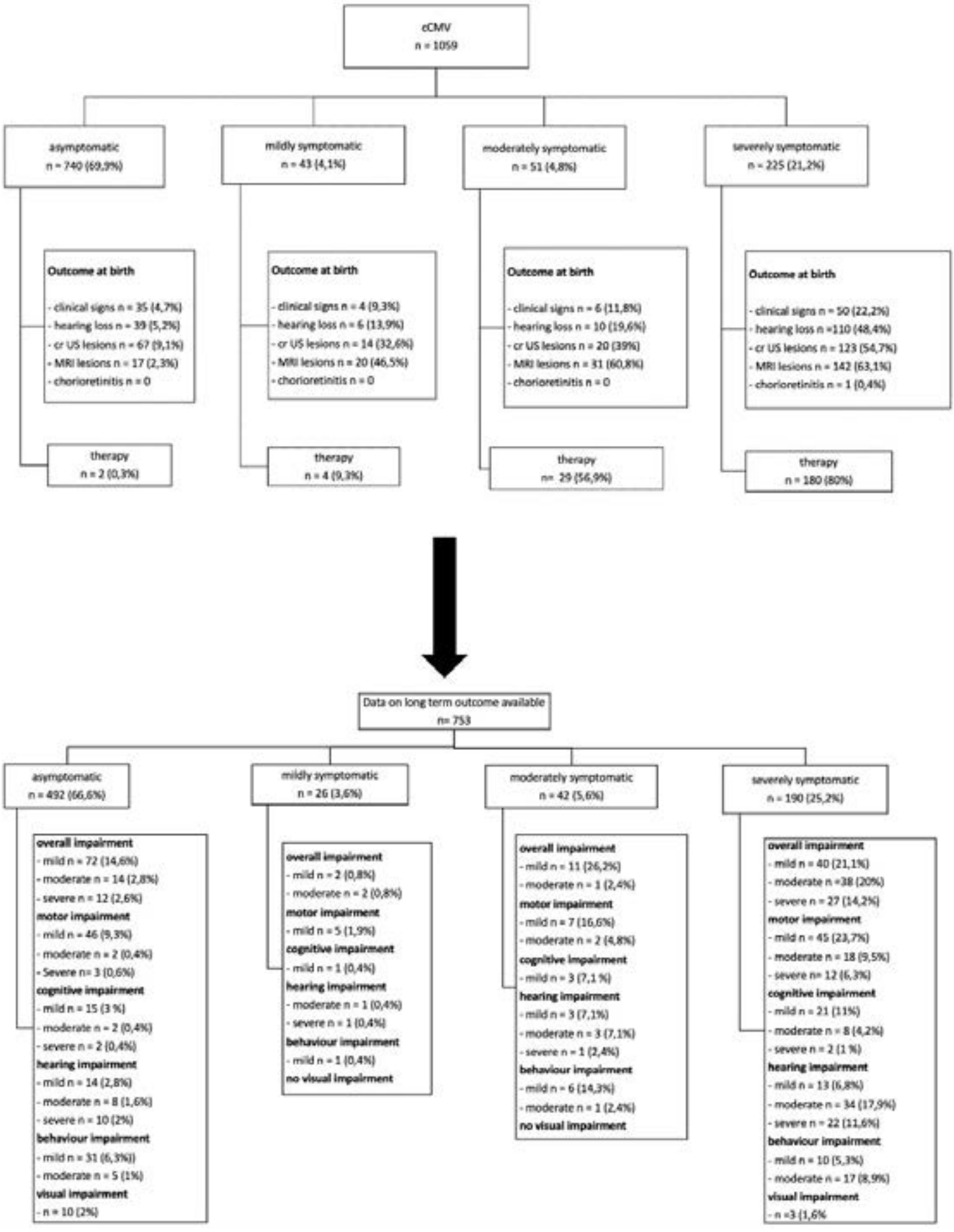
Our results show that, during follow-up of children with cCMV infection, special attention should be given to audiological follow-up, to the detection of hypotonia at young age which might impact motor development, to the possible higher risk of autism spectral disorder and to the risk of speech and language impairment even in absence of hearing loss.

Figure 1 presents an overview of the cCMV-population in Flanders between 2007 and 2020.

When comparing our data with what is described in literature, our data seem to confirm some hypotheses regarding cCMV or support the current recommendations for counselling and management. However, some data, although sometimes acquired in small groups, add to the discussion between experts on some topics on cCMV. One of those is whether or not cranial ultrasound (crUS) and cerebral magnetic resonance imaging (MRI) have both a place in the assessment of children with congenital cytomegalovirus infection. In our study, one in five children with normal crUS showed abnormal findings on MRI which suggests that both are complementary in the assessment of CNS involvement in children with cCMV (7).

During the 14 years of data collection, an additional study was set up to evaluate the potential of dried blood spots (DBS) as a congenital cytomegalovirus (cCMV) testing specimen. For this purpose, the laboratory diagnostic accuracy of polymerase chain reaction (PCR) on DBS was compared to viral urine cultures from neonates suspected for cCMV. The results of this study have shown that CMV-PCR on DBS could be valuable as screening tool but not for diagnostic purposes (8).

Figure 1: General overview of our cCMV-population in Flanders



Conclusion

The importance of registries is well established: the provided data can help develop clinical research, improve patient care and can be a valuable source of data on patient outcomes. This is one of the most important goals of the Flemish registry, founded in 2007.

Conducting this registry enabled us to describe both the perinatal characteristics and the long-term neurodevelopmental outcome of children with cCMV, included in the registry between 2007 and 2020. It is, to our knowledge, the first time that outcome data are presented in such a large cohort of children with congenital CMV. The fact that many of our data correspond well with what is known in literature or described in other cohorts, shows that our results could be representative of the (primary) cCMV population in Flanders. Our research also underscores the need for a thorough follow-up in all cCMV infected children, in order to estimate the true disease burden of this most common congenital infection worldwide.

Some data add to ongoing discussions on topics of cCMV and some preliminary findings raised interesting research questions that will require further studies. There are still many gaps in our understanding on cCMV. Hence, there is an ongoing need of collecting data on perinatal management and long-term follow-up of children with cCMV, in order to estimate the true long-term disease burden of this most common congenital infection worldwide. With the Flemish registry, an important step is taken to achieve this goal.

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Gunstige effecten van synbiotica op gastro-intestinale symptomen bij zuigelingen die lijden aan een KMEA

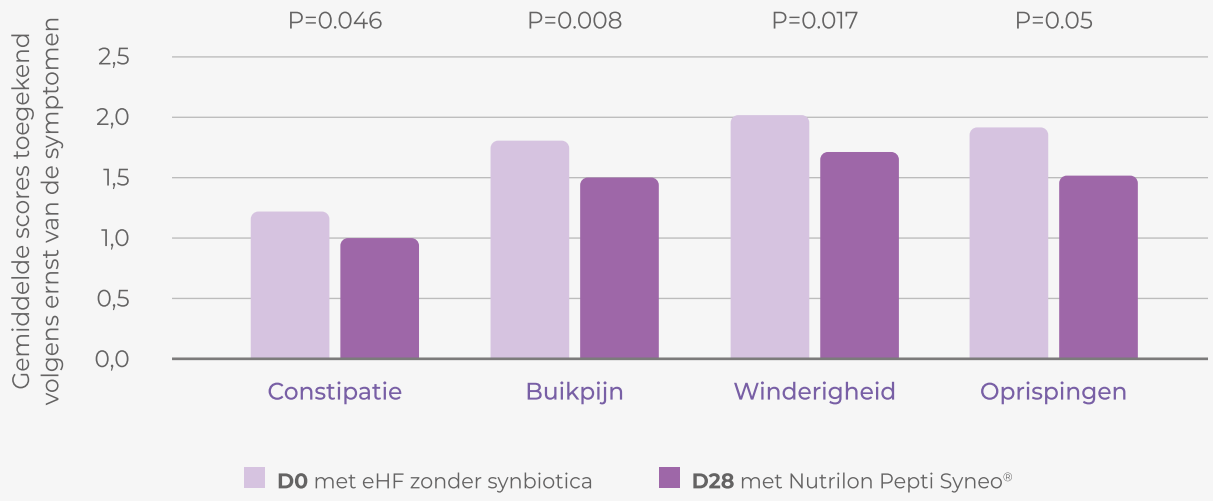
Koemelkeiwitallergie (KMEA) is een van de meest voorkomende voedselallergieën bij kinderen. Ze wordt meestal vastgesteld in de loop van het eerste levensjaar. KMEA gaat gepaard met een reeks symptomen ter hoogte van de luchtwegen, de huid en het gastro-intestinaal stelsel, zoals constipatie of buikpijn.[1,2]

Darmdysbiose, nauw verbonden met KMEA

De ontwikkeling van de darmmicrobiota van zuigelingen is een cruciale periode. Ze heeft namelijk een invloed op de immuunfunctie en de inflammatoire respons. Een verstoring van deze ontwikkeling kan een impact hebben op de gezondheid van het kind en op zijn vatbaarheid voor bepaalde ziekten later in het leven. Dysbiose wordt gedefinieerd als een verstoring van het evenwicht van de darmmicrobiota. Ze wordt gekenmerkt door een verminderde microbiële diversiteit, een verhoogde aanwezigheid van pathogene soorten (Clostridia en Coliformes) en een afname van het aantal gunstige soorten, zoals Bifidobacterium (meer specifiek *Bifidobacterium breve en Bifidobacterium bifidum*), in de darmmicrobiota. Het is duidelijk aangetoond dat zuigelingen die lijden aan KMEA dysbiose vertonen. Het loont dan ook de moeite om een wijziging van de darmmicrobiota te bestuderen als mogelijke strategie voor het management van KMEA.[2]

Figuur 1: Verbetering van de gemiddelde ernstscores voor gastro-intestinale symptomen op dag 28, vergeleken met dag 0.[1,10]

Een superieure effectiviteit in de verlichting van gastro-intestinale symptomen



NUTRILON PEPTI SYNEO® VERLICHT AANZIENLIJK

- ✓ Constipatie
- ✓ Buikpijn
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- ✓ Oprispingen

bij zuigelingen met een koemelkeiwitallergie die reeds op een eHF waren gestart

Het evenwicht van de darmmicrobiota herstellen

Talrijke bewijzen tonen aan dat voedingsbestanddelen zoals pre- en probiotica de darmmicrobiota moduleren. Door het evenwicht in de darmmicrobiota te herstellen, kunnen we de symptomen geassocieerd met atopie verlichten.[1,3]

Recente analyses[4,5] wezen uit dat het gebruik van een bereiding op basis van aminozuren (AAF) met synbiotica (prebiotica en *Bifidobacterium breve* M-16V) kan leiden tot het herstel van de darmmicrobiota, wat geassocieerd is met een lager risico op infecties en ziekenhuisopname en een afname van het geneesmiddelengebruik.[1,2]

Bifidobacterium breve M-16V wordt beschouwd als de meest doeltreffende stam om ontsteking te verminderen in geval van allergie[1,6,7,8] *Bifidobacterium breve* M-16V (probiotica) maakt deel uit van een specifieke synbiotische mix met galacto-oligosachariden met korte keten (scGOS) en fructo-oligosachariden met lange keten (lcFOS) (prebiotica). Deze pre- en probiotische componenten werden geselecteerd omwille van hun synbiotisch vermogen, met andere woorden hun vermogen om de gunstige effecten van pre- en probiotica afzonderlijk te versterken. Het is bewezen dat deze combinatie de soorten, die gunstig zijn voor de darmmicrobiota en de biomarkers voor gezonde darmen, significant verbetert. Bovendien vermindert ze ook het aantal infecties, het gebruik van geneesmiddelen en gastro-intestinale problemen bij zuigelingen met KMEA significant.[1,9]

Een extensief eiwithydrolysaat met een mix van synbiotica, een gunstige combinatie

De voordelen van deze combinatie van een extensief eiwithydrolysaat met een mix van synbiotica zijn bevestigd in een in 2022 gepubliceerde, prospectieve, longitudinale en multicentrische studie. In deze studie kregen zuigelingen met KMEA gedurende 28 dagen een eHF op basis van wei-eiwit (SeHF), die synbiotica bevatte: scGOS/lcFOS en *Bifidobacterium breve* M-16V.[1]

Impact van SeHF op de gastro-intestinale symptomen

De evaluatie van de gastro-intestinale symptomen vormde het primaire resultaat.
Op het einde van de studie werden significante verbeteringen vastgesteld van de ernst van de buikpijn, de oprispingen, de winderigheid en de constipatie (Figuur 1).
Er werd geen enkel ernstig symptoom geregistreerd (tegenover 27% voor alle symptomen samen, bij baseline). De andere gastro-intestinale symptomen (braken, misselijkheid, opgeblazenheid en diarree) waren grotendeels afwezig/licht van aard bij baseline en bleven ongewijzigd ($p > 0,05$, NS).[1]

Op het gebied van secundaire resultaten werd in de loop van de tijd bovendien een significante verbetering vastgesteld ($p < 0,05$) van rinitis (41%), jeukende ogen (73%) en atopische dermatitis bij zuigelingen met ernstige symptomen bij inclusie (afname van de PO-SCORAD©: 34,7-18,2 ($p = 0,003$)). De analyse bracht ook een significante toename van alle absolute antropometrische metingen en van de relatieve groei voor de geëvalueerde parameters (lengte, gewicht en hoofdomtrek) aan het licht. Daarnaast werd een verbetering van de levenskwaliteit van de verzorgers vastgesteld (score op de FAQL-PB-vragenlijst: +26,7%, $p < 0,05$). Het aantal ziekenhuisbezoeken en het gebruik van geneesmiddelen waren significant verminderd (respectievelijk -1,61 en -2,23, $p < 0,005$) in de loop van de 6 maanden na het opstarten van de SeHF.[1]

Darmdysbiose is frequent bij KMEA en vormt een grote uitdaging in de verzorging en dieetbehandeling van zuigelingen. Modulatie van de darmmicrobiota, meer in het bijzonder door toediening van pre- en probiotica, kadert in een aanpak van 'actief management' van KMEA en is gebaseerd op solide bewijzen. De resultaten van deze pilootstudie tonen aan dat SeHF's met synbiotica de gastro-intestinale symptomen van zuigelingen met KMEA significant verbeteren en zijn een meerwaarde vergeleken met eHF's zonder synbiotica. Deze studie is nog maar eens een bewijs voor de gunstige effecten van het gebruik van hypoallergene bereidingen met synbiotica in het management van KMEA.[1,2]

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The influence of maternal antibodies on the immune responses of term and preterm born infants

Ph D thesis presented on 15 October 2021 at the University of Antwerp, Belgium.

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Abstract

Vaccination during pregnancy is effective in providing protection against vaccine-preventable diseases in young infants. Here, timely (second rather than third trimester) pertussis vaccination during pregnancy is recommended, conveying protection against Bordetella pertussis in both term and preterm born infants. Additionally, breastfeeding during the first months of life can be advised to achieve additional mucosal protection. One must note that after infant vaccination, humoral and limited cellular interference by maternal antibodies was observed. However, clinical relevance of maternal interference has yet to be determined, as evidence of good serological and cellular immunogenicity against DTaP-IPV-HB-PRP~T vaccine after primary and booster vaccination was provided.

Introduction

The immune system of the young infant, although uniquely adapted to cope with various early life changes, relies on maternal help to overcome first encounters with pathogens (1). The transfer of maternal antibodies (Mabs) and other immune components in utero and later via the breast milk, is essential to protect the newborn against infectious diseases during the first months of life. The strategy of vaccinating pregnant women augments the disease-specific Mab concentrations in the newborn and offers protection against the targeted pathogen until the start of the infant's own primary immunization schedule or until the period of vulnerability is over (e.g. around 6 months for RSV) (2). The successes of this public health intervention have become more apparent over the last decades, as routine vaccination of pregnant women with tetanus toxoid, acellular pertussis (whooping cough), and inactivated influenza (flu) vaccines have led to a global reduction of neonatal tetanus, decreased pertussis outbreaks and have lowered the burden of seasonal influenza in pregnant women (3-5). The reassuring safety and efficacy data of vaccinating pregnant women with inactivated (non-live) vaccines has inspired many new targets for maternal immunization to improve global maternal and neonatal health against infectious diseases like e.g. RSV, CMV, GBS, and Zika (6). Yet, several questions regarding the strategy of in-pregnancy vaccination remain, for example: the optimal timing to vaccinate pregnant women or the effect of the strategy on preterm born infants. In addition, the observation that Mabs interfere with (or modulate) the infants' antibody responses at the time of the infants' vaccination, often resulting in significantly lower antibody concentrations amongst infants born to vaccinated mothers, has raised some concerns to the strategy (7, 8). Here, we explored the benefit of maternal pertussis vaccination (per example of a recommended maternal vaccine) in a preterm cohort and provide evidence on the impact of high Mabs on both humoral and cellular immune responses after infants' primary and booster vaccination.

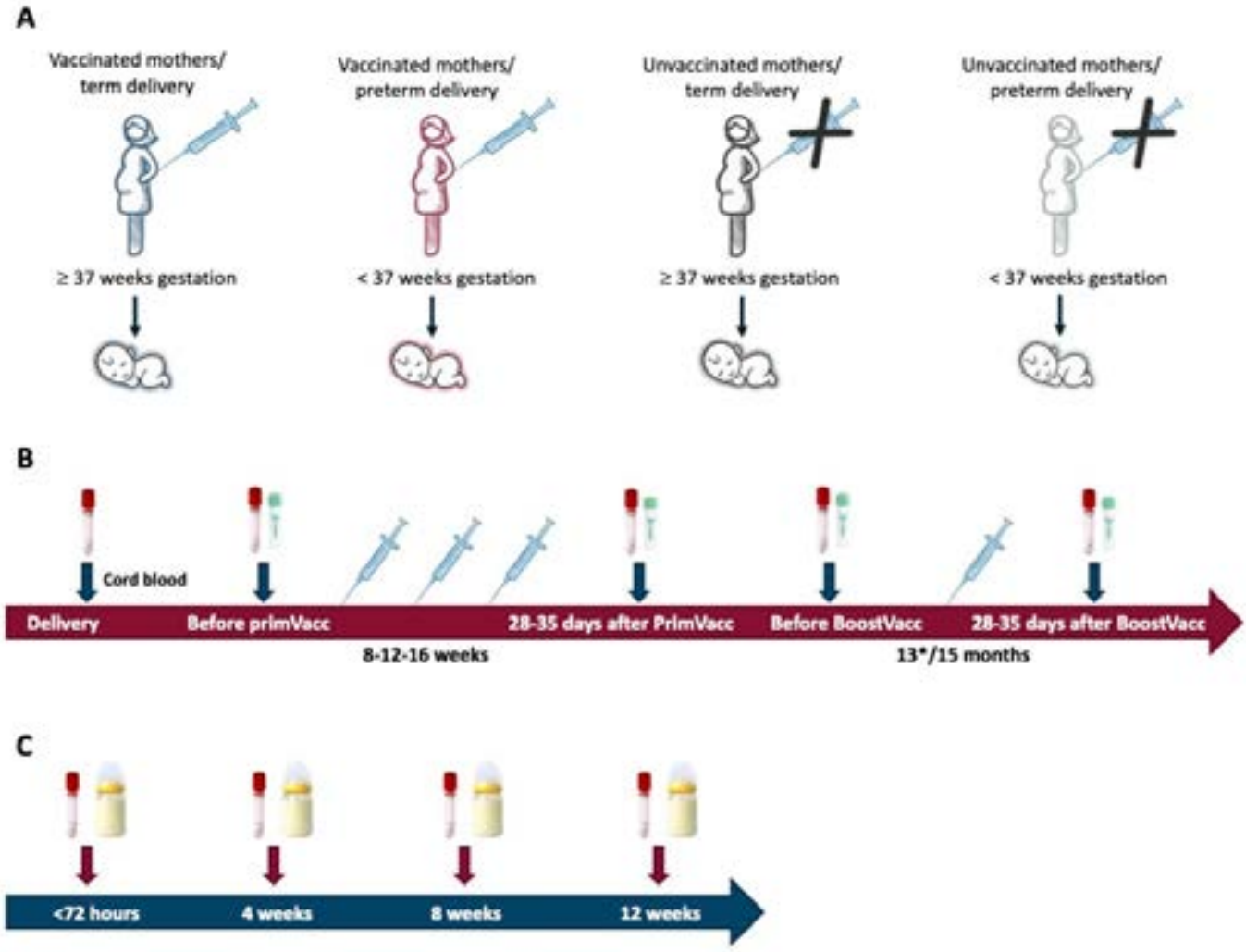
Results

A prospective observational study (NCT02511327) conducted in Belgium, included mother-infant pairs who were either vaccinated or not vaccinated with a pertussis-containing vaccine (Tdap, Boostrix®, GSK Biologicals) during pregnancy and did or did not deliver prematurely (Figure 1). Infants were vaccinated with DTaP-IPV-HB-PRP~T vaccine (HexyonÆ, Sanofi Pasteur) at 8-12-16 weeks (primary vaccination) and at 13 or 15 months of age (booster vaccination for preterm and term born infants, respectively), according to the recommended Belgian vaccination schedule.

This study confirmed that premature delivery is linked to a reduced transplacental transport, resulting in lower maternal-fetal transplacental transport ratios in preterm infants born to in-pregnancy vaccinated and unvaccinated women (9). Additionally, no influence of the maternal vaccination status on these transplacental transport ratios was detected. Nevertheless, at birth and before primary vaccination significantly higher Tdap antibody levels were observed in preterm infants from vaccinated women compared with term and preterm infants from unvaccinated women. Moreover, longer in-pregnancy vaccination to delivery intervals were significantly correlated with higher transplacental transport ratios in both term and preterm infants. These findings illustrate that preterm infants can profit from Tdap vaccination during pregnancy, even more so when the vaccination-delivery interval is increased by vaccinating earlier in pregnancy (e.g. second trimester rather than third trimester) (9).

Additional advantages of maternal pertussis vaccination might be attained when preterm infants are being breastfed, as we demonstrated comparable pertussis specific antibody levels in breast milk between in-pregnancy vaccinated mothers who delivered term or preterm babies that remained detectable up until 12 weeks after delivery (10). This strengthened the hypothesis that antibodies in breast milk could help bridge the vulnerability gap induced by a shortened period of transplacental transport of antibodies linked to prematurity, and potentially offer additional mucosal and clinical protection.

Figure 1: Schematic representation of the study design (A), serum and heparin sample collection in infants (B), serum and breast milk sample collection in women (C). * vaccination timepoint for preterm born infants.



Next to the benefits of maternal Tdap vaccination in preterm infants, our research also provides a first report on the antibody responses to Hexyon® in preterm infants (Figure 2) (9). We hereby show that primary vaccination induces comparable antibody levels for all pertussis antigens in term and preterm infants, yet booster vaccination promoted significantly lower antibody levels for some pertussis antigens in preterm infants born to Tdap-vaccinated women when compared to their term counterparts. Nevertheless, their antibody levels for all Tdap vaccine antigens remained comparable to those of term and preterm infants from unvaccinated women after booster vaccination, supporting immunogenicity of Hexyon® vaccine after primary and booster vaccination in preterm infants.

Despite this good serological immunogenicity in both term and preterm infants, the presence of high Mab concentrations at the time of primary vaccination significantly reduced the infant's humoral immune responses to some of the Tdap antigens (Diphtheria Toxoid [DT] and Filamentous Hemagglutinin [FHA]) (9). After booster vaccination, this interference by Mabs was only observed for the DT antigen in term infants of vaccinated mothers. Still, all infants achieved antibody levels above the correlate of protection for DT, suggesting that interference by Mabs did not increase the infant's susceptibility to Diphtheria. Unfortunately, it remains difficult to predict the clinical significance of this interference, especially for pertussis where no serological correlate of protection has been defined.

So far research has focused on the effect of Mabs on the infant's humoral immune response, however knowledge regarding the influence on the infant's cell-mediated immune (CMI) responses are lacking (11). Previous data demonstrated that the infants' T cell compartment remains largely unaffected after vaccination in the presence of Mabs, with some studies observing differences in cytokine secretions (12). Overall, it remains challenging to confirm the hypothesis that Mabs do or do not modulate the CMI responses of the infant, as most data originate from animal studies and no information on maternal vaccines like pertussis and influenza vaccination are available (11). Within our research the cellular responses of term and preterm infants born to in-pregnancy vaccinated women was evaluated. We demonstrated that both term and preterm born infants are capable of mounting a CMI response after primary and booster vaccination with Hexyon® vaccine, providing evidence on the immune competence of young infants (13). With regards to the hypothesis of cellular interference by Mabs, no significant differences in the specific T lymphocyte responses of infants born to vaccinated or unvaccinated mothers were recognized after primary vaccination. However, infants who were cellular non-responders for IL-13 one month after booster vaccination were observed to have significantly higher Mab concentrations at birth, implicating that Mabs might modulate the infant's CMI responses later in life. In addition, a positive correlation between the infants' serum antibodies and their lymphoblast proliferation and cytokine secretions after primary and booster vaccination was observed, adding weight to this hypothesis. Still, more research on the impact of high Mabs on the immune development of the infant and their possible long-term effects are needed.

In general, our research provides confidence towards the strategy of in-pregnancy vaccination for term and preterm infants, as both transplacental and antibodies provided by breast milk can offer additional protection during the first months of life. However, vaccinating term and preterm infants in the presence of high Mab concentrations resulted in lower antibody levels to some of the Tdap antigens. Moreover, modulation of the infant's CMI response by Mabs after booster vaccination was also observed. Yet, good serological and cellular immunogenicity against Hexyon® was established in both term and preterm infants, raising questions on the possible long-term effects of maternal immunization and its clinical significance.

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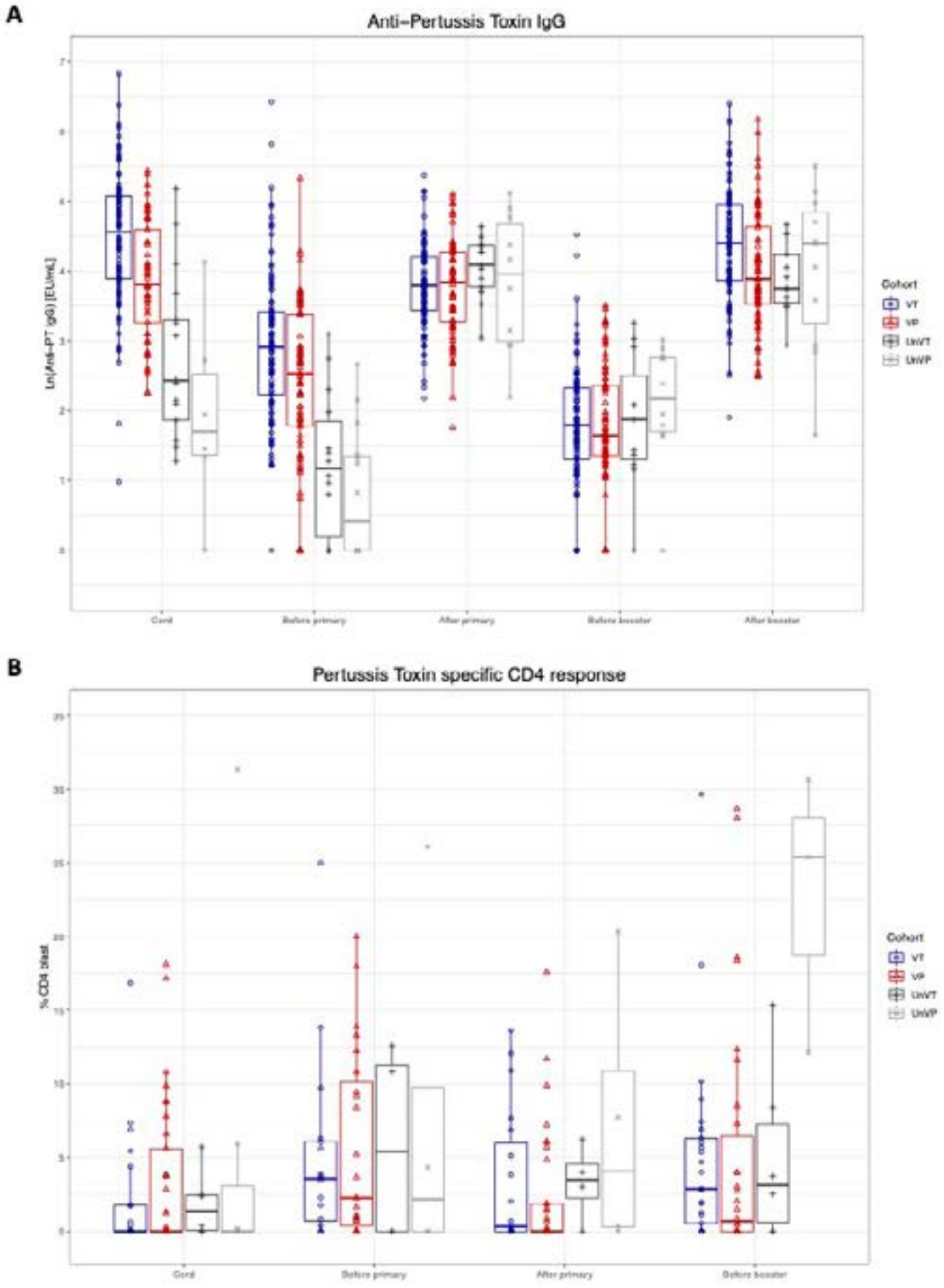
Figure 2: Antibody concentrations (with anti-pertussis toxin [PT] as an example [A]) and PT-specific cellular immune responses (CD3+CD4+ response as an example [B]) in term infants from vaccinated women (VT cohort), preterm infants from vaccinated women (VP cohort), term infants from unvaccinated women (UnVT cohort) and preterm infants from unvaccinated women (UnVP cohort) at the different study time points. Full depiction of the infants antibody responses against the DTaP-IPV-HB-PRP~T (Hexyon®) vaccine available in Maertens et al. (9) and full report of cellular responses available in Orije et al. (13). PT antibody concentrations are expressed in EU/mL and on a natural logarithmic scale. CD3+CD4+ lymphoblasts populations are presented in percentages (%CD4 blast; after correction with the unstimulated culture).



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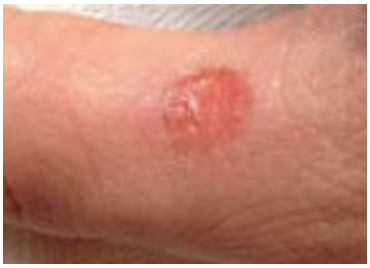

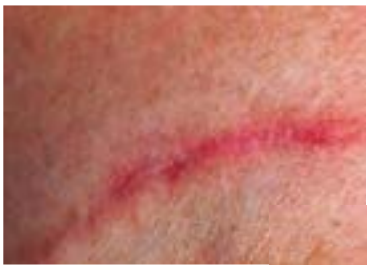

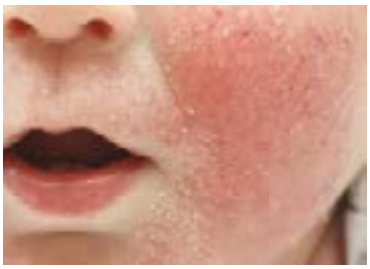

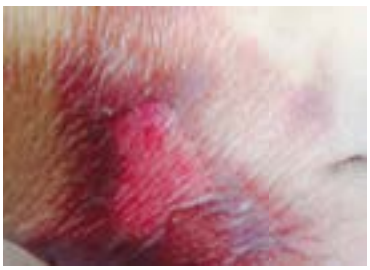

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Visuoperceptual profiling and game-based rehabilitation in children with cerebral visual impairment

PhD thesis presented on 20/12/2021 at KU Leuven, Leuven, Belgium.

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Abstract

Cerebral visual impairment (CVI) is a brain-based visual disorder. Children with CVI experience heterogeneous impairments both in their basic visual orienting behaviours and in their visual perception. For instance, children show eye movement difficulties, are unable to recognize objects, or cannot find their favourite toy in a cluttered toy box. CVI lowers quality of life and poses a great economic burden, but despite these concerns, no standard treatment for CVI exists. In this PhD, we developed a quantification schema of visual orienting functions and visual perception, enabling the development of an individualized and adaptive game-based rehabilitation programme for CVI.

PhD summary

The heterogeneity present in cerebral visual impairment (CVI) calls for 1) quantified profiling of a child's strengths and difficulties to better understand the child's needs, and 2) development of a rehabilitation strategy that can be individualized and adapted to each child's profile, as one therapy cannot fit all children.

To better understand the heterogeneity in CVI, in the first two studies, we developed a means to quantify children's profiles in daily life using a questionnaire and in the clinic using a visuoperceptual test battery. In the **first study**, using an exploratory factor analysis, we retrieved a five-factor biologically and clinically plausible model which explained 56% of the total variance in the responses on 485 parent-reported Flemish CVI questionnaires, indicating daily life CVI symptoms (1). The five factors retrieved were: 1) object and face processing impairments, 2) visual (dis)interest, 3) clutter and distance viewing impairments, 4) moving in space impairments, and 5) anxiety-related behaviours. We found that children with CVI scored significantly higher on factor 1 to factor 4 compared to children without CVI, hence this model differentiated between children with and without CVI. By scoring children's daily life visual functioning according to this factor structure, a clearer picture of the type and severity of impairments present is obtained, serving as a first step towards more targeted therapy.

In the **second study**, we developed a visuoperceptual profiling schema reflecting children's visuoperceptual strengths and difficulties (2). We conducted a Delphi study including individual interviews and two questionnaire rounds involving both researchers and clinicians, experts in the field of visual perception. The Delphi study provided an understanding of which visuoperceptual dimensions are targeted by which visuoperceptual subtests administered in the clinic during the CVI diagnostic procedure. Expert consensus resulted in six visuoperceptual dimensions, namely, 1) visual discrimination and matching, 2) object or picture recognition, 3) visual spatial perception, 4) figure-ground perception, 5) motion perception, and 6) visual short-term memory. We found that while all six dimensions differentiated children with CVI from those without CVI, the most discriminating dimensions were object/picture recognition ($r = 0.56$), visual spatial perception ($r = 0.52$), visual discrimination and matching ($r = 0.47$), and figure-ground perception ($r = 0.39$). Therefore, quantifying a profile according to these six visuoperceptual dimensions can be used to characterise/map dysfunction and intact functions in children with CVI, further highlighting the most important skills that need training (see Table 1).

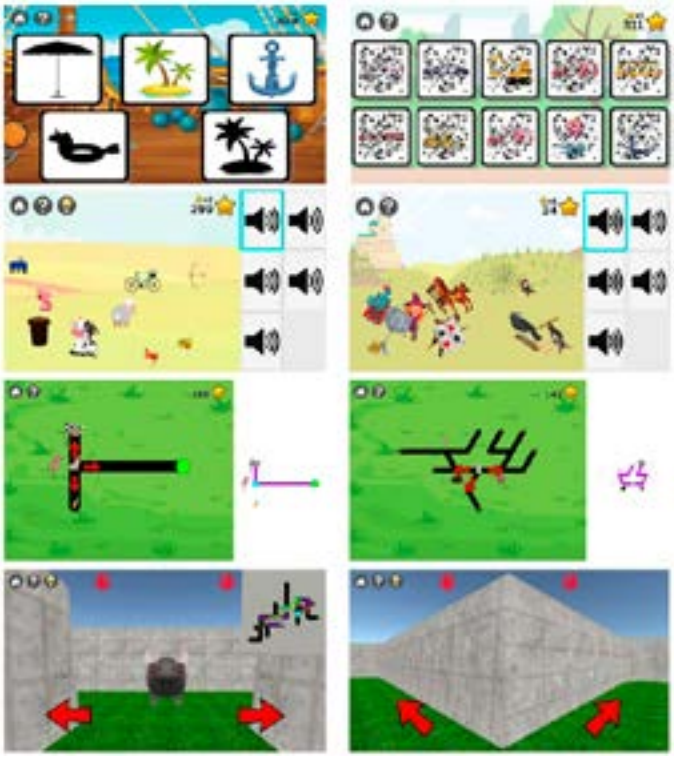
Results

In the **third study**, based on the visuoperceptual profiling schema, we developed individualized and adaptive mini-games (iVision mini-games) for children with CVI with a developmental age between 3-12 years (3). First, an informant-led design entailing focus groups with parents and therapists was used to elicit the user requirements and the gameplay of children with CVI, therapy goals, context of use, and the barriers and facilitators with which our rehabilitation would need to comply. Second, we proceeded to perform brainstorming sessions to generate game ideas within the development team, which resulted in the creation of four mini-games. The four mini-games named 1) MatchMaker, 2) Hurricane Chaos, 3) Maze Explorer 2D, and 4) Maze Explorer 3D can be seen in Figure 1. In MatchMaker, the goal is to find the most similar pair of cards, while prototypical images on the cards have undergone different manipulations, more specifically, details differ, different poses, missing parts, partial, atypical, silhouettes, contour, closure, noise, and viewpoints. MatchMaker aims to train mostly visual discrimination and matching, object/picture recognition, and figure-ground perception. In Hurricane Chaos, a hurricane has jumbled the objects and after clicking on the loudspeaker icon, a voice-over instructs which object the player has to find in the "chaos" in the jumbled scene. Hurricane Chaos aims to mostly train object/picture recognition and figure-ground perception, as well as visual discrimination and matching. In Maze Explorer 2D and Maze Explorer 3D, children have to navigate through and exit a

2D maze or 3D maze, respectively. The correct path and maze finish point are indicated in the mini map (another map on the right-hand side of the screen). These two games aim to target visual spatial perception, motion perception, and visual short-term memory. These mini-games integrate three key features, 1) Entry-level individualization: each child's average z-score on each of the six visuoperceptual dimensions is defined after the child undergoes visuoperceptual testing with an extensive test battery and 2) In-game adaptivity: the automatic adaptation of difficulty levels of the mini-games to the child's performance. These key features aim to place the child in the "flow" state in which a match between challenge and skill level is constantly attained. For instance, when the game is too easy, a more difficult level is shown next, whereas, when many errors are made and the child takes too much time, an easier level is provided. 3) Gameplay log-data: collected via an online dashboard that stores information such as the child's score, use of hints, time taken per game, errors etc. Third, in workshops, researchers and clinicians evaluated the rehabilitative game content by rating the manipulated images on their perceptual difficulty to create differing difficulty levels. Fourth, the researchers and clinicians linked the visuoperceptual dimensions to the mini-games and entry-level difficulty as well as defined adaptivity rules and evaluation criteria. Finally, we conducted formative testing including usability and player experience with researchers, clinicians, and neurotypical children. Researchers and clinicians rated the games highly, while neurotypical children highlighted several usability difficulties specifically in understanding the instructions, however, player experience was high. Feedback hereof was used to modify the games.

In the **fourth study**, we tested the feasibility of the newly developed visuoperceptual mini-games in 21 children with CVI. Children played the iVision mini-games in three sessions, in which their usability and player experience were registered using observations and questionnaires (Ben Itzhak N, Franki I, Laenen A, Wagemans J, Ortibus E. Usability and user experience of an individualized and adaptive game-based therapy for children with cerebral visual impairment. 2022, under review). While children reported a positive player experience, usability testing revealed problems in terms of effectiveness, understandability, and game design. Gameplay log-data revealed that in MatchMaker, children were challenged by the closure, missing parts, atypical, and noise manipulations. In Hurricane Chaos, children's visual search improved. Playing Maze Explorer 2D increased their navigational efficiency, while training with Maze Explorer 3D with both an egocentric (turning mini-map, self-centred) and allocentric (static mini-map, independent of view of child, based on environmental cues) representation was needed to improve navigation. Usability observations revealed the importance of integrating different elements into game design. Specifically, lessons learnt revolved around the following themes: tailored interactions/gestures/instructions, language, providing player control, familiarization time, balancing help and challenge, autonomy, avoiding fine motor skills and multiple sequences of actions, and integrating visual simplicity and consistency. Moreover, lessons learnt from player experience highlighted the necessity to integrate reward, challenge, immersive realistic experiences, immediate feedback on actions, and a rich media experience. This study resulted in further modifications of the games in terms of game content, visuals, and integration of stricter evaluation criteria. Therefore, a future Randomized Controlled Trial (RCT) should evaluate the effectiveness of training with these games on improving visuoperceptual functions and the transfer to tasks more similar to those encountered in daily life.

Figure 1: Example levels from the four iVision mini-games (3).
Notes. The left column shows examples of easier levels, while the right column shows examples of harder levels in the mini-games. The top row shows the MatchMaker game, the 2nd row the Hurricane Chaos game, the 3rd row the Maze Explorer 2D game, and the bottom row the Maze Explorer 3D game.



Finally, in the fifth study, since not only higher-level visuoperceptual skills but also basic visual orienting functions are impaired in CVI, we integrated a preferential looking eye tracking paradigm into the testing of children with CVI during their intake procedure (4). In this eye tracking paradigm, children were shown six different visual stimuli (e.g., simple cartoons) in one of four quadrants while their spontaneous eye movements were recorded. We aimed to quantify and relate a child's visual orienting functions to their daily life functioning and visuoperceptual abilities. Children who had impaired object and face processing impairments, greater visual (dis)interest, worse visual spatial perception and worse object and scene recognition had slower orienting responses to the visual stimuli. These novel results indicated that the integration of visual orienting function measurements with existing visuoperceptual assessments provide a better clinical picture. This study demonstrated the intricate relation between basic and higher-order stages of vision and the impact of visual orienting and visual perception difficulties on daily life functioning. In addition, it highlighted that, in clinic as well as in research, CVI should be approached from a holistic perspective.

To conclude, the development of serious games for children with CVI is a complex process, for which several steps following a multidisciplinary perspective are needed. Strengths and difficulties in everyday life and in standardized neuropsychological testing in children with CVI can now be quantified, providing ways to train skills in a personalized manner. In addition, visual orienting dysfunctions, easily detected by the preferential looking eye tracking paradigm we used, are potentially an early marker of higher visual perceptual deficits and add to the child's visual profiling. In the game development process, usability and player experience piloting phases provide invaluable information for optimizing games and should include researchers, clinicians, neurotypical children, as well as the target population.

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Table 1: Visuoperceptual subtests linked to the dimensions of the visuoperceptual profile (2).

Notes. Each child undergoes visuoperceptual testing and receives a z-score on each of the subtests and one average z-score on each visuoperceptual dimension. Beery-VMI-6: The Beery-Buktenica developmental test of visual-motor integration sixth edition; TVPS-3: Test of visual perceptual skills third edition; RAKIT-2: Revisie Amsterdamse Kinderintelligentie Test; PJLO: Preschool judgement of line orientation; NEPSY-II-NL: Developmental neuropsychological assessment second edition; OR: Object/picture recognition; VSP: Visual spatial perception; VDaM: Visual discrimination and matching; FGP: Figure-ground perception; MP: Motion perception; VSTM: Visual short-term memory. X's indicate the subtests that are used to quantify each dimension of the visuoperceptual profile.

TESTS	SUBTESTS	VISUOPERCEPTUAL DIMENSIONS					
		OR	VSP	VDaM	FGP	MP	VSTM
Beery-VMI-6	Visual perception		X	X			
	Visual-motor integration		X				
	Motor coordination		X				
TVPS-3	Visual discrimination		X	X			
	Visual spatial relationships		X	X			
	Visual memory		X	X			X
	Visual sequential memory		X	X			X
	Visual figure-ground		X	X	X		
	Visual closure		X	X			
	Form constancy		X	X	X		
L94	De Vos-task	X	X	X			
	Visual matching	X	X	X			X
	Line drawings occluded by noise	X			X		
	Overlapping line drawings	X		X	X		X
	Unconventional object views	X	X				
RAKIT-2	Figure recognition	X					
	Hidden figures	X	X	X	X		
PJLO		X	X	X			
NEPSY-II-NL	Geometric puzzles		X	X			
	Arrows		X				
Motion perception tasks	Motion-defined form	X			X	X	
	Global motion coherence					X	
	Motion speed					X	
	Biological motion	X				X	
	Average z-score	X	X	X	X	X	X

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Identifying pitfalls and opportunities of magnetic resonance imaging in spondylarthritis

PhD thesis presented on April 15, 2021 at Ghent University, Ghent, Belgium

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Keywords

Spondyloarthritis, sacroiliac joint, magnetic resonance imaging, immunoscintigraphy, certolizumab pegol

Introduction

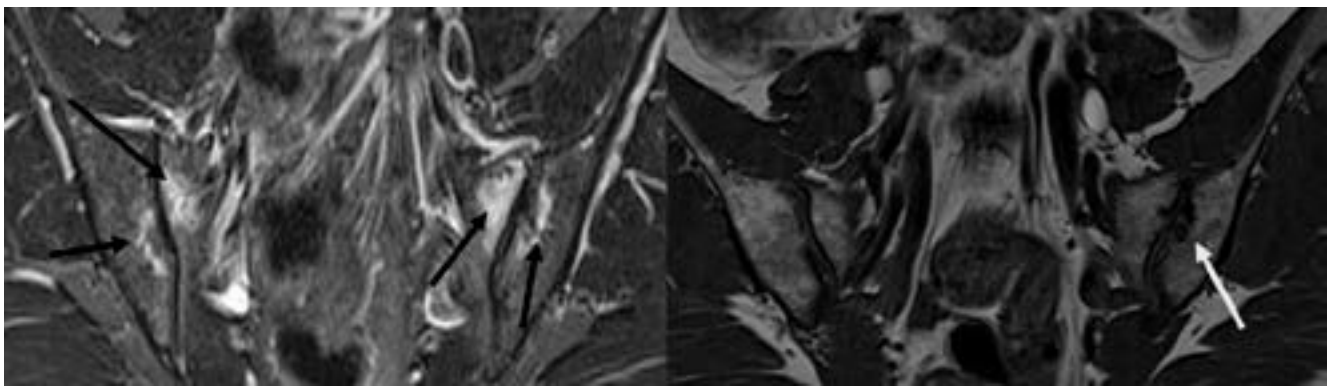
Spondyloarthritis (SpA) is a disease concept characterized by inflammation of joints and/or entheses in combination with characteristic extra-articular manifestations, including inflammatory bowel disease, psoriasis, and acute anterior uveitis. SpA can be classified as either peripheral (i.e. pSpA) or axial (i.e. axSpA), depending on the pattern of joint involvement (1,2). pSpA mainly presents with arthritis and/or enthesitis of the extremities, whereas axSpA is characterized by sacroiliitis and/or spondylitis, which manifests as inflammatory back pain. Considering its heterogeneous presentation, the diagnosis of SpA relies on pattern recognition in which the presence of clinical manifestations, laboratory features such as HLA-B27 positivity, and imaging findings are combined. Imaging of the sacroiliac joints (SIJs) is considered to be an important pillar in the diagnosis of axSpA. Before the availability of magnetic resonance imaging (MRI), sacroiliitis was detected by conventional radiography. Nevertheless, radiography solely visualizes structural changes secondary to inflammation and not acute inflammation itself. Structural changes are in many axSpA patients a late radiographic finding and may even never occur in some, leading to a significant diagnostic delay. In contrast, MRI has the ability to detect acute sacroiliitis in a pre-radiographic stage, presenting as bone marrow edema (BME) of the SIJs. This, in combination with an improved awareness among health professionals has reduced the diagnostic delay in axSpA (1). The Assessment of SpondyloArthritis international Society (ASAS) classification criteria are often wrongfully applied in clinical practice as diagnostic criteria. Moreover, the ASAS definition of a positive MRI for sacroiliitis may be non-specific (3). These concerns raise the possibility of an overdiagnosis of axSpA. We therefore took an in-depth look into the challenges and opportunities of MRI in the assessment of SpA. Our general aims were to define important pitfalls of MRI in the diagnosis of axSpA with a focus on the impact of biomechanical stress and to explore its potential in assessing the disease extent and treatment response in pSpA. Furthermore, we aimed to provide suggestions to bypass the identified pitfalls. This thesis aimed to work towards a more rational use of MRI.

Methodology

In the first part of this thesis, we focused on the MRI appearance of the SIJs and spine in non-SpA subjects and its relation to biomechanical stress. SIJ MRI was performed in 35 postpartum women on different time points (within 10 days after giving birth, 6 months, and 12 months if 6-month MRI was positive for sacroiliitis) to delineate the relationship between biomechanical stress on the pelvis during pregnancy and delivery and the occurrence of SpA-like MRI lesions (4). In a second study, SIJ MRI studies in 22 military recruits before and after 6-week standardized intense training aimed to measure the impact of vigorous physical exercise on the occurrence of inflammatory and structural lesions (5). Finally, to further assess the prevalence of SpA-like MRI lesions in non-SpA subjects, SIJ and spinal MRI was performed in 95 healthy subjects aged 20-49 years (6). This study aimed to establish an atlas of SIJ and spinal MRI lesions in healthy subjects without chronic back pain across different age categories.

In the second part, the focus shifted towards pSpA. Fifty-six early, active, newly-diagnosed pSpA patients underwent MRI of the SIJs and spine prior to treatment with golimumab, a tumor necrosis factor α (TNF) inhibitor, and at time point

Figure 1: MRI examinations of the sacroiliac joints in a 31-year-old postpartum woman. Panel A shows extensive bilateral sacroiliac joint bone marrow edema on short tau inversion recovery sequences in the first ten days after giving birth, mimicking active sacroiliitis. Panel B shows the development of sacroiliac joint erosions on T1 sequences 12 months later.



of sustained clinical remission when treatment was withdrawn to explore the possibility of drug-free remission (7). A subset of 32 patients with lower limb arthritis and/or enthesitis on physical exam and ultrasonography underwent MRI studies of the joints and entheses of the pelvis, hips, knees, ankles, hindfeet, and midfeet at both time points (8). Both studies aimed to assess the disease extent of pSpA and explore the value of MRI in the prediction of disease relapse versus sustained remission after treatment discontinuation. The applied semi-quantitative MRI scoring system for inflammation of the joints and entheses of the lower limbs was assessed for reliability, validity, and sensitivity to change (9).

Finally, SIJ immunoscintigraphy with radiolabeled certolizumab pegol, a TNF inhibitor, was performed in seven axSpA patients (10). Tracer uptake on immunoscintigraphy was compared with the presence of BME on MRI. The aim of this study was to assess the ability of immunoscintigraphy to reliably detect active sacroiliitis by demonstrating the presence of TNF in vivo at the site of clinical inflammation.

Results

Twenty-seven out of 35 postpartum women (77%) displayed BME on SIJ MRI in the first 10 days after giving birth, with 60% fulfilling the ASAS definition of a positive MRI for sacroiliitis (Figure 1) (4). Fifteen out of 33 subjects (46%; two were lost to follow-up) still displayed SIJ BME after six months with five subjects having a positive MRI for sacroiliitis. Four out of these five subjects still had a positive MRI 12 months after giving birth. SIJ BME mainly persisted over time in subjects older than 30. Of interest, the presence of BME on SIJ MRI was associated with a shorter duration of labor (r=0.46, P=0.005) and the lack of epidural anesthesia (mean Spondyloarthritis Research Consortium of Canada (SPARCC) score 5.2 versus 11.5, P=0.05). No association was found between the presence of back pain and the observed MRI lesions. In nine military recruits (41%), SIJ BME on MRI was seen at baseline with five subjects (23%) having a positive MRI for sacroiliitis (5). The number of subjects (n=11, P=0.63) displaying BME and the SPARCC scores (mean (SD) 2.4 (0.4) versus 3.7 (1.3), P=0.11) did not significantly increase after 6-weeks of intense physical training. The high exertion load before start of the study presumably reflected the lack of effect of physical exercise, as these recruits were already well trained. This hypothesis may also explain the high prevalence of lesions at baseline. Furthermore, the MRI appearance of the SIJs and spine was charted across different age categories in healthy individuals without back pain (6). While rarely occurring in subjects <30 years, a positive MRI for sacroiliitis was found relatively frequently in older subjects (17%). Erosions (20%) and fat metaplasia (14%) were the most commonly detected structural SIJ lesions occurring in all age groups, although erosions occurred more frequently in subjects above the age of 40 (39.3%). Although spinal BME (36%) and fat metaplasia (29%) were common in subjects older than 40, only one subject had a positive MRI for spondylitis. SIJ SPARCC scores (r=0.21, P=0.039), erosions (r=0.24, P=0.020), and total structural lesions (r=0.20, P=0.041), and spinal SPARCC (r=0.36, P<0.001), fat lesions (r=0.34, P<0.001), and total structural lesions (r=0.24, P=0.021) were significantly correlated with the subject's age. No children were included in these studies. Nonetheless, a recent study by Herregods et al. in 251 children without juvenile spondyloarthritis showed that an increased signal intensity was present in 74.7% of the sacroiliac joint spaces on MRI (7). In 18.4% of the joint spaces, this signal was as intense as fluid.

In the second part, we explored the role of axial skeleton and lower limb MRI in early pSpA patients in assessing disease extent and outcome. Twenty pSpA patients (36%) showed SIJ BME before treatment initiation (8). All of these patients fulfilled the ASAS definition of sacroiliitis. No association with back pain was found. Six patients (11%) displayed deep BME lesions and in nine patients (16%) intense BME lesions were observed. Those pSpA patients with BME on SIJ MRI showed a similar distribution and range compared to axSpA patients from the Belgian Inflammatory Arthritis and Spondylitis cohort. Importantly, structural lesions occurred frequently in our pSpA population (12 patients, 21%). Erosions were the most frequent structural lesions of the SIJs, occurring in 16%. Spinal BME was limited: median inflammation scores were low and no patients had ≥5 inflammatory corner lesions. Upon clinical remission a significant decrease in SIJ SPARCC scores was detected (mean 8.9 versus 3.7, P=0.041). At clinical remission, no significant differences in SIJ SPARCC scores were noted between patients relapsing versus those maintaining remission after treatment discontinuation (mean SPARCC 1.7 versus 1.2, P=0.51). In the subset of patients with involvement of the joints and/or entheses of the lower limbs a substantial amount of subclinical involvement was seen on MRI, mainly in the ankle joints and heel entheses (9). Whereas 80% of the joints that were clinically involved at baseline showed no effusion on remission MRI, two out of three entheses involved at baseline showed residual inflammation. Moreover, patients who experienced a relapse after treatment discontinuation displayed more entheseal soft tissue inflammation on remission MRI compared to those maintaining drug-free remission (P=0.028). The semi-quantitative MRI scoring system demonstrated sensitivity to change, reliability, and validity in a post-hoc analysis (10). Collectively, our data point towards a much broader pattern of joint and entheseal involvement than clinically anticipated in these patients, indicating a higher global inflammatory burden.

Finally, a novel imaging tool was explored (11). Immunoscintigraphy showed good correlation with BME on SIJ MRI in seven axSpA patients, confirming the presence of TNF-driven disease. An especially good correlation was found between immunoscintigraphic findings and deep BME lesions on MRI, indicating a higher specificity of these lesions for axSpA.

Conclusion

Several pitfalls of MRI in the context of SpA were identified. Both inflammatory and structural SIJ lesions occur relatively frequently in non-SpA subjects, especially in the context of augmented biomechanical stress and age-related degeneration, indicating their limited specificity. Consequently, the risk of SpA overdiagnosis seems considerable. This may also be the case in children. However, biomechanical stress and age-related changes is presumably less prevalent in this population. Diagnostic SIJ MRI should therefore only be performed in individuals with a high suspicion for SpA. Incorporation of deep BME lesions, BME adjacent to structural lesions, particular thresholds for sacroiliac joint lesions, and the combination of different structural lesions may increase specificity. New imaging modalities, such as immunoscintigraphy, may have higher specificity for axSpA compared to MRI. Our data also demonstrate that MRI may have a role in assessing disease extent and treatment response in pSpA patients. Subclinical enthesitis on MRI at time point of clinical remission may warrant prolonged treatment.

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Interventions for increasing fruit and vegetable consumption in children aged five years and under

Anne-Catherine Vanhove, Trudy Bekkering, Filip Cools

Cochrane Belgium, Belgian Centre for Evidence-Based Medicine (Cebam)

info@cochrane.be

Question

Are interventions designed to increase the consumption of fruits, vegetables or both amongst children 5 years and under effective, cost effective or associated with any adverse events?

Context

Eating sufficient amounts of fruit and vegetables is associated with a reduced risk of future non-communicable diseases (e.g. cancer and cardiovascular disease). While daily recommended amounts of fruit and vegetables for children do vary internationally, population surveys have indicated that these recommendations are often not being met. As early childhood also represents a critical period for establishing dietary habits that will continue into adulthood, interventions targeting fruit and vegetable intake in young children may be effective strategies to increase public health long-term.

This Cochrane review update therefore assessed the impact of interventions designed to increase eating of fruit, vegetables or both in children five years and under. This review was originally published in 2012 and has been maintained as a living systematic review since 2017. The review authors continue to monitor the publication of trials and update the review when needed as there are multiple ongoing trials that might impact the conclusions of this review in the future. The most recent version, discussed in this Cochrane Corner, was published in 2020.

Criteria for study selection

The review included studies assessing interventions aimed at increasing the intake of fruit or vegetables or both in children five and under. The studies had to compare these to other such interventions, standard care or no intervention. Moreover, the studies had to incorporate a dietary or biochemical assessment of vegetables or fruit consumption, e.g. changes in the number of portions or in grams consumed or changes in markers such as carotene.

Summary of the results

In total, the authors included 80 trials with 12965 participants. The mean age of participants varied widely for some interventions e.g. from 4 months to 5 years. Fifty trials examined the effect of child-feeding practices (e.g. repeated exposure or rewards) and 15 studies investigated parent nutrition education. Fourteen studies assessed the impact of multicomponent interventions which combined for example parent nutrition education and preschool policy changes. Few trials assessed the effect of nutrition education for children (2 trials) and of a child-focused mindfulness intervention (1 trial). Most of the trials took place in so-called developed countries, but studies focusing on disadvantaged populations and the general population were analyzed together. Seventy-six trials measured vegetable intake while only 36 assessed fruit consumption.

Child-feeding practices may have a small positive effect on child vegetable consumption compared to no intervention, resulting in an increase of 5.30 grams consumption of vegetables per day (no intervention: 7.7 grams vs child-feeding: 13 grams (95% CI*: 10.78 to 15.23); 19 studies, 2140 participants, low-certainty evidence). Similarly, multicomponent interventions probably have a small positive effect on consumption of fruit and vegetables, resulting in an increase of 0.34 cups per day (no intervention: 1.08 cups vs multicomponent: 1.42 cups (95% CI: 1.17 to 1.66); 9 trials, 2961 participants; moderate-quality evidence). These intake outcomes were measured in the short-term (<12 months) with mean follow-up being 8.3 weeks and 5.4 weeks respectively. It is uncertain whether there are any short-term differences in fruit and vegetable intake when comparing parent nutrition education to no intervention (very low-certainty evidence). The two trials on child education could not be combined in one analysis, but both reported a positive effect on fruit and vegetable intake (low-certainty evidence).

Unfortunately, very few studies assessed long-term impacts, cost effectiveness and unintended adverse consequence of the interventions so the authors were unable to draw any conclusions regarding these outcomes.

Conclusion

Although the authors identified 80 relevant trials, the evidence remains limited both regarding magnitude of effect as well as certainty of the evidence. Child-feeding practices may lead to, and multicomponent interventions probably lead to only small increases in fruit and vegetable intake by young children. Moreover, it remains uncertain whether parent nutrition education interventions increase children's fruit and vegetable intake.

As this is a living systematic review which incorporates relevant evidence as it becomes available, the conclusions are likely to change in the (near) future. The authors have already identified 15 new studies published between 2020 and 2022, which will be included when the review is updated.

Implications for practice

Multicomponent interventions could currently be considered the best option to increase fruit and vegetable intake for small children. Interventions that reported positive effects were largely those that focused exclusively on fruit and vegetable consumption (rather than nutrition generally), involved parents in some component of the intervention and included nutrition education. However the effects of both child-feeding and multicomponent interventions remain small (possibly not clinically relevant) and there is no data on costs and unintended consequences. This may limit the potential public health benefits of implementing these interventions.

^ **CI:** confidence interval

REFERENCE:

Hodder RK, O'Brien KM, Tzelepis F, Wyse RJ, Wolfenden L. Interventions for increasing fruit and vegetable consumption in children aged five years and under. Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD008552. DOI: 10.1002/14651858.CD008552.pub7.

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Ce matériel a été établi le 5 août 2022 – LAC/22/005/FR

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Lactéol® Baby est un complément alimentaire. Les compléments alimentaires ne doivent pas être utilisés comme substitut d'une alimentation variée et équilibrée et d'un mode de vie sain. Lactéol® Baby doit être utilisé sous contrôle médical. Consultez votre médecin ou votre pharmacien en cas d'utilisation concomitante de médicaments ou de problèmes de santé. Ne pas dépasser la dose journalière recommandée. Tenir hors de portée des jeunes enfants.

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Onze gloednieuwe groeimelk voor peuters vanaf 1 jaar.
Le tout nouveau lait de croissance pour les enfants dès 1 an.

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Le lait de croissance **NAN Complete** est un **nouveau lait de croissance** spécialement développé pour les enfants **dès 1 an** qui boivent du **lait de confort** et représente assurément le meilleur choix grâce aux ingrédients suivants :

- **L. reuteri**
  - Verbeteren het spijsverteringscomfort[1,2] / Améliore le confort digestif[1,2]
  - Verbeteren de stoelgangsfrequentie[3] / Améliore la fréquence des selles[3]
- **GOS/FOS vezels / Fibres GOS/FOS**
  Verbeteren de frequentie en de consistentie van de ontlasting[4,5] / Améliore la fréquence et la consistance des selles[4,5]
- **Magnesium / Magnésium**
- **Zetmeel / Amidon**
  Aangepaste viscositeit / Viscosité adaptée
- **Optimale eiwitten / Protéines optimales**
  - Verminderen het risico op obesitas[6] / Diminution du risque d'obésité[6]
  - Verminderen de nierbelasting[7]/Diminution de la charge rénale[7]

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UITSLUITEND VERKOCHT IN DE APOTHEEK
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Referenties / Références : **1.** Indrio et al. L.reuteri accelerates gastric emptying and imporves regurgitation in infants,Eur J Clin Invest 2010. **2.** Harb et al. Systematic review and meta-analysis confirm effectiveness of L.reuteri for infantile colic J Pediatr Gastroenetrol Nutr 2016. **3.** Coccorullo et al. L.reuteri DSM 17938 in infatnts with chronic constipation: a double-blind,randomizes,placebo-controlled study J Pediatr 2010;157:598-602. **4.** Costalos et al.Early Hum Dev 2008;84: 45-49. **5.** Vivatvakin et al.Asia Pac J Clin Nutr 2010;19:273-80. **6.** Rolland-Cachera et al. Nutrient intakes in early life and risk of obesity. Int J Env Res Publ Health 2016. **7.** Escribano et al. Increased protein intake augments kidney volume and function in healthy infants. Kidney Int 2011.

Dit document is voorbehouden voor gezondheidsspecialisten. / Ce document est exclusivement réservé à l'information des professionnels de la santé.

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

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

PID2942 – September 2022. / Septembre 2022. V.U./R.E. : S. Alexander, Nestlé Belgilux SA/NV, Rue de Birminghamstraat 221 - 1070 Bruxelles/Brussel, BCE/KBO 0402.231.383.