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VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

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## Articles



## Case Report



## Made in Belgium



## Paediatric Cochrane Corner



Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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# Editorial

Dear Colleagues,

Writing this editorial gives a very strange feeling.

Not only Covid-19 is still confusing us, but also other events.

We are overwhelmed by sadness and joy. Sadness about losses, joy about beautiful memories. (and promising future prospects)

On July 20th 2020 we lost Prof Paul Casaer. As chief editor he was one of the pioneers of the modern version of our Belgian Journal of Paediatrics (BJP). In this issue tribute is paid to this remarkable man, known to many of us not only as *an exceptional and passionate clinician, mentor and teacher, leader, a wonderful colleague,* but especially *as a warm personality, a good friend.* He managed our Journal with a fruitful mind, accurate decisions and a correct scientific generosity. We want to express our deep sorrow to Mrs Casaer and Paul's family. *The void and griefs are great, beautiful are the memories.*

Some months ago, Prof Samy Cadranel announced his resignation as chief editor of our BJP. Great panic within the board, how to replace such a brilliant Master in pediatrics, our rock in the sea, never-stopping-searching to optimize the quality of our Journal. Warm thoughts and anecdotes can be read by co-editors who had the pleasure to share his intelligence, his diplomacy, his creativity, his joviality and "plaisanterie et joie de vivre".

The cover of this issue is referring to his brain-child, a pretty small organism that made him world famous.

Thanks, dear Samy for so much beauty we can look after! You paved the way for many of us and especially for the younger generation, that we welcome with open arms in our renewed editorial board.

Indeed, our board has been extended with young enthusiastic colleagues who want to spent time and energy to the co-editorship of our Journal.

Christophe Chantrain (CHC, MontLégia, Liège) has accepted to become the successor of Samy Cadranel and will join Marc Raes, as the French speaking chief editor of the BJP.

The current issue of our Journal is a transition issue between the former and the present editorial policy with for the last time some articles in Dutch.

Very interesting original manuscripts, systematic reviews, intriguing case reports and two marvelous PhD theses are published.

The association between **Hirschsprung** disease and CAKUT, based on a common genetic pathway is described. Our role as pediatricians to create a better future for children confronted with **abandonment** is discussed. The definite version of the manuscript about neonatal hypertension is published. Data about the epidemiology of **invasive meningococcal disease i**n Belgium helps us to decide about the positioning and the use of available meningococcal vaccines in children and adolescents. A systematic review provides evidence that **Virtual Reality** might be a promising distraction method to improve procedural pain experience in some children. Starting from a case report, attention is stressed on the possible vague physical presenting symptoms and complaints of **celiac disease**.

**Plastic Bronchitis** is a rare disease with high morbidity and mortality to be considered in any rapid respiratory deterioration, even in previously healthy children. Urgent bronchoscopic intervention is paramount, both diagnostically as therapeutically. **Varicella-zoster** infection, complicated by cerebral arteriopathy, is reported. **Pediatric scurvy** is a rare disease and should be suspected in children with malabsorption or restricted diets, presenting with musculoskeletal symptoms. **Posterior Reversible Encephalopathy Syndrome (**PRES) is a clinical and radiological picture characterized by neurological and radiological abnormalities.

How a "simple" fall can uncover a severe **neurometabolic disease** is illustrated. The combination of seizures and acute encephalopathy in a previous healthy child is always a very challenging **paediatric emergency**.

In our PhD-related Made in Belgium session, Athina Van Gasse (UZAntwerpen) illustrates how complex the unraveling of **beta-lactam hypersensitivity** could be. Karen Van Hoeve (UZLeuven) describes the discovey of prognostic diagnostic factors for therapeutic stratification in **paediatric IBD** patients.

Does using reflective curtains improve the effectiveness of **phototherapy** of unconjugated hyperbilirubinaemia in newborn infants? You can find the answer in our Cochrane Corner.

The decision to cancel the 48th **annual BVK/SBP congress** 2020 is already announced. Arrangements have started to prepare the March **2021** meeting, organized by the pediatric team of UGent, in close collaboration with the colleagues and scientific committee of HUDERF. A very actual and exciting title was chosen: "**The Changing Face of Pediatrics**".

We are looking forward meeting all of you in person, face-to-face, hopefully in March 2021

At the latest, we also want to invite you to renew your **BVK/SBP membership**. This support enables the society to accomplish her scientific objectives on a national level as optimal and independently as possible, in consultation and collaboration with the Belgian Academy of Pediatrics, who coordinates the existing official pediatric societies in Belgium. Many advantages are offered to the BVK/SBP members: BJP, website, annual congress, educational events…Thanks to your contribution, projects of young researchers and trainees can be encouraged and stimulated.

We hope all of you enjoyed relaxing holidays being recharged to face the busy and challenging winter months.

On behalf of the entire editorial board,

We wish you much reading pleasure

Warm regards

**Marc Raes and Christophe Chantrain, editors-in-chief**

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

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SOCIÉTÉ BELGE DE PÉDIATRIE

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# Tribute to Samy

Dear Samy,

Some months ago you let us know that you want us to look for a successor as French speaking chief-editor of the Belgian Journal of Paediatrics (BJP). Imagine! How to replace such an eminent icon in the field of pediatrics, such an intelligent scientist, such a polyvalent man, such a charming personality? Mission impossible!

In 2006, Professor Lucien Corbeel, founder of the Tijdschrift van de Belgische Kinderarts/Journal du Pédiatre Belge, transmitted the editorship to you and Paul Casaer. In the first issue of 2007, prof Dirk Matthys described both of you as "eminences grises" in the Belgian pediatric field. He certainly didn't focus on your scarce grey hairs, but for sure on your grey brain cells.

In 2015, I was asked to succeed the late professor Casaer and to become your "compagnon de route" as Dutch speaking editor-in-chief of the Belgian Journal of Paediatrics. What an honor for me!

I one of the mails we exchanged during the last months, I stated that I learned a lot of you, and that I admired your outstanding diplomacy, your brilliant memory, your writing art, your friendly interactions, your wise advices, your permanent preparedness to help whenever you could…

**Mark W** added to this list of qualities your incredible creativity, spontaneity and joviality that allowed for lively and engaging discussions. He also referred to the in between countless anecdotes and memories or stories about books, art, travel, family, grandchildren. He called you "El matador del Helicobacter", referring to your life's work and worldwide fame about this bacterium you (re)discovered as a pathogen in children with peptic ulcers and chronic gastritis but also other less frequent gastrointestinal manifestations.

**Nadine F** is grateful she was integrated in a sympathetic and dynamic editorial board with a good ambiance and nice motivation and discovered another aspect of you, Samy besides the professor well-known for his erudition and scientific and medical competence: warm and always inviting, inexhaustible source of pleasant anecdotes and sparkling histories about medicine. A pillar of our Journal.

As new French-speaking editor-in-chief, **Christophe Ch** wants to thank you for your efforts to create cohesion, open-mindness and dynamism in the editorial committee. He wants to continue your commitment to represent and to respect the diversity of our Belgian paediatric community and in particular our young colleagues in training.

As a young member of the editorial board, **Christophe B** was especially impressed by your charisma, your enthusiasm and your professionalism that encouraged him to continue his engagement to this review.

**Anne R** wants to thanks you for your warm-heartedness, your infectious enthusiasm, good advice and to the point suggestions. She describes your leadership as contagious for young and old.

Since her start in the board, **Stéphanie DR** got to know you as an amiable, gentle person, always open for respectful discussions; an observant and thoughtful man with a never ceasing interest in science and research. As formal co-editor and close colleague-friend, **Françoise B** admired your didactic and linguistic qualities, your fruitful and constructive discussions. She enjoyed your "plaisanterie" in between the serious work and "studious" atmosphere within our editorial board. As editorial secretary since 2013, **Natacha M** knew you as a warm, enthusiastic and dynamic person. Always ready to tell us "une belle petite anecdote".

Dear Samy, we want to thank you from the deepest of our hearts for showing us the way and for so much beauty we can look after. We will remember you as "our" warm, affectionate sweet Samy that we all cherish.

Marc Raes
Mark Wojciechowski
Nadine Francotte
Christophe Chantrain
Christophe Barrea
Anne Rochtus
Stéphanie De Rechter
Natacha Meignen

# In Memoriam

## PAUL CASAER
## (1940 – 2020)

It is with great sadness that the we share the passing of emeritus professor Paul Casaer on July 30th 2020.

In 1975 Paul Casaer was the pioneer of pediatric neurology in Flanders. He was the founding director of the pediatric neurology department in Leuven, which he developed into a large international program with subspecialty care programs. Professor Casaer was a gifted clinician, a talented teacher and educator for students and residents/fellows, and a successful clinical researcher. Paul Casaer was the initiator and co-founder of the Pediatric Rehabilitation Centre Pulderbos. He was co-founder (1976) and the first president of the Belgian Society of Pediatric Neurology (BSPN), the first president of the European Society of Pediatric Neurology (ESPN), and secretary-general and president of the International Child Neurology Association (ICNA). Along with professor Victor Dubowitz he was co-founding editor-in-chief of the European Journal of Pediatric Neurology.

In addition to his career and achievements in the pediatric neurology field, Paul Casaer greatly contributed to the advancement of pediatrics. He was a pediatrician with heart and soul. Between 1995 and 2005 he was the chairman of the university children's hospital in Leuven. He contributed to the Belgian Society of Pediatrics as executive board member, and he was co-founder and president of the Belgische Academie voor Kindergeneeskunde.

Paul Casaer will be deeply missed. We will remember him, with great respect and gratitude, as an exceptional and passionate clinician, mentor and teacher, leader, a wonderful colleague, a warm personality, a good friend.

We extend our sincerest condolences to his family and friends, and the many colleagues around the world who had the privilege of being trained by him and of working with him.

Gunnar Buyse, MD PhD

Chairman of Pediatrics, University Hospitals Leuven
President, Belgian Society of Pediatric Neurology
Executive Board Member, Belgian Society of Pediatrics

# In Memoriam

## PAUL CASAER
## (1940 – 2020)

In 2015, when Professor Paul Casaer decided to resign as chief-editor of our journal then known as TBK/JPB (Tijdschrift van de Belgische KInderarts-Journal du Pédiatre Belge) both current chief-editors wrote a tribute to him in Dutch ("De leermeester, dank betuiging" by Marc Raes) and in French ("Un septennat heureux ou une coopération fructueuse" by Samy Cadranel).

Since then, the review has changed name, becoming the BJP (Belgian Journal of Paediatrics) and this decision, in view of obtaining an international recognition and reference in Pub Med, had been properly discussed and was warmly welcomed by the retiring Paul.

We know that the decease of such an important character in our paediatric community will be duly evoked by the numerous colleagues, students and fellows who worked with him. He directed the Department of Paediatrics of UZ Leuven, as a respected chief, during many years. Paul was an eminent paediatric neurologist, renowned not only in Belgium and Europe but also internationally and his research, including research in Africa (see his CV in PubMed), has contributed to improve this specific scientific field.

We wish to focus on his direction of our review. When Acta Paediatrica Belgica merged with European Journal of Paediatrics (EJP), late Prof. Lucien Corbeel bravely founded and managed a new paediatric Belgian Journal with the aim of giving a local platform, mainly to our specializing fellows. Indeed, the EJP gave little space to our researchers and late Prof Dirk Matthys, the then president of BVK/SBP, suggested to directly assume the responsibility of the publication through the BVK / SBP. He asked the French speaking Samy Cadranel and the Dutch speaking Paul Casaer, both recently retired, to accept the job...which they joyfully did and celebrated with a beer *(pintje or chope)* during the 2007 Annual Congress of the BVK/SBP.

The collaboration between the two chief editors and their deputies was excellent and the tribute to Paul's retirement in 2015 was qualified (TBK/JPB 2015; 17 (1): 6) as « Seven happy years of fruitful cooperation". Indeed, the editorial board meetings were caring and friendly with the obvious wish to get consensus and avoid all forms of ill will. The soft speaking voice of Paul matched ideally with the more passionate Samy's voice. However, on the run, it was easy to observe that the two were pursuing the same goal and becoming good friends.

After he became a co-editor in 2002, Marc Raes succeeded Paul as Dutch speaking chief- editor in 2015. In his tribute Marc Raes stressed Paul's phenomenal scientific knowledge, his constructive and diplomatic editorial guidance and his never-ending efforts to further optimize the quality of "his" Journal. Paul's Art to stimulate Science was praised.

Our current chief editors, Marc Raes and Samy Cadranel, deeply regret the death of Prof Paul Casaer and, together with all the members of the editorial board, wish to express their deep sorrow to Mrs Casaer and Paul's family.

Let us quote the beautiful epitaph inserted in the announcement of Paul's passing away. It describes very accurately the feelings Paul Casaer could induce in those working with him.

*Groot is de leegte en het verdriet, mooi zijn de herinneringen.*
*Great are the void and the grief, beautiful are the memories*

Samy Cadranel and Marc Raes on behalf of the members of the editorial board.

# Urgent message from BVK/SBP:

## cancellation annual congress

Dear Colleagues,

The SARS-CoV2 virus continues to dominate our society.

Precautionary measures need to be implemented. Planned activities have to be postponed and even cancelled.

Indeed, we have to announce you the sad news that the 48th annual BVK/SBP congress, postponed from March to October 2020 **is definitively cancelled**. 2020 registrations fees will automatically be transferred to the 2021 congress. Reimbursement can also be requested if needed. Arrangements have already been started to prepare the March 2021 meeting, organized by the pediatric team of UGent, in close collaboration with the colleagues and scientific committee of ULB. They have chosen a very actual and appropriate title: “The Changing Face of Pediatrics”.

We are looking forward meeting you in person, face-to-face, hopefully in March 2021

Many thanks for your understanding.

Kind regards

Marc Raes, president BVK/SBP
Pierre Smeesters, congress president 2020
Sabine Van Daele, congress president 2021


BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE

SOCIETE BELGE DE PEDIATRIE

# Renouvellement cotisation 2021

Cher collègue,

La Société belge de pédiatrie (BVK/SBP) s'efforce de soutenir ses membres dans le domaine scientifique. Elle organise annuellement un congrès national pédiatrique de deux jours. Elle est responsable de la publication du peer-reviewed Belgian Journal of Paediatrics offrant des numéros thématiques sur divers sujets ainsi que des contributions locales. Elle soutient explicitement les jeunes scientifiques. Elle propose un site Web avec des liens vers des e-learnings et des formations universitaires, des informations sur différents congrès, des publications scientifiques, des dossiers et des recommandations pratiques, ainsi que l'accès à la littérature médicale internationale par l'intermédiaire de la bibliothèque numérique du CEBAM et le Journal Club mensuel. Elle tient ses membres informés des problèmes actuels dans le domaine des soins de santé et formule des conseils, en collaboration avec des experts, tant auprès des membres qu'à d'autres fournisseurs et organismes de soins de santé. Grâce à des prix scientifiques, elle soutient la recherche scientifique. Elle contribue à la formation des boursiers en pédiatrie et soutient la mise en œuvre des sous-spécialisations pédiatriques en Belgique. La Société belge de pédiatrie représente l'ensemble des aspects médicaux et psychosociaux de l'enfant, de l'adolescent et de leur famille et s'efforce d'être un forum scientifique pour répondre aux questions à ce sujet.

Les membres du Conseil d'administration souhaitent donc **vous inviter à devenir membre** de notre société. Grâce à votre contribution, le BVK/SBP peut réaliser ses missions scientifiques de manière optimale et aussi indépendante que possible, en collaboration avec l'Académie belge de pédiatrie, qui coordonne les organisations pédiatriques officielles existantes en Belgique.

En plus du soutien de la mission scientifique du BVK,/SBP l'adhésion offre plusieurs avantages : via le site web du BVK/SBP, les membres ont accès à la bibliothèque numérique du **CEBAM** (Belgian center for Evidence-Based Medicine). Cet accès permet de lire et de télécharger les articles des principaux journaux pédiatriques (Pediatrics, Journal of Pediatrics, Pediatric Infectious Disease Journal, etc.). Le site donne également accès aux « big five » (New England Journal of Medicine, Lancet, BMJ, JAMA et Annals of Internal Medicine) ainsi qu'à de nombreuses bases de données de la Evidence Based Medicine (Cochrane Library, etc.) et de livres électroniques. La vue d'ensemble mensuelle des articles internationaux les plus intéressants dans le domaine de la pédiatrie se trouve dans la rubrique: **Journal Club**. Le seul « peer-reviewed » journal national de pédiatrie: **«Belgian Journal of Paediatrics»** peut être consulté en ligne.

En tant que membre de la société, vous bénéficiez d'un tarif très avantageux lorsque vous vous inscrivez au **congrès scientifique annuel de la BVK/SBP**. Grâce à votre adhésion, nous pouvons continuer à stimuler les (jeunes) chercheurs dans leur recherche par une **bourse de promotion scientifique**.

L'adhésion à la société belge de pédiatrie est réservée à tous les médecins qui travaillent ou en formation en pédiatrie. L'adhésion court jusqu'en septembre 2021

**Les cotisations annuelles restent inchangées :**

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Cordialement,

également au nom de tous les membres du conseil d'administration de la société belge de pédiatrie

**Dr Marc Raes**
**Président SBP/BVK**

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# Hernieuwing lidgeld 2021

Beste Collega,

De Belgische Vereniging voor Kindergeneeskunde (BVK/SBP) wil haar leden ondersteunen op wetenschappelijk vlak. Ze organiseert jaarlijks een tweedaags nationaal congres en verzorgt de publicatie van de Belgian Journal of Paediatrics, met themanummers omtrent diverse onderwerpen en vooral bijdragen van eigen bodem en steunt expliciet jonge wetenschappers. Haar website biedt links naar E-learnings en universitaire opleidingen, congres informatie, wetenschappelijke publicaties, dossiers en richtlijnen. Via de website krijgen leden toegang tot de internationale medische literatuur via de digitale bibliotheek van CEBAM en de maandelijkse Journal Club. BVK/SBP houdt haar leden op de hoogte van actuele problemen binnen de gezondheidzorg en formuleert adviezen, in overleg en samenwerking met experten, zowel naar de leden als naar andere zorgverstrekkers en instanties. Via wetenschappelijke prijzen steunt ze het wetenschappelijk onderzoek. Ze draagt bij aan de opleiding van de fellows kindergeneeskunde en bouwt mee aan de verdere implementatie van de pediatrische subspecialisaties in België. De Belgische Vereniging voor Kindergeneeskunde behartigt alle medische en psycho-sociale apecten van het kind, de adolescent en hun families en streeft ernaar het nationale wetenschappelijk forum te zijn om vragen daaromtrent te beantwoorden.

De Raad van bestuur wenst u dan ook uit te nodigen **om lid te worden** van onze vereniging. Door uw bijdrage kan de BVK haar wetenschappelijke opdrachten zo optimaal en zo onafhankelijk mogelijk realiseren, in samenwerking met de Belgische Academie voor Kindergeneeskunde, die de bestaande officiële pediatrische organisaties in België coördineert.

Naast de steun aan de wetenschappelijke missie van de BVK biedt het lidmaatschap meerdere voordelen: via de website van de BVK, hebben de leden toegang tot de numerieke bibliotheek van de **CEBAM** (Belgian Center for Evidence Based Medicine). Die toegang maakt het mogelijk de artikels van de belangrijkste pediatrische tijdschriften te lezen en te downloaden (Pediatrics, Journal of Pediatrics, Pediatric Infectious Disease Journal, etc.). De site geeft ook toegang tot de "big five" (New England Journal of Medicine, Lancet, BMJ, JAMA en Annals of Internal Medicine) alsook tot talrijke databases van Evidence-Based Medicine (Cochrane Library, etc) en elektronische boeken. Het maandelijks overzicht van de meest interessante internationale artikels binnen het domein van de kindergeneeskunde vinden zij terug onder de rubriek: **Journal Club**. Het enige nationale peer-reviewed tijdschrift voor kindergeneeskunde: **"Belgian Journal of Paediatrics"** kan online worden geconsulteerd.

Als lid van de vereniging geniet u van een zeer voordelig tarief bij de inschrijving voor **het jaarlijks tweedaags wetenschappelijk congres van de BVK**. Mede door uw lidmaatschap kunnen wij (jonge) researchers via een **aanmoedingsbeurs** blijven stimuleren in hun wetenschappelijk onderzoek.

Het lidmaatschap tot de BVK is voorbehouden aan alle artsen die werkzaam of in opleiding zijn in de kindergeneeskunde. Lidmaatschap loopt tot september 2021

**De jaarlijkse bijdragen blijven ongewijzigd:**

- **-120€ voor de kinderartsen**
- **- 60€ voor de assistenten**
- **- 60€ voor de kinderartsen op rust.**

Lid worden kan via de website www.bvk-sbp.be

Hartelijk dank voor jullie steun en engagement.

Genegen groeten,

mede in naam van alle leden van de Raad Bestuur van de BVK

**Dr Marc RAES**

**Voorzitter BVK/SBP**

NOUVELLE MISE À JOUR DU SCHÉMA DE VACCINATION !

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| Prix public Belgique | 86,52€ |
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# BEXSERO

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

Le **premier** vaccin contre le méningocoque de **sérogroupe B**.[1]

Le **seul** indiqué dès l'âge de **2 mois**.[1,2]

**2+1**

pour les nourrissons à partir de **2 mois**.[1]

**RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT** Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT** Bexsero suspension injectable en seringue préremplie Vaccin méningococcique groupe B (ADNr, composant, adsorbé) - EU/1/12/812/001 Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09 **COMPOSITION QUALITATIVE ET QUANTITATIVE** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de *Neisseria meningitidis* groupe B [1, 2, 3] 50 microgrammes Protéine recombinante NadA de *Neisseria meningitidis* groupe B [1, 2, 3] 50 microgrammes Protéine de fusion recombinante fHbp de *Neisseria meningitidis* groupe B [1, 2, 3] 50 microgrammes Vésicules de membrane externe (OMV) de *Neisseria meningitidis groupe* B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4 [2] 25 microgrammes [1] produite dans des cellules d'*E. coli* par la technique de l'ADN recombinant [2] adsorbée sur hydroxyde d'aluminium (0,5 mg $Al^{3+}$) [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H) **INDICATIONS THÉRAPEUTIQUES** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **POSOLOGIE ET MODE D'ADMINISTRATION** Posologie **Tableau 1.Résumé de la posologie**

| Age lors de la première dose | Primovaccination | Intervalles entre les doses de primovaccination | Rappel |
|---|---|---|---|
| **Nourrissons de 2 à 5 mois** | Trois doses de 0,5 ml chacune | 1 mois minimum | 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] |
| | Deux doses de 0,5 ml chacune | 2 mois minimum | |
| **Nourrissons de 6 à 11 mois** | Deux doses de 0,5 ml chacune | 2 mois minimum | 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] |
| **Enfants de 12 à 23 mois** | Deux doses de 0,5 ml chacune | 2 mois minimum | Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel [c] |
| **Enfants de 2 à 10 ans** | Deux doses de 0,5 ml chacune | 1 mois minimum | Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d] |
| **Adolescents (à partir de 11 ans) et adultes*** | | | |

[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 au-delà de l'âge de 24 mois. [c] Voir rubrique 5.1 du RCP complet. La nécessité et le moment d'administration d'une dose de rappel n'ont pas encore été déterminés. [d] Voir rubrique 5.1 du RCP complet. * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, sous-cutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **CONTRE-INDICATIONS** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **MISES EN GARDE SPÉCIALES ET PRÉCAUTIONS D'EMPLOI** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entraîner le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vaso-vagales (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 contre-indication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination par Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation. Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles post-vaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique. Les personnes ayant des déficits hétréditaires du complément (par exemple les déficits en C3 ou C5) et les personnes recevant un traitement inhibiteur de l'activation de la fraction terminale du complément (par exemple, l'éculizumab) ont un risque accru de maladie invasive due à *Neisseria meningitidis* du groupe B, même après avoir développé des anticorps après vaccination par Bexsero. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. Tracabilité Afin d'améliorer la traçabilité des médicaments biologiques, le nom et le numéro de lot du produit administré doivent être clairement enregistrés. **EFFETS INDÉSIRABLES** Résumé du profil de sécurité La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6837 étaient des nourrissons et des enfants (de moins de 2 ans), 1051 étaient des enfants (entre 2 et 10 ans) et 2677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69% à 79 % des sujets lorsque Bexsero était co-administré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et *Haemophilus influenzae* de type b), contre 44% à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) Fréquent : (≥ 1/100 à < 1/10) Peu fréquent : (≥ 1/1 000 à < 1/100) Rare : (≥ 1/10 000 à < 1/1 000) Très rare : (< 1/10 000) Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles) Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans)** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Troubles du métabolisme et de la nutrition Très fréquent : troubles alimentaires Affections du système nerveux Très fréquent : somnolence, pleurs inhabituels, céphalée Peu fréquent : convulsions (y compris convulsions fébriles) Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire) Affections vasculaires Peu fréquent : pâleur (rare après le rappel) Rare : syndrome de Kawasaki Affections gastro-intestinales Très fréquent : diarrhée, vomissements (peu fréquents après le rappel) Affections de la peau et du tissu sous-cutané 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 musculo-squelettiques et systémiques Très fréquent : arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité Peu fréquent : fièvre (≥ 40 °C) Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois) **Adolescents (à partir de 11 ans) et adultes** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Affections du système nerveux Très fréquent : céphalée Fréquence indéterminée : syncope ou réaction vaso-vagale 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 gastro-intestinales Très fréquent : nausées Affections musculo-squelettiques et systémiques Très fréquent : myalgies, arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois) Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique** Agence fédérale des médicaments et des produits de santé Division Vigilance Boîte Postale 97 B-1000 Bruxelles Madou Site internet: www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be **Luxembourg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy – Hôpitaux de Brabois Rue du Morvan 54 511 VANDOEUVRE LES NANCY CEDEX Tél : (+33) 3 83 65 60 85 / 87 Fax : (+33) 3 83 65 61 33 E-mail : crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments Allée Marconi - Villa Louvigny L-2120 Luxembourg Tél. : (+352) 2478 5592 Fax : (+352) 2479 5615 E-mail : pharmacovigilance@ms.etat.lu Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie **DATE D'APPROBATION DU TEXTE** 04/2020 (v10) **MODE DE DELIVRANCE** Sur prescription médicale.

1. Medini D, Stella M, Wassil J, Vaccine 2015; 33; 2629-2636. 2. Bexsero SMPC.

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# Hirschsprung Disease and Congenital Anomalies of the Kidney and Urinary Tract (CAKUT): a genetic disorder or just a coincidence?

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## Keywords

Hirschsprung; CAKUT; RET; Genetics; Associated anomalies

## Abstract

Hirschsprung disease (HD) and congenital anomalies of the kidney and urinary tract (CAKUT), two pathological entities with their own, complex, genetic background, could be associated based on a common genetic pathway. Although this association has been described in literature, little is known on its prevalence and clinical relevance. We performed a literature research on prevalence and described genotypes of the combination of these entities. In addition, we performed a retrospective cohort study of the UZ Leuven HD population. The literature search and cohort study confirmed the underestimated prevalence of the association between both diseases and the lack of genetic characterization of this population. We emphasize the need for a systematic nephrological ultrasound screening and genetic investigation, with focus on RET-GDNF-GFRalpha1-complex, of all HD patients.

## Introduction

Hirschsprung disease (HD) is defined as a congenital absence of parasympathetic ganglia in the distal gut, more specifically in the submucosal plexus of Meissner and myenteric plexus of Auerbach, in combination with submucosal neural hyperplasia. It extends from the anorectal junction to the rectum and colon with a variable height. The resulting aganglionic segment fails to relax, causing a tonically contracted bowel segment. This leads to a functional obstruction, resulting in a proximal megacolon and explaining the clinical symptoms of the disease[1].

HD has an incidence of 1/5000 live births. The occurrence of the disease can be sporadic or familial. Depending on the length of the aganglionic segment, it is subdivided in a short- and long-segment HD. Extension up to the splenic flexure is called short-segment disease and is present in up to 80% of patients. Most frequently the disease will affect only the recto-sigmoid. Long-segment disease extends proximal to the splenic flexure (up to 20% of patients). Within this group, total colonic aganglionosis can be present, with or without inclusion of the terminal ileum. The disease is more common among boys, with a 4:1 male/female ratio. The treatment of HD is surgical. Thanks to the improved management, the mortality rate is below 1% [1-3].

The pathophysiology of HD is failure of normal development of the enteric nervous system following abnormal migration, proliferation, differentiation and/or survival of neural crest cells. It is thereby regarded as a neurocristopathy[1,4-6].

It is not surprising that changes in genes contributing to the development of the enteric nervous system can interfere with colonization of hindgut nerve cells[3-5]. So far, over 20 genes have been associated with HD. The involvement of heterogeneous genetic pathways in HD also explains why HD is a multigenetic disorder which can occur both isolated (70%) or associated with other anomalies (18%)/chromosomal abnormalities (12%) in which almost all organs and tissues can be involved. The most frequently associated disorder is trisomy 21[1,3].

The most important gene in the pathogenesis of HD is REarranged during Transfection (RET). RET has an influence on growth and differentiation in different organs including the enteric nervous system[1,7-10]. Other genes belonging to the RET-signaling cascade that have been identified to date are Gliall Cell Derived Neurotrophic Factor (GDNF), a RET ligand, and GDNF Family Receptor alpha 1 (GFRalpha1), a co-receptor of RET. Different studies have demonstrated that formation of the GDNF-RET-GFRalpha1 complex influences migration of neurons and is necessary to prevent aganglionosis[1,6,11].

The RET-signaling pathway is also of importance in the development of the kidneys and urinary tract [12-14]. CAKUT (congenital anomalies of the kidney and urinary tract) is an acronym and collective name for different clinical entities affecting the kidneys or structures of the urinary tract. It includes renal agenesis, renal hypoplasia, renal dysplasia, hydronephrosis, vesicoureteral reflux, megaureter, ureteropelvic junction/vesicoureteric junction obstruction, posterior urethral valves, duplex collecting system and horseshoe kidney[12,15]. CAKUT represent a broad range of disorders from mild, asymptomatic malformations to severe, life-threatening pathologies. It is one of the most important causes of chronic renal failure in children (40-50% of children with chronic renal failure worldwide) and represents approximately 30% of all congenital malformations. In 30% of the cases there is an associated, nonrenal anomaly with more than 200 syndromes described. CAKUT, like HD, is a genetically heterogenous disorder where HNF1Beta and PAX2 are currently the two most known affected genes[8,16-19]. Mutations in the RET pathway are reported in 5% of living patients with CAKUT, in 7% of fetuses with CAKUT and in 30% of fetuses with unilateral or bilateral renal agenesis[8]. RET is important in the development of the kidneys and urinary tract, by its interaction with GDNF and GFRalpha1. RET, GDNF, GFRalpha1 null mice die at birth due to bilateral renal aplasia or agenesis. Mice with aberrant RET expression display a spectrum of renal anomalies, suggesting the importance of RET in renal development. Within the kidney RET mainly is important for number of

nephrons and kidney size. Furthermore, it is an important component in maturation of the lower urinary tract, involved in the insertion of the Wolffian duct into the cloaca. Both loss and overexpression of RET can cause lower tract anomalies[7-8].

Based on the common genetic background of kidney and enteric nervous system development, an association between HD and CAKUT has been hypothesized and reported in case series. To explore and specify this association, a review of the literature in combination with a retrospective cohort study in UZ Leuven was performed.

## Methods

A **review of the literature** published between 1955 and 2019 was conducted on the electronic databases such as PubMed , Cochrane Library, ScienceDirect and Lime. The used key words were 'Hirschsprung', 'CAKUT', 'Congenital Anomalies of the Kidney and Urinary Tract', 'RET', 'Genetics', 'Associated anomalies' . Publications reporting the association of HD AND CAKUT were included when they described clinical cases or genetic background.

Further on, a **retrospective cohort study** from the UZ Leuven database was performed after approval of the ethic committee. Patients with a confirmed diagnosis of HD through anatomopathological examination on biopsies of the rectum were included. As the study focused on non-syndromic patients, HD patients with associated anomalies other than CAKUT were excluded. Following data were retrospectively collected from the patient file: gender, HD characteristics, renal phenotype, genetic background.

## Results

1. Review of the literature:

Ten studies[13,20-28] reported on the association of HD AND CAKUT (Table 1). A total of 1315 patients with HD were screened for the presence of CAKUT and 95 cases were reported with a HD CAKUT association. This resulted in a total prevalence of 7.2%. Gender was reported in only 45% (43 cases) but revealed a male predominance (34/43, 79%, male/female ratio: 3.7:1.0). The aganglionosis extend, reported in 54% (51 cases), included classical rectosigmoid disease (short-segment) in 33, long-segment aganglionosis in 9, total colonic aganglionosis in 8 and total intestinal aganglionosis in 1 patient. CAKUT phenotypes consisted of 25 renal hypoplasia, 24 hydronephrosis, 23 vesicoureteral reflux, 14 megaureter, 8 renal dysplasia, 6 renal agenesis, 6 duplex collecting system, 2 posterior urethral valves and 1 horseshoe kidney. After the introduction of the CAKUT acronym in the late 1990s, four studies were published, including the only three prospective studies[13,26-28]. These four studies, including 408 patients with HD, identified 56 cases of associated CAKUT leading to a prevalence of 13%. There is an important difference in prevalence between the seven retrospective studies (4%) and the three prospective studies (19,7%).

Genetic investigation was done in only one study[13]. They screened for mutations in RET, GDNF and GFRalpha1 in a total of 34 patients with HD, either associated (n=12) or not associated (n=22) with CAKUT, and compared to a group with isolated CAKUT (n=27). They found 4 RET-mutations in the HD without CAKUT group and 1 RET-mutation in the HD with CAKUT group. A GDNF-mutation was found in 2 HD without CAKUT patients and in 1 isolated CAKUT patient. There were no mutations found in the GFRalpha1-gene.

**Table 1:** Overview of the literature

**Abbreviations: HN: hydronephrosis; VUR: vesicoureteral reflux; DCS: duplex collecting system; MU: megaureter; RH: renal hypoplasia; RA: renal agenesis; RD: renal dysplasia; UV: urethral valves; HSK: horseshoe kidney*

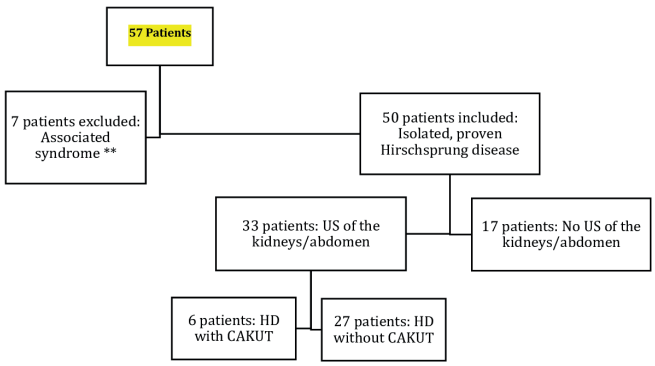
| Nr | Reference + name (date of publication) | n patients with HD | HD phenotype (n) | n patients with associated CAKUT (%) | CAKUT phenotype | Genetics | Study characteristics |
|---|---|---|---|---|---|---|---|
| 1 | 20Lee et al. (1965) | 40 | Unknown | 1 (2.0) | HN | No | Retrospective - Methodological limitations (not clear if all patients had an ultrasound of the kidneys) |
| 2 | 21Ehrenpreis et al. (1970) | 62 | Unknown | 7 (11.0) | HN, VUR, DCS | No | Retrospective |
| 3 | 22Swenson et al. (1973) | 501 | Unknown | 12 (2.5) | MU | No | Retrospective – Methodological limitations (not clear if all patients were investigated and which investigation was used |
| 4 | 23Klein et al. (1984) | 26 | Unknown | 3 (11.5) | VUR, RH, RA | No | Retrospective – methodological limitations (not clear if all patients were investigated and which investigation was used) |
| 5 | 24Yazbeck et al. (1986) | 64 | Unknown | 8 (12.5) | VUR, RH, HN, RD, UV | No | Retrospective |
| 6 | 25Van der Sanden et al. (1994) | 214 | Short segment-HD (3), Long segment-HD (5) | 8 (3.0) | VUR, RH, RA, HN, RD | No | Retrospective – methodological limitations (not clear if all patients were investigated and which investigation was used) |
| 7 | 26Amiel et al. (2008) | 160 | Unknown | 7 (4.4) | RA, RD | No | Retrospective – methodological limitations (not clear if all patients were investigated and which investigation was used) |
| | | 1067 | | 46 (4) | | | Summary Retrospective Studies |
| 8 | 13Pini Prato et al. (2009) | 84 | Short segment-HD (13), Long segment-HD (3), Total colonic aganglionosis (5) | 21 (25.0) | RH, HN, DCS, VUR, HSK | 1 mutation in RET in patient with HD and CAKUT | Prospective |
| 9 | 27Pini Prato et al. (2013) | 106 | Short segment-HD (17), Long segment-HD (1), Total colonic aganglionosis (3), Total intestinal aganglionosis (1) | 22 (20.7) | RD, RH, VUR, DCS, HN, UV | No | Prospective |
| 10 | 28Granéli et al. (2019) | 58 | Unknown | 6 (10.0) | RH, HN, MU, RA, RD | No | Prospective |
| | | 248 | | 49 (19,7) | | | Summary Prospective Studies |

2. Retrospective study UZ Leuven

In UZ Leuven 57 patients with a confirmed diagnosis of HD on anatomopathological examination, born between 1980 and 2014, were identified. Seven patients were excluded because of a confirmed underlying genetic disorder/syndrome (4 trisomy 21; 3 Waardenburg syndrome) (Figure 1). Of the 50 included patients, the male/female ratio was 3.5:1.0. Eight patients (16%) had a long-segment HD and 42 patients (84%) a short-segment. Nine patients (18%) had a familial history of HD, of whom four had a long-segment HD.

**Figure 1:**

** patient 1: dysganglionosis without aganglionosis on APO; patient 2: chronic obstipation without proven HD; patient 3: familial presence of HD without disease in the patient;*
*** 4 patients: Trisomy 21; 3 patients: Waardenburg Syndrome*




Thirty-three patients (66%) underwent an ultrasound of the abdomen/kidneys and urinary tract. In six (18.2%) CAKUT was diagnosed (4 hydronephrosis, 1 megaureter, 1 ectopic kidney, 3 vesicoureteral reflux, 1 posterior urethral valves and 1 duplex collecting system). Genetic investigations for RET were performed in 19 patients (38%). The CAKUT status of five of these patients is unknown as they did not receive an abdominal ultrasound. A mutation in RET was found in six patients which were all considered pathogenic (table 2). One patient had an in-frame deletion of one amino acid, p.Phe150del, of which the pathogenic characteristics of are not known. Of the six patients with a RET mutation, five received an ultrasound but none was diagnosed with CAKUT. The only HD-CAKUT patient receiving genetic investigation for RET mutations, didn't have a mutation. Eight patients received an evaluation of other genes (other than the RET-GDNF-GFRalpha1-pathway). Four of them had the HD-CAKUT association. In 50% (2/4) a genetic anomaly was found. One patient had a deletion of 2,58 MB in chromosome 7q and the other patient a DF508-mutation.

## Discussion

HD is a multifactorial disorder with a low, incomplete and sex dependent penetrance and a variable expression according to the length of the aganglionic segment and the severity of the obstructive symptoms[3]. Probably, the involvement of and interaction of multiple genes with low penetrance, but also environmental modifiers and other possible variable factors, will influence the clinical picture of HD[29]. HD stands, therefor, as a model for different genetic disorders with complex patterns of inheritance[3]. Like in HD, genetic factors also play an important role in the pathogenesis of CAKUT. The hypothesis of an association between HD and CAKUT, based on the partial, common genetic background, is not new. The first indications were acquired through mice models with absent expression of RET or GDNF or mice with mutations in these genes. They displayed anomalies in the renal system as well as in the enteric nervous system[3,7,8,12,30-33].

Before the use of CAKUT as acronym for different clinical entities affecting the kidneys or other structures of the urinary tract in 1999, most studies report on urogenital malformations. The prevalence of urogenital malformations in patients with HD varied around 6%[12,34-36]. The literature review focused on studies where it was possible to distract the data following the CAKUT criteria. There is a significant higher incidence of CAKUT in patients with HD (7.2%) compared to the general population (0,4-2%). It is important to recognize that retrospective studies report a significantly lower prevalence (4%) than prospective studies (19.7%).

The discrepancy in the results between retrospective studies and prospective studies is probably a consequence of lacking data or delayed diagnosis of an asymptomatic patient with CAKUT. This underestimation of the real prevalence of CAKUT in patients with HD, advocates for systematic screening for CAKUT in every patient with HD.

Only one study described the genetic investigations in 34 patients with HD of which 7 (21%) had a mutation in RET or GDNF[13]. Only one of these patients had the HD-CAKUT combination. This makes it impossible to draw any conclusion about a possible underlying genetic association.

The retrospective cohort study demonstrated the importance of systematic ultrasound screening as this was done in only 66% of cases and genetic testing of RET in only 38%. The CAKUT prevalence of 18.2%, is however, in accordance with the prospective studies [13,27,28]. This confirms the higher incidence of CAKUT in patients with HD compared to the general population and argues for systematic ultrasound screening of the kidneys and urinary tract in patients with HD.

The genetic screening performed in 38% of the cohort discovered a genetic diagnosis in 15% but none of these patients had the HD-CAKUT association. Although RET-mutations are common within HD, the penetrance is low. Moreover, there is no precise hotspot and mutations in RET associated with HD occur in all of the 20 exons, as well in the coding as in the non-coding sequences[10]. This together with the retrospective character of our study can be an explanation for the lack of genetic results.

**Table 2:** Patients with mutations in RET

**Patient 4 didn't have an US of the abdomen/kidneys which makes it impossible to diagnose CAKUT*

| Patient | Sex | Mutation in RET | HD | CAKUT | Other |
|---|---|---|---|---|---|
| 1 | M | Exon 6 (c.1196C>T) | Familial – Total colon aganglionis | no | DCDA-twin – brother with cheilo-pallato – gnathoschisis |
| 2 | F | Exon 6 (c.1196C>T) | Familial – long form | no | no |
| 3 | M | c.448_450delTTC | Not familial – short form (rectosigmoïd) | no | Exocrine pancreatic insufficiency |
| 4 | M | Exon 13 (c.2508C>T) | Not familial – long form | Uncertain* | No |
| 5 | M | Exon 10 (c.1879+1del15. – heterozygote deletie) | Not familial – short form | no | No |
| 6 | F | Exon 9 ( c.1672T>C ) | Familial – short form | no | No |

In our study there were 4 patients with mutations in other genes than RET as well. Two patients of them were also diagnosed with CAKUT. Literature review however didn't show an association between these mutations/ genes and HD or CAKUT [29-31].

The literature search and cohort study confirmed the underestimated prevalence of the HD-CAKUT association and the lack of the genetic characterization of this population. Systematic screening and genetic investigation with focus on RET-GDNF-GFRalpha1-complex, is warranted in every patient with HD. Accumulation of data might help to understand this multifactorial congenital disorder and the link with CAKUT.

## Conclusion

Based on the literature review and the cohort study, an association between HD and CAKUT is present in almost 1/5 patients with HD. We emphasize the need for a systematic ultrasound screening for the presence of CAKUT in every patient with HD. Despite the possible role of RET, described in different animal models, it is not yet clear if this is the case in humans due to lack of data. To confirm this genetic association larger HD patient groups with prospective genetic and ultrasound evaluation will be necessary.

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# Fate of a sickle cell child abandoned at birth

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## Keywords

Abandonment, adoption, placement, sickle cell anemia

## Abstract

Abandonment of a child is generally understood as an act by which a parent expresses, explicitly or tacitly, his renunciation of his duty of protection, support and education of his child, which should be therefore assumed by a third party.

Sickle cell disease is a genetic disease inherited in an autosomal recessive pattern. Characteristic features of this disorder include haemolytic anaemia, repeated infections, and periodic episodes of pain. Sickle cell disease is the most common inherited blood disorder in Africa.

There are no apparent links between these two subjects and yet when they are present in the same child, they will significantly influence its future.

This leads us to reflect on the place of children in our society and on the essential role of the paediatrician.

## Introduction

The abandonment of children has always existed and is a great source of distress. Our aim in this article is to describe its history and focus on our experience with a case at the Ambroise Paré Hospital in Mons (Belgium).

The question of child abandonment has arisen throughout human history. In order to avoid infanticide and abandonment on the public highway, societies have tried to organize the modalities.

In the Roman Empire, the «abandoned» were assigned as slaves to those who collected them or were adopted by the state as children of the Fatherland.

In Europe, since the early Middle Ages, the Church has tried to fight against infanticide by encouraging abandonment[1]. The fate of abandoned children was more favourable if they were harboured by religious congregations or in hospitals run by these communities. The children were "fostered" by a nursing mother until they were 3 or 4 years old. Between the ages of 6 and 8, they were entrusted to a schoolmaster and then to a foster family to learn a trade. This family was committed to raise them as if they were their own children.

In the 17th century, many children were abandoned at church gates, hospitals or with midwives. The usual causes were non-marital births, or the inability of legitimate parents to take care of their child. The Church favoured abandonment at the cost of any method of contraception or abortion which it strongly condemned.

In 1630, Saint Vincent de Paul, desperate about the fate of abandoned children, encouraged the recruitment of nannies to fight against this scourge. His work will be recognized and officialised forty years later with the creation of the «Hôpital des Enfants-Trouvés» in Paris.

In the 18th century, the increase in abandonment was due to the misery of the working classes, but also to the increase in illegitimate births linked to the freedom of morals that characterizes this century. The writings accompanying the abandoned children were quite eloquent: "January 1789, Rouen. I was born today, January 7, of legitimate marriage. My father and mother, suffering from extreme misery, were unable to make me receive baptism and to render me the services that my tender youth compel them to give me. It is only with the most humiliating affliction and the most sensitive pain that they abandon me and expose me while waiting for heaven to favour them to be able to call me back into the bosom of my family"[2].

In the 19th century, the frequency and causes of abandonment remained the same. In 1811, a Napoleonic decree formalized the "foundling wheels". These turnstiles allowed parents to drop off their child anonymously and safely. The opening of the tourniquet was on the street side; they only had to drop the child in the baby box, to ring the bell and the box turned towards the inside of the hospice where a sister was taking the child. Families at that time left signs of recognition in the children's nappies in order to identify them in the hope of future restitution. In 1863, the foundling wheels were removed and replaced with admission offices to whom mothers could entrust their child.

In the 20th century, French legislation created «under X» childbirth, ensuring total anonymity about the mother's identity. It became the main form of abandonment in France.

Today, precarious socio-economic conditions remain the main cause of abandonment. Women who resort to abandonment are often young or even adolescent girls, without resources and faced with an unwanted pregnancy. Since the 1920s, "nursery" centres and maternity homes have been set up to admit mothers and their babies when they leave the maternity ward. Unlike in France, childbirth under X doesn't exist in Belgium.

## Clinical case

We lack anamnestic data concerning the biological parents of this child as well as the circumstances of his conception. The mother is of Cameroonian origin and stays in Belgium with a student visa in precarious financial conditions. She was not followed during pregnancy, goes to hospital shortly before term and indicates that she wants to abandon her baby.

In the blood sample taken during this consultation, thrombocytopenia (101 000/mm$^3$) and anaemia (11 g/dl) were observed with lowered ferritin (8 µg/l). Haemoglobin electrophoresis shows a lowered haemoglobin A of less than 60% and the presence of 40% haemoglobin S, which is compatible with heterozygous sickle cell disease. The rest of biology was unremarkable.

At an estimated gestational age of 41 weeks, she gives birth to a male baby (birthweight 3825g, Apgar 9/10/10). She doesn't want to see him or know his sex. The nursing team chooses a first name, he is admitted to the neonatal centre andprogresses very well. Routine blood sampling is normal apart from thrombocytopenia (85 000/mm$^3$). Knowing the mother's haematological status, an electrophoresis of the haemoglobin is performed. It reveals the absence of haemoglobin A (< 0.5%), a predominant haemoglobin F (89%) and the presence of haemoglobin S (11%). There was no intra-erythrocyte enzyme deficiency.

During his stay at the neonatal centre, the child is referred to the haematology consultation at the Queen Fabiola Children's University Hospital and prophylactic treatment with antibiotics (amoxicillin 30 mg/kg/day in 2 doses) and folic acid (1 mg 1x/day) is prescribed. He then has a favourable medical evolution but without any parental presence.

The mother wished to give birth under "X", but this provision doesn't exist in Belgium, so the child's file is entrusted to our social workers and to the adoption service of the "Office de la Naissance et de l'Enfant" (ONE).

As the weeks went by, the empathy of the staff in the paediatric ward, with little knowledge of adoption legislation, prompted several spontaneous initiatives within the team to adopt this child when it appeared that his pathology would make the search for a family even more difficult. In the end, these spontaneous initiatives did not materialise because any adoption procedure requires preparation and supervision by an accredited body, both for international and national adoptions.

The ONE's adoption service has sought the help of a non-profit organisation service approved by the Ministry of Youth Assistance which specialises in the adoption of children with special needs. From its experience, this organisation knew that it would be very difficult to find an adoptive family. They had already been confronted with a child with the same pathology and with a very heavy medical history. As a result, they turned to the Youth Assistance Service (Service d'Aide à la jeunesse - SAJ) in order to consider a foster placement. This solution, which was unexpected to say the least, went against the very principle of adoption, as it required, among other things, to lift mother's anonymity.

A staff member, who had taken the necessary measures to become a foster family was entrusted with the child at the dawn of his 3 months.

The child's staturo-ponderal development was quite favourable with growth at the 90th percentile. At the age of 5 months blood examination revealed anaemia (haemoglobin 7.8 g/dl) with low haematocrit (21.5%) and a mean corpuscular volume of 76 fl, justifying the start of hydroxyurea treatment.

From psycho-social point of view, his host family started an adoption procedure after a few months, which is still ongoing.

## Discussion

Sickle cell disease, also known as sickle cell anaemia or haemoglobinopathy S is the most common genetic disease in the world, with a worldwide incidence of 310000 births each year[3].

It is caused by the substitution of a single amino acid residue on the β haemoglobin chain. This genetic mutation located on chromosome 11 leads to the replacement of the glutamate in position 6 by a valine, giving haemoglobin S (HbS). Under deoxygenation conditions, this haemoglobin polymerizes, which stiffens the erythrocytes and deforms them into a "sickle". Sickle cell disease is clinically expressed only in subjects homozygous for HbS (HbSS) or in those who are heterozygous for HbS with other hemoglobinopathies. In contrast, heterozygous subjects for HbS (HbAS) are healthy carriers.

In patients, irreversible erythrocyte sickling induces three major categories of clinical manifestations: chronic haemolytic anaemia with acute episodes of aggravation, susceptibilities to bacterial infections and vaso-occlusive manifestations.

In severe forms, management will require the use of transfusions (even exchange transfusion), treatment to increase foetal haemoglobin (hydroxyurea) levels or hematopoietic stem cell transplantation.

In Belgium, when a woman is faced with an unwanted pregnancy and doesn't wish to reveal it, it is currently impossible for her to give birth with partial or complete anonymity.

The adage "mater semper certa est" is universally applicable[4]. The woman who gives birth is the legal mother and designated as such in the birth certificate, which establishes filiation. Even if she wishes to abandon, she will not avoid her involvement in an adoption procedure. The court requests the opinion of the biological mother, even if the latter expresses the wish not to participate in the said proceedings, including in the case that she wishes to hide the existence of her newborn baby from her family and friends.

In the French community, the mother is allowed to reconsider her decision for two months, at the end of which she will have to sign her final abandonment agreement.

In France, in order to simplify legal procedures, parturients can give birth "under X", thus leaving no trace of their identity. Children are then deprived of the right to know their biological origins, with all the consequences for their health, both physical and psychological[5].

Today in Europe, regulations on the anonymity of the biological mother differ from country to country. A legal framework for anonymous delivery is planned in France, Italy, Austria and Luxembourg. France has set up an organisation allowing abandoned children to find their origins if they wish. In contrast, Bulgaria, Romania and Germany have adopted a policy of tolerance in this respect. "Baby boxes" are still allowed in Germany, Italy and Austria. In Belgium, there are two, one in Antwerp since 2000 and another in Evere since 2017.

Several bills providing for "discreet" delivery have emerged in Belgium. The idea is to reconcile as well as possible the woman's right to control her body and the child's right to know his origins. Discreet childbirth considers the distress of mothers by allowing a birth certificate to be drawn up which does not mention the name of the woman giving birth, while ensuring the preservation of information in a register accessible to the child, mother and presumed father. In this way, the child's right to know his origins is respected, even though the information doesn't guarantee any legal bond of filiation, thus protecting the woman in distress who is unable to assume the responsibilities of her motherhood[6].

In 2018, in the Wallonia-Brussels Federation, 43 mothers or couples started abandonment procedures. Out of all these situations, 12 (28%) resulted in an adoption plan, including 2 as part of a binding measure (Youth Court). Of the 31 (72%) other cases, 17 went back on their initial plan to entrust the child to adoption, 3 were redirected to another adoption agency, 4 situations were taken into care by a Youth Support Service and the remaining 7 situations were still unsolved as at December 31, 2018[7].

One of the solutions to abandonment is so-called "long-term" foster care, because it suggests that it will persist until the child reaches the age of majority. The placement is entrusted to foster families who submit an application. Their request is studied by the Provincial Foster Care Service, and professionals such as psychologists and social workers select and accompany them.

There are also authorised adoption services that include for children with special needs. They intervene at 3 levels. With biological parents who are faced with the handicap of their unborn or already born child for support purposes. With children with disabilities by looking for suitable homes able to adopt them. Finally, with candidate adoptive families by informing them as best as possible about the disability or illness of the child they are about to adopt.

One can wonder about the role of the paediatrician who is faced with such a situation. Should it strictly be limited to care? Doesn't he or she have a role to play, complementary to that of other childhood professionals such as medico-social workers, social workers and psychologists?

With further training on this aspect of childhood and its legal aspects, he can undoubtedly provide informed advice and guidance to the various stakeholders.

## Conclusion

Society has helped to reduce child abandonment by introducing preventive systems such as contraception, but while it may have decreased over time, it has not disappeared. This act is often the consequence of misery, precariousness, or simply the impossibility of taking care of a child.

In addition, the creation of a whole series of structures or channels for the care of these children made it possible to put them in the best conditions for a better future and more favourable social and emotional development.

However, the fact that an abandoned child is also suffering from a serious pathology further limits the possibilities of reception.

The paediatrician has a vision and a sometimes different knowledge of the history, the experience of the child in question and this vision can sometimes be useful for people who will have to make a choice about the future of this child.

It would therefore be appropriate to include training in this delicate subject in the paediatric curriculum, allowing paediatricians to play a full role in supporting and caring for these children in great difficulty

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*Hereby we publish the final version of the manuscript entitled: "Management of neonatal hypertension". By mistake, de non-revised draft was published in the previous issue. Our apologies to the authors and the reviewers.*

# Management of neonatal hypertension

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## Keywords

hypertension, blood pressure, neonate

## Abstract

Neonatal hypertension remains a rare condition. However, it is important for pediatricians to be able to interpret blood pressure (BP) measurements in neonates, since unrecognized and untreated hypertension can result in severe organ damage. This narrative review summarizes the current evidence on hypertension in neonates based on the recent literature. The definition of hypertension, considerations on optimal BP measurements in neonates as well as the etiology, diagnostic workup, and briefly the treatment are reviewed.

Overall, neonatal hypertension, is defined as BP above 95th percentile. In neonates, intra-arterial (invasive) measurement is gold standard for BP measurement. Determinants of neonatal BP, including both maternal and neonatal factors, are not yet completely clear. The etiology of neonatal hypertension is variable, with umbilical arterial catheterization, renovascular, renal parenchymal and pulmonary diseases as most frequent causes. Although the general prognosis is good, it is essential to apply a systematic diagnostic workup in which the confirmation of the hypertension ensuring the right measurement technique should be the first step.

## Introduction

With advances in neonatal care, awareness for neonatal hypertension is increasing although it still remains a rare condition. Nevertheless it is important for pediatricians to be able to interpret blood pressure (BP) measurements in newborns since untreated and unrecognized hypertension can result in severe end organ damage including shock, encephalopathy, congestive heart failure and even death[1]. The incidence of hypertension in neonates is difficult to determine given the lack of a standardized definition, and the fact that it often remains unrecognized. The estimated overall incidence is between 0.2 and 3.0% (systolic or diastolic BP > 95$^{th}$ percentile for age)[2,3].

Hypertension seems to be more common in patients with patent ductus arteriosus, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage and umbilical arterial catheterization (UAC)[4]. In a retrospective study of 1987, Friedman and Hustead reported an incidence of hypertension of 2.6% in 650 infants in follow-up after discharge from the neonatal intensive care unit (NICU)[5]. Mean age at diagnosis was 2 months post-term. More recently (2018) Kraut investigated the incidence of neonatal hypertension from the multicenter AWAKEN database. They reported an incidence of 5.5%[6]. The higher incidence compared to old reports may reflect increased awareness of hypertension in neonates. In addition, neonatal care has changed dramatically last decades. These observations support the recommendation of the Fourth Report on BP management in children and the American Academy for Pediatrics to routinely monitor BP also after NICU discharge[7].

We will first discuss normal BP values, the (physiological) changes in BP during the first days and weeks of life, determinants of BP, as well as optimal BP measurement techniques in neonates. Subsequently, we aim to provide the pediatrician with a current overview on neonatal hypertension, including definition, diagnosis and etiology. We will discuss very shortly the treatment and the long term prognosis for this population.

## Definition

Although a consensus definition of neonatal hypertension is currently lacking, it is arbitrarily defined as: a BP >2 standard deviations above baseline for neonates of similar age[1], or a systolic BP (SBP) or diastolic BP (DBP) >95$^{th}$ percentile for neonates of similar size, gestational age (GA) and postnatal age (PNA)[2,8]. When BP is between the 95$^{th}$ and 99$^{th}$ percentile without organ damage, it is considered moderate hypertension. Malignant hypertension concerns a BP above the 99$^{th}$ percentile with or without end organ damage[2].

## Optimal BP measurement in neonates

The gold standard to measure BP in neonates is intra-arterial (invasive) BP measurement. This can be done through an UAC or catheterization of a peripheral artery (e.g. radial or posterior tibial artery)[1]. This method is commonly used in unstable preterm, and critically-ill term neonates. Non-invasive BP measurement is usually performed by an automated oscillometric device. This is a reasonable alternative to invasive BP measurement but it may underestimate SBP in small for gestational age (SGA) neonates and overestimate SBP and DBP in critically-ill neonates[2]. Although the reason for this misestimation is unclear, König speculate that overestimation of arm-measurements and underestimation of leg-measurements can be related to minimal muscle mass in preterm infants, in particular upper limbs[9]. Dionne showed that the first BP reading is usually less accurate than subsequent readings. It is therefore recommended to measure BP three times and average the results[8]. If the first reading is elevated, take the average of the following two measurements[2]. An appropriately sized cuff is needed for optimal measurement. The cuff should cover at least 85% of the limb circumference and at least two thirds of the length of the limb segment[10]. Measurements should preferably be taken at the right upper arm[1,10]. The infant should be in supine position and asleep or quietly awake at least 30 minutes after the last feed because crying can increase SBP up to 17–25 mmHg when compared with quiet neonates[1,10]. Pejovic showed lower BP when the infant was asleep compared to awake[10].

## Normal BP values in neonates

Defining normative data for BP in neonates is challenging since multiple factors may have an impact. Neonatal BP is mainly determined by GA, postmenstrual age (PMA), and birth weight (BW), with PMA as strongest predictor[10,11]. Also appropriateness for GA, PNA and neonatal disease determine BP. Other factors

such as maternal health and maternal medication influence BP as well[1].

Zubrow provided normal BP and 95th percentiles for the first days of life based on BW, PMA and GA for neonates admitted to the NICU[11]. **Figure 1** shows normal trends in SBP, DBP and mean BP (MBP) according to BW and GA on the first days of life, as well as trends according to GA for the first week PNA, as published by Pejovic [10]. **Table 1** represents normative values for neonates older than two weeks of age based on PMA derived by Dionne based on literature data[8]. Around the world NICU's are using these reference values to evaluate BP in neonates.

## Determinants of neonatal BP

Both maternal and neonatal factors determine neonatal BP.

Maternal factors influencing neonatal BP include maternal underlying health (e.g. hypertension, preeclampsia) and medication, but also type of anesthesia and mode of delivery. However, evidence on the effect of some of these factors on neonatal BP is often not conclusive.

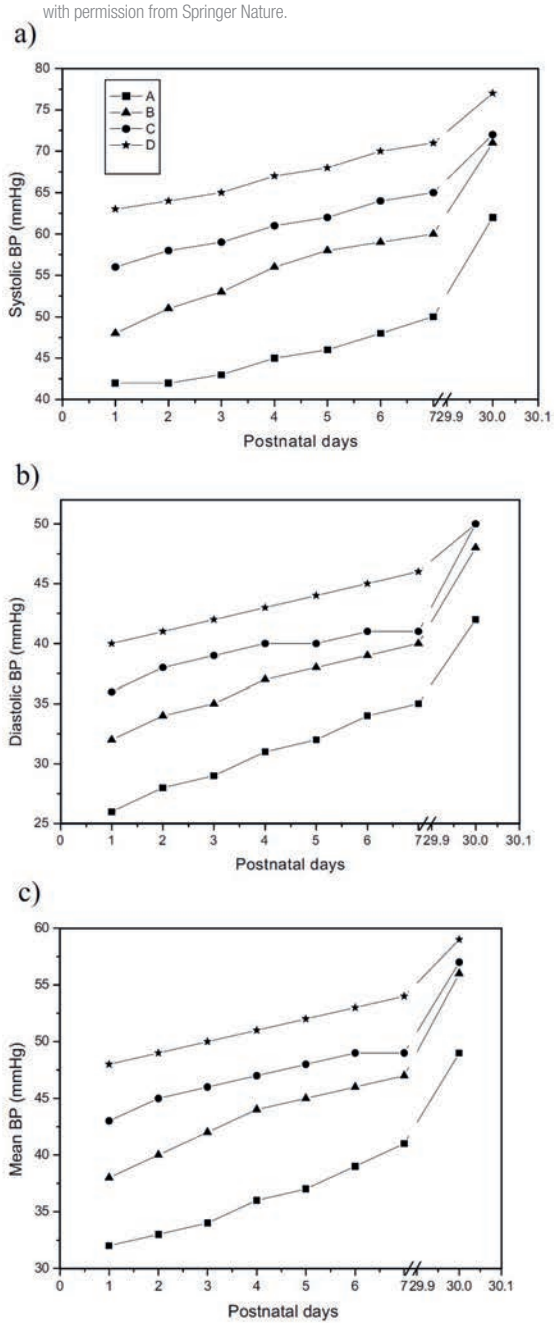
A. Maternal factors:

1. Spinal anesthesia during delivery results in lower SBP on day 1 in comparison to epidural, general or no anesthesia, which can cause fetal acidosis[12]. Spinal anesthesia is often associated with maternal hypotension. This sudden decrease in maternal BP results in liberation of maternal moderators which in turn could affect neonatal SBP[12].
2. Maternal BP (such as chronic hypertension or preeclampsia) also seems to influence neonatal BP. A possible mechanism is considered through endothelial dysfunction with reduced production of vasodilators to modify the pressure response. Findings suggest that endothelial dysfunction might be present in the neonate as well, affecting BP similarly as in the preeclamptic mother resulting in higher neonatal BP during the first week of life[13]. Other authors however found that maternal preeclampsia results in higher risk for neonatal hypotension[14]. Further research is needed to explore the impact of maternal BP on neonatal BP, and more specifically, the long term effects into child- and adulthood[15].
3. Administration of corticosteroids prior to preterm delivery results in higher BP in preterms during the first 24-48 hours of life. In 163 neonates, indeed a significantly higher SBP (p=0.04) and mean arterial BP (p=0.04) at birth has been reported in cases with versus without exposure to antenatal steroids[16]. Consequently, there is less requirement for BP support resulting in reduced mortality and morbidity in these preterm neonates[15]. Seliem *et al* found an eightfold increase in the risk of neonatal hypertension after antenatal steroid administration[17]. However, results differ between studies. LeFlore *et al* compared BP in very low birth weight (VLBW) neonates who received antenatal corticosteroids versus VLBW neonates who did not and found no significant difference in SBP, DBP or MBP during the first 72h of life[18].

B. Neonatal factors influencing neonatal BP include GA, PMA, BW and appropriateness for GA. In a large multicenter study Zubrow *et al* recorded BP 8-hourly in 600 NICU patients. They showed that BP on day 1 is strongly correlated with BW and GA[11]. Lower BW resulted in lower BP. However, a large Australian study, including over 400 healthy term neonates, documented that BP on day 1 was not influenced by GA or BW[19].

Pejovic observed that GA remains a significant predictor of BP throughout the first 30 days of life[10]. Different mechanisms contribute to the increase of BP with increasing PNA e.g. decreased activity of vasodilators and intrinsic changes in vascular smooth muscle function[10]. Appropriateness for GA has an impact on neonatal BP as well. Smal compared BP in SGA neonates with neonates appropriate for gestational age (AGA) and observed a similar BP rise during the first week of life in both groups. In the SGA neonates however, BP was inversely correlated with BW. The SGA neonates with the lowest BW had the highest BP[20]. When the fetus is exposed to high levels of endogenous cortisol to compensate for placental insufficiency, an alteration in hypothalamic-pituitary axis is seen which results in chronic elevation of cortisol levels in the fetus and predisposition for hypertension[20].

**Figure 1:** Increase in systolic (a), diastolic (b), and mean (c) blood pressure during the first month of life in infants classified by estimated gestational age: A ≤ 28 weeks, B 29–32 weeks, C 33–36 weeks, D ≥37 weeks. Reproduced from Pejovic et al(10) with permission from Springer Nature.




## Etiology of neonatal hypertension

Most frequent causes of neonatal hypertension are renal etiologies, including renovascular and renal parenchymal diseases, and catheter-associated thromboembolism[2,21]. Mainly umbilical arterial catheterization is associated with an increased risk of hypertension, most often due to renal artery thrombosis. Besides this, pulmonary, cardiac, endocrine, exogenous (e.g. drug-induced), neurologic etiologies, or hypertension secondary to neoplasmata can also occur[2,21]. Nevertheless, in 50% of cases no explanation for hypertension can be found[22].

### Renovascular etiologies

Umbilical arterial catheterization is correlated with an increased risk of hypertension. Up to 9% of neonates with UAC develop hypertension[4]. Most often this is due to thrombus formation affecting either the renal arteries and/or the aorta. UAC is associated with a significant increase in plasma tissue factor (TF). Placement of an UAC is associated with mechanical vascular endothelial injury resulting in direct exposure of blood to TF. This initiates the extrinsic coagulation pathway resulting in increased risk for thrombus formation[23]. The thrombus may subsequently embolize the renal parenchyma[2].

**Table 1:** Estimated BP values after 2 weeks of age in infants from 26 to 44 weeks postconceptional age.

| Postconceptional age | 50th percentile | 95th percentile | 99th percentile |
|---|---|---|---|
| 44 weeks | | | |
| SBP | 88 | 105 | 110 |
| DBP | 50 | 68 | 73 |
| **MAP** | **63** | **80** | **85** |
| 42 weeks | | | |
| SBP | 85 | 98 | 102 |
| DBP | 50 | 65 | 70 |
| **MAP** | **62** | **76** | **81** |
| 40 weeks | | | |
| SBP | 80 | 95 | 100 |
| DBP | 50 | 65 | 70 |
| **MAP** | **60** | **75** | **80** |
| 38 weeks | | | |
| SBP | 77 | 92 | 97 |
| DBP | 50 | 65 | 70 |
| **MAP** | **59** | **74** | **79** |
| 36 weeks | | | |
| SBP | 72 | 87 | 92 |
| DBP | 50 | 65 | 70 |
| **MAP** | **57** | **72** | **71** |
| 34 weeks | | | |
| SBP | 70 | 85 | 90 |
| DBP | 40 | 55 | 60 |
| **MAP** | **50** | **65** | **70** |
| 32 weeks | | | |
| SBP | 68 | 83 | 88 |
| DBP | 40 | 55 | 60 |
| **MAP** | **48** | **62** | **69** |
| 30 weeks | | | |
| SBP | 65 | 80 | 85 |
| DBP | 40 | 55 | 60 |
| **MAP** | **48** | **65** | **68** |
| 28 weeks | | | |
| SBP | 60 | 75 | 80 |
| DBP | 38 | 50 | 54 |
| **MAP** | **45** | **58** | **63** |
| 26 weeks | | | |
| SBP | 55 | 72 | 77 |
| DBP | 30 | 50 | 56 |
| **MAP** | **38** | **57** | **63** |

Reproduced from Dionne et al [8] with permission from Springer Nature
SBP, Systolic Blood Pressure
DBP, Diastolic blood pressure
MAP, Mean arterial pressure

However, hypertension can occur even when thrombi cannot be demonstrated[8]. It is recommended to remove the UAC after 5 to 7 days since longer duration is associated with an increased risk for thrombi[1,24]. For each additional day of UAC in situ, adjusted Odds Ratio of developing thrombosis is reported to be 1.2 (95% CI: 1.1, 1.3)[24]

Renal venous thrombosis mostly occurs in a setting with high risk prothrombotic disorders such as maternal diabetes or factor V Leiden mutation. Mechanical compression of one or both renal arteries due to an abdominal mass or severe hydronephrosis can result in hypertension as well. Other vascular abnormalities such as idiopathic arterial calcification, renal artery stenosis due to congenital Rubella infection and aortic coarctation are other well known risk factors for development of hypertension[8,25].

Few case reports have described mid-aortic syndrome as a rare cause of neonatal hypertension[26,27].

### Renal parenchymal disease

Renal parenchymal disease causing hypertension can be explained by a combination of mechanisms, including impaired renal sodium and water excretion resulting in volume expansion, activation of the Renin-Angiotensin System (RAS) with excessive release of vasoconstrictors, vasodilator deficiency (e.g. nitric oxide) and sympathetic activation due to increased vascular resistance and cardiac output resulting in vasoconstriction[28].

While these mechanisms are usually common, the underlying disease can differ (congenital or acquired). Polycystic Kidney Disease (PKD) is a well-known congenital cause of neonatal hypertension. Both autosomal recessive and dominant PKD may present with hypertension in the neonatal period.

Less frequently, neonatal hypertension is caused by multicystic dysplastic kidneys[29].

Acquired renal parenchymal disease includes interstitial nephritis, severe acute tubular necrosis, cortical necrosis and rarely unilateral renal hypoplasia. Recently, additional analyses on a multicenter database on neonatal acute kidney injury (AKI) epidemiology (AWAKEN study) showed a significant association with neonatal hypertension and AKI (defined as a rise in serum creatinine of ≥ 0.3 mg/dL or ≥50% from previous lowest value and/or urine output <1ml/kg/h on PNA day 2 to 7)[6,30]. In this study, additional risk factors for hypertension were vaginal delivery, outborn, Caucasian race, congenital heart disease and hyperbilirubinemia[6]. In addition, urologic abnormalities like ureteropelvic-junction obstruction can cause hypertension, which is reported to remain even after correction of the obstruction[31].

### Pulmonary disease

Studies demonstrated a possible relationship between neonatal systemic hypertension and chronic lung disease of prematurity or BPD[2]. Alagappan found an overall incidence of hypertension of 6.8% compared to 12% in neonates with BPD[32]. More recently, Sahu reported BPD as a significant risk factor for development of hypertension with an odds ratio of nearly five[33]. Again, the underlying pathophysiology is considered multi-factorial. Some authors suggest hypoxemia to play a role, while others claim that due to pulmonary hypertension higher SBP is required to maintain pulmonary blood supply[2]. In addition, changes in the angiotensin-renin system due to angiotensin converting enzyme 2 in the lung may play a role in BPD[34]. Furthermore, infants with BPD are often administered steroids which also might contribute to systemic hypertension[35]. In a multicenter study (2017) of preterms with and without chronic lung disease, cases with hypertension presented in both groups around 40 weeks PMA and resolved within another 25 weeks. Resolution of hypertension occurred in all cases[22]. Recently, Farnbach et al explored the etiologic spectrum of hypertension in preterm neonates over time. While high renin-hypertension was more common in the past, they suggested that increasing incidence of transient low-renin hypertension may at least in part be phthalate-induced (e.g. phthalates in respiratory therapy tubing and IV tubing)[36]. However, this topic needs further study.

### Other causes

**Table 2** provides an overview of known categories of causes of neonatal hypertension. After the major categories described above, some additional, less frequent causes are summarized below. In the category of cardiovascular etiologies, aortic coarctation is most common and hypertension may persist or

reappear even after surgical correction. Blood pressure in these patients should be monitored closely, even after discharge[37]. Although not fully understood, decreased compliance of the arterial wall after correction of coarctation probably plays a role[38]. Other underlying pathologies such as acute neurologic diseases (e.g. seizures, intracranial hypertension, pain), endocrinologic causes (e.g. congenital adrenal hyperplasia, hyperaldosteronism, hyperthyroidism, pseudohypoaldosteronism type II), or tumors (due to mechanical compression of the renal vasculature or ureters, or due to catecholamines release) can cause hypertension as well[39,40]. Hypertension in neonates can also be evoked by extrinsic factors such as administration of total parenteral nutrition (TPN) or maternal and neonatal drug (ab)use. Prolonged administration of TPN may induce hypertension due to salt and water overload, vitamin A and D intoxication and hypercalcemia[41]. Maternal use of cocaine or heroin during pregnancy on the other hand has an impact on the developing kidney, resulting in hypertension[42,43]. Drugs administered to neonates evoking hypertension include corticosteroids, bronchodilators and vasopressors, but also caffeine, high doses of adrenergic agents, prolonged used of pancuronium, or phenylephrine ophthalmic drops may raise BP[8,21].

## Diagnostic evaluation

An overview of the recommended workup is represented in **Table 3**.

After identification and confirmation of hypertension, a detailed neonatal and familial history, and a full physical examination are needed. This can be indicative for underlying etiology, e.g. absent femoral pulses indicating aortic coarctation and specific dysmorphic features in syndromic abnormalities[1,8]. Femoral pulses therefore need to be checked routinely when a neonate presents at a medical consultation. Further initial workup consists of a blood analysis (complete blood count, electrolytes and renal function)[1,10], urine analysis (to assess urinary protein, creatinine and micro-albumin to diagnose renal parenchymal disease)[8], and initial imaging (i.e. chest X-ray, renal ultrasound with Doppler and cranial ultrasound)

Renal ultrasound with Doppler has to be obtained in all hypertensive neonates since it is an accurate, inexpensive and noninvasive examination to determine renovascular abnormalities. Cranial ultrasound may exclude intraventricular hemorrhage, due to hypertension. Echocardiography needs to be part of the initial imaging in cases with e.g. cardiomegaly or circulatory failure[44,45]. Although acute hypertensive crisis is rare in neonates, it can present with circulatory failure. Findings of aortic regurgitation with left ventricular hypocontractility hereby should alert for possible underlying hypertension[45]. Echocardiography can provide critical markers[44]. Depending on results and/or suspected diagnosis, subspecialty advice (e.g. pediatric nephrologist, cardiologist) with additional investigations are needed. For example, quantification of cortisol, plasma renin activity and aldosterone or evaluation of thyroid function should be done in case of clinical suspicion, while echocardiography is e.g. indicated to confirm a diagnosis of aortic coarctation[46]. In essence, when hypertension is confirmed and initial workup has been performed, we recommend to contact a pediatric nephrologist. Early referral is important especially to guide optimal treatment. When a cardiac etiology is suspected based on clinical examination, it is recommended to directly refer to a pediatric cardiologist.

## Treatment

Neonatal hypertension has a low incidence but can result in severe co-morbidity. Consequently, it is recommended to discuss treatment options with experts in specialized centers as soon as hypertension is confirmed, to avoid delay in initiation of treatment and to choose the optimal antihypertensive drug. External factors causing hypertension need to be identified and corrected[8]. Complications and end-organ damage should be treated accordingly. In specific cases surgery may be warranted[8]. Recommendations for pharmacological treatment of hypertension in neonates are scarce and mostly based on expert opinion or evidence in older children. The fourth report on BP management in children recommends initiating treatment when BP is consistently above the 99$^{th}$ percentile adjusted for age and weight. One should aim to correct BP to be <90$^{th}$ percentile[7]. Few

**Table 2:** Causes of hypertension in neonates

| Category | Example |
|---|---|
| Renovascular[8] | Umbilical arterial catheterization[4]<br>Renal venous thrombosis<br>Renal artery thrombosis<br>Renal artery stenosis (e.g. due to congenital Rubella)<br>Mid-aortic syndrome[26,27]<br>Mechanical compression on renal arteries<br>Idiopathic arterial calcification[25] |
| Renal parenchymal disease | Polycystic Kidney Disease<br>Dysplastic kidneys[29]<br>Unilateral renal hypoplasia<br>Severe acute tubular necrosis<br>Interstitial nephritis<br>Cortical necrosis<br>Acute Kidney Injury<br>Ureteropelvic-junction obstruction[32] |
| Cardiovascular | Aortic coarctation |
| Pulmonary disease | Bronchopulmonary Dysplasia[32-33,35] |
| Endocrinologic [22] | Congenital adrenal hyperplasia<br>Primary hyperaldosteronism<br>Hyperthyroidism<br>Pseudohypoaldosteronism type II |
| Drugs / exogenous exposures[41] | * Maternal drug use[42-43] - Cocaine, heroin<br>* Neonatal drugs[8] - Corticosteroids, bronchodilators, vasopressors, caffeine, high doses of adrenergic agents, prolonged use of pancuronium, phenylephrine ophthalmic drops<br>* Other: nutritional (salt and water overload, vitamin A and D intoxication and hypercalcemia due to prolonged TPN), phthalate exposure[36] |
| Tumors[40] | Wilms tumor<br>Nephroblastoma |
| Neurologic[39] | Seizures<br>Intracranial hypertenison<br>Pain |

**Table 3:** Diagnostic evaluation of the hypertensive neonate

| |
|---|
| **Identify and confirm hypertension** (using appropriate equipment, serial measurement, reference values) |
| **History** |
| - Familial history<br>- Personal history (clinical course)[1,8]<br>- Postnatal interventions (for example umbilical arterial catheterization)<br>- Drugs (current and previous)<br>- Perinatal asphyxia<br>- Meconium aspiration |
| **Physical examination[1,8]** |
| - BP in 4 extremities (3 measurements, quietly awake or sleeping)<br>- Femoral pulses (should routinely be checked when a neonate presents at general practitioner, pediatric or public health consultation)<br>- Cardiac (heart murmur, cardiac failure)<br>- Abdominal (masses, epigastric bruit)<br>- Dysmorphic features (Turner syndrome, Williams syndrome, hyperandrogenicity in congenital adrenal hyperplasia) |
| **Blood analysis[1,10]** |
| - Complete blood count (thrombosis could present as thrombopenia)<br>- Electrolytes (sodium, potassium, calcium, bicarbonate)<br>- Renal function (BUN, creatinine) |
| **Urine analysis[8]** |
| - Proteinuria, micro-albuminuria<br>- Creatinine<br>- RBC |
| **Initial imaging** |
| - Renal ultrasound with Doppler<br>- Chest X-ray (cardiomegaly, congestive heart failure)<br>- Cranial ultrasound (intraventricular hemorrhage)<br>- Echocardiography (in case of e.g. cardiomegaly or circulatory failure)[44,45] |
| **Depending on results and/or suspected diagnosis, additional investigations may be indicated and advised by subspecialist (e.g. pediatric nephrologist, cardiologist):**<br>* (Blood) cortisol, plasma renin activity, aldosterone, TSH, fT4<br>* (Urine) catecholamines<br>* Full abdominal ultrasound<br>* Echocardiography[44,45] |

BP= Blood Pressure, BUN = Blood Urea Nitrogen, RBC= red blood cell count, TSH= Thyroid Stimulating Hormone, fT4 = Free thyroxine

antihypertensive drugs have been studied in neonates. The final choice of drug is often based on expertise and knowledge of the treating physician according to the underlying etiology[8]. The major drug classes used are diuretics, calcium channel blockers, beta-adrenergic blockers, direct vasodilators and angiotensin converting enzyme inhibitors. Since a detailed discussion on treatment options (i.e. individual compounds and dosing) is beyond the scope of this review, we refer the interested reader to respective references on this topic[7,8,21,47–55].

## Prognosis

Overall, of infants in the NICU diagnosed with hypertension, 41% are discharged with oral antihypertensive treatment[17]. As mentioned above, hypertension associated with BPD almost always resolves[36]. General prognosis of neonatal hypertension is good but depends on underlying etiology and the presence of end-organ damage. Hypertension secondary to UAC usually resolves over time[56,57]. Certain conditions may warrant chronic treatment such as underlying renal diseases. Currently, no studies are available comparing long-term effects of short versus long-term treatment on renal and cardiovascular outcomes.

Mackenzie[58] and Keller[59] suggested that reduced nephron mass plays an important role in the development of hypertension in adulthood. Observational studies in low birth weight neonates show lower nephron number at birth and an increased risk for development of hypertension later in life[58,59]. Raaijmakers. investigated that among young adolescents, extremely low birth weight (ELBW) infants, had higher BP, a 5- to 9-fold higher risk of prehypertension or hypertension, and smaller kidney size with lower glomerular filtration rate derived from serum cystatin C, compared to those born at term. These observations are in line with other reports, but the add-on value of their study was that, in ELBW children, the high BP was associated with lower plasma renin activity, which was not explained by any difference in the 24-hour sodium excretion. They suggested that the pathogenesis of hypertension after preterm birth is therefore unlikely to be mediated through a RAS-dependent mechanism[60].

## Conclusion

Although neonatal hypertension is a rather uncommon condition, it may have a major impact on the child's health. The etiology of neonatal hypertension is highly variable, with UAC, renovascular, renal parenchymal and pulmonary diseases as most frequent causes. Nevertheless, in preterm infants, etiology of hypertension remains unknown in almost 50% of cases. The first step in evaluation of neonatal hypertension is to confirm the hypertension ensuring the appropriate measurement technique. After initial workup, early referral to a pediatric nephrologist or cardiologist is indicated. Although prognosis is usually good, both treatment and long-term outcome of neonatal hypertension needs future research.

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# Epidemiology of invasive meningococcal disease in Belgium and implications for use of meningococcal vaccines in children and adolescents

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## Keywords

Belgium, vaccine, meningococcal disease, Neisseria meningitidis, epidemiology

## Abstract

Invasive meningococcal disease (IMD) cases are mostly caused by six serogroups of *Neisseria meningitidis* (MenA, B, C, W, X, Y). Despite its low incidence, IMD poses an important burden, especially in infants and children who can suffer from lifelong severe sequelae or even succumb to the disease. In Europe, including Belgium, MenB causes most of IMD cases in infants and children. However, increases of MenW and MenY cases have been recently observed. These epidemiological changes led to the revision of immunisation programmes in some European countries.

In Belgium, recommendations have been updated in 2019, recommending replacement of the previous MenC vaccination by a quadrivalent MenACWY conjugate vaccine at 15 months of age, with an additional dose at 15-16 years. Additionally, two MenB vaccines are now available for individual childhood and adolescent immunisation. This review summarises the epidemiology of *N. meningitidis* in Belgium, discussing the latest available surveillance data and the recent changes in vaccines recommendations.

Vaccination of children can help protecting against a disease that leaves little time to react. Moreover, targeting the adolescent population may further reduce transmission and then decrease incidence of IMD due to some serogroups, by reducing the high bacterial carriage observed in this age group. Immunisation programmes using MenB and MenACWY vaccines have the potential to broadly prevent IMD. In Belgium, these vaccines are optional and administered at own cost. Medical doctors need to inform parents about the different serogroups and the protection conferred by each vaccine to help them in their decision-making process.

## Introduction

Invasive meningococcal disease (IMD) is caused by *Neisseria meningitidis (N. meningitidis)*, a gram-negative bacterium that is mostly carried asymptomatically in the upper respiratory tract of ~10-20% of people [1, 2]. Transmission of the bacterium occurs through close contact with a carrier or infected person via respiratory secretions or saliva. At least 12 serogroups of *N. meningitidis* have been identified based on capsular polysaccharides; 6 of which (A, B, C, W, X, and Y) are responsible for most of IMD worldwide [3, 4].

IMD is a rare, but potentially devastating and life-threatening disease [4]. Meningitis and/or septicaemia are the most common presentations. Less common manifestations include pneumonia, arthritis, otitis media and epiglottitis [5, 6]. IMD can easily be misdiagnosed as early symptoms are similar to other common viral illnesses such as influenza [7]. Later onset of symptoms such as neck stiffness and purpuric rash may accompany the progression of the disease [7, 8]. In young children, clinical manifestations can be more insidious, with non-specific signs such as irritability and lethargy [9].

IMD has a rapid disease course and causes significant morbidity and mortality, even despite appropriate medical treatment [4]. Approximately 8-15% of cases are fatal, often within 24-48 hours after the onset of symptoms, and 20% of survivors may have lifelong physical, neurological, or psychological sequelae, or a combination of sequelae [4]. Major sequelae including limb amputations, seizures, major hearing loss, and cognitive impairment are seen in 10% of children [10, 11].

Most cases of IMD occur in previously healthy subjects without underlying medical conditions [12-15]. The disease can affect individuals of all ages, but the highest rates of IMD are found in infants below 12 months and children up to 5 years of age. There is a second smaller peak of incidence in adolescents/young adults (aged 15-24) where nasopharyngeal carriage rates peak (~23%) [1, 16].

In Europe, 2018 incidence rates of IMD ranged from 0.0 to 1.8 per 100 000 population and seem to be highly unpredictable in nature, across countries, and over time [16]. *N. meningitidis* serogroup B (MenB) caused 48% of all IMD cases and 68% of IMD in children under the age of 5 years [16]. MenB is known to predominate in Europe since many years, although recently there have been increasing trends in serogroup W (MenW) and Y (MenY) [17]. As a result, several countries (e.g. the Netherlands in 2017, the United Kingdom in 2015) have now implemented vaccination against serogroups A, C, W, and Y (MenACWY) in adolescents and/or infants in their immunisation plan [18, 19].

Similarly, the Belgian Superior Health Council (SHC) has recently reviewed its previous positions about the vaccination of children and adolescents against IMD [20]. The SHC now recommends vaccination with a quadrivalent MenACWY conjugate vaccine in replacement of the previous vaccination against serogroup C (MenC) at the age of 15 months, and to administer an additional MenACWY vaccine dose in adolescents aged 15-16 years (with catch up vaccination in 15-19-year-olds). With regards to MenB, the SHC confirms that the recombinant 4-component protein vaccine against MenB (4CMenB, *Bexsero*, GSK), that has been available since 2017 [21], has proven efficacy in children under the age of 2 years and has no major side effects [20, 22]. The SHC recommends considering MenB vaccination with 4CMenB on an individual basis for children aged 2 months to 5 years, adolescents aged 15-19 years and at-risk groups. A second MenB vaccine (MenB-FHbp, *Trumenba*, Pfizer), available since September 2019, may also be considered on an individual basis for adolescents aged 15-19 years and at-risk groups. To date, the SHC has not recommended the inclusion of MenB vaccination in the national immunisation calendar, but the SHC plans to perform a regular re-assessment of this advice based, notably, on the evolving epidemiological situation in Belgium [20].

Epidemiological surveillance is devised to trace the incidence of diseases over time and to detect sporadic and regional outbreaks. Such regimented approaches help establish and evaluate management strategies and timely vaccination programmes for disease control. In Belgium, the surveillance of IMD is based on the mandatory notification to the regional health authorities or the Belgian Meningococcal Reference Centre that characterizes isolates from peripheral laboratories since 1971 [23]. Despite the publication of annual surveillance reports of IMD in Belgium, no recent analysis of the collated information is available. The purpose of this narrative review is to provide an up to date overview of the epidemiology of IMD in Belgium in light of the recent changes in SHC recommendations and the available vaccines.

## Materials and Methods

We compiled data from the Belgian Scientific Institute of Public Health (Sciensano) [24-27] and published literature about IMD surveillance and immunization in Belgium.

## Results

### Epidemiology in Belgium

*Incidence, prevalence and serogroup distribution*

A first epidemic of IMD, since beginning of measurement in 1950, occurred in 1969, lasted until 1976 and was driven by MenB disease. Peak incidence rates with up to 5 cases per 100 000 population and 519 cases were reported in 1972 [29]. Most cases were caused by MenB serotype 2 (B:2b:P1.2) [28, 29]. Afterwards, the incidence dropped to interepidemic rates around 1/100 000 population per year. [28]

A second rise in IMD occurred in the '90s; until 1996 driven by MenB serotype 4 (B:4:P1.4) [30] and later by MenC (mainly C:2a and C:2b, belonging to the hypervirulent ST-11/ET-37 and the ST-8 complexes, respectively) [31]. In 2001, MenC cases peaked and became the predominant cause of IMD in Belgium, of which overall incidence was 3.55 per 100 000 population (Figure 1) [31]. As a result, regional immunisation campaigns with MenC vaccines were put in place from 2001 to control the outbreak (targeting children 1-5 years and 1-18 years in Wallonia and Flanders, respectively) [31, 32]. Since 2002, MenC vaccination has been included in the national immunisation programme for children aged 12-15 months, which has led to a significant decrease in MenC IMD in all age groups, from 188 cases in 2001 to less than 10 cases per year in most recent years[24-26].

At the same time, a natural downward trend in the number of MenB cases was observed, even though it remained by far the predominant serogroup [24-26, 31]. The reason for this decline remains unknown and should not be linked to cross-protection of the vaccine [33].

From 1997 till 2012, MenB P3.4 was the most frequent serotype [31]. Since 2008, the overall IMD incidence has reached a steady state of around 1 case per 100 000 population annually, with MenB still representing 50-83% of cases (or 53-104 cases annually) [24-26]. In 2019, 53 cases of MenB were reported, representing 50% of cases [26]. More recently, slight increases in MenY and MenW cases have been observed since 2011 and 2015 respectively [24]. In 2019, 17 cases of MenY and 28 cases of MenW were reported, together accounting for 42.1% of all cases in Belgium [26]. The hypervirulent serotype W clonal complex 11 (cc11) (UK 2013 clone) that has been emerging in Europe since several years (especially in neighbouring countries such as the Netherlands [34] and the United Kingdom [35]), was also first isolated in Belgium in 2017 [24]. In 2019, 14 out of 28 MenW cases were linked to cc11 and mainly observed in Flanders (personal communication, Wesley Mattheus, Sciensano database, 2020) [27]. In the southern part of the country, another MenW clone (ST-9316) is circulating [27]. This contributes to a further increase in the number of MenW cases, in contrast to MenY, that seems to be decreasing or at least stabilizing [24-26]. Sporadic cases of MenX also occurred recently [24].

*Age-specific trends*

IMD is known to predominate in infants under the age of 1 year (15.3 cases per 100 000 in 2019), young children aged 1-4 years (3.0 cases per 100 000), and adolescents aged 15-24 years (1.2 cases per 100 000) but age-specific distribution seems to be serogroup dependent [26, 36]. Most recent 2019 data show that MenB disease occurs in all age groups but mainly affects very young children below 5 years of age (37.7% of MenB cases in 2019, 3.3 cases per 100 000), and more specifically children under the age of 1 year (17.0% of MenB cases, 7.6 cases per 100 000) [26, 36]. The peak MenB incidence among infants under the age of 1 year was at 4-6 months of age in 2018 [24]. A secondary and smaller peak in incidence occurs in adolescents aged 15-24 years (20.8% of MenB cases) (Figure 2). MenW has become relatively more common in young children below 5 years of age and in adults above 65 years with 35.7% of MenW cases in each group. Sporadic cases of MenC occur as of adolescence (15 years of age and older). In the age group of infants below 1 year of age, MenB accounted for 9 out of 18 cases (50%), followed by MenW (7 cases) and MenY (2 cases) [26].

**Figure 1:** Absolute number of IMD cases per serogroup in Belgium and overall IMD incidence per 100 000 population (1991-2019 data)
Data obtained from the annual reports of the Belgian Scientific Institute of Public Health (Sciensano) 24-26. IMD, invasive meningococcal disease

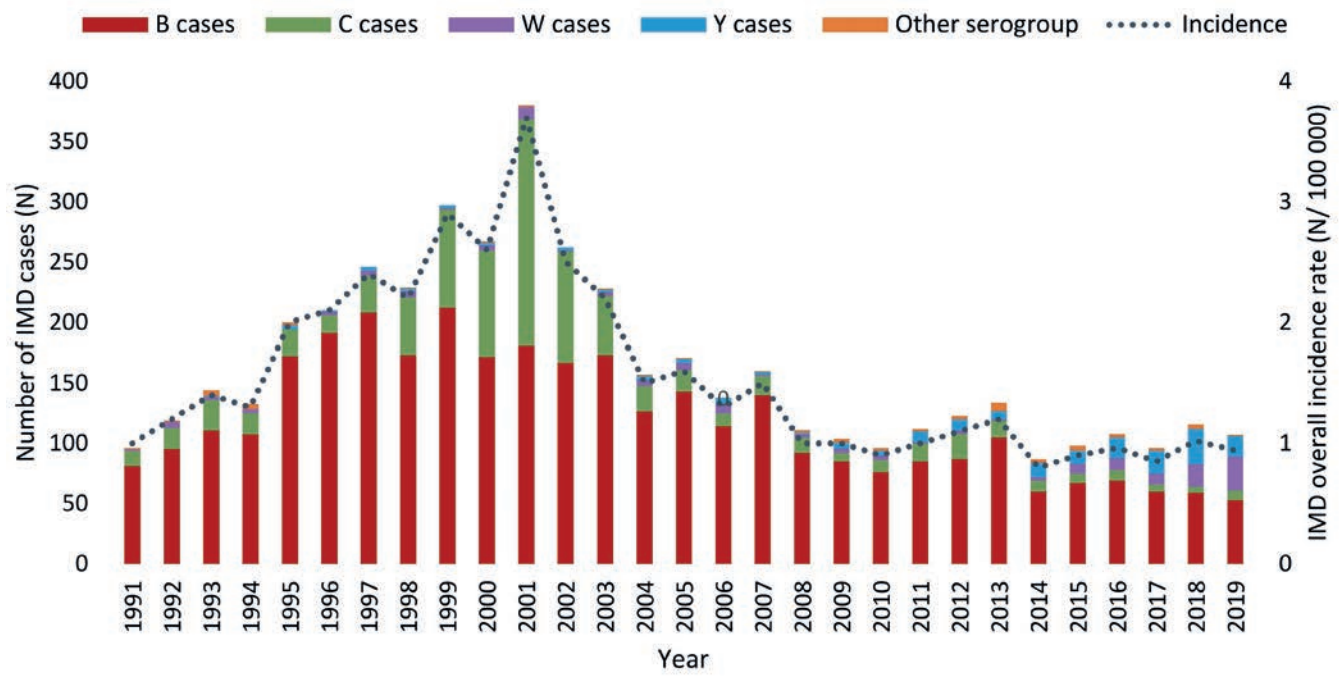
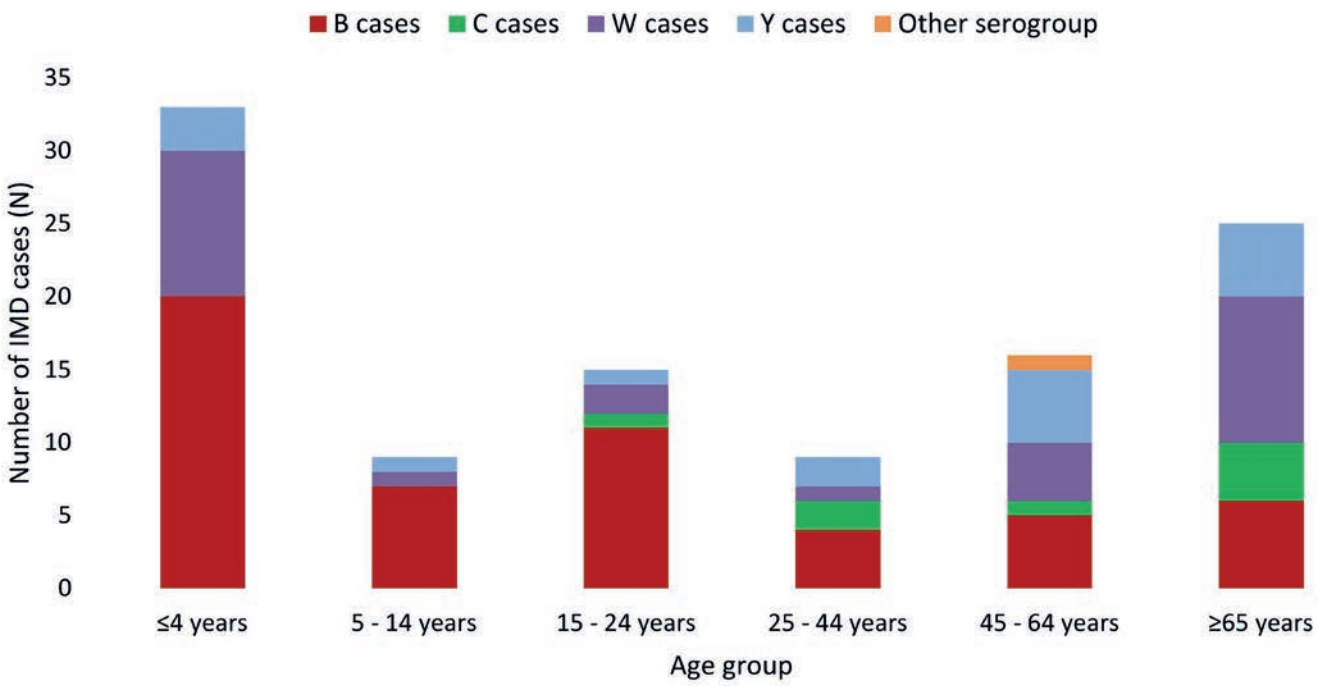


**Figure 2:** Number of cases of IMD by age group and per serogroup in Belgium in 2019
Data obtained from the 4th 2019 quarter annual reports of the Belgian Scientific Institute of Public Health (Sciensano) 26. IMD, invasive meningococcal disease




*Case fatality*

Over the period 2012-2019, the case fatality rate (CFR) attributable to IMD varied from 5.1% in 2015 to 13.1% in 2019 [24-26]. Major differences were identified according to serogroup. In 2019, the highest CFR was found for MenC (37.5%, 3 out of 8 cases), followed by MenY (17.7%, 3 out of 17 cases), MenW (14.3%, 4 out of 28 cases) and MenB (7.6%, 4 out of 53 cases) [26]. However, given the low number of cases (e.g. for MenC), values may not be representative and should be interpreted with caution.

*Regional variations*

During the '70s epidemic, MenB (B:2b:P1.2 strain) was predominant in Namur, Brabant (Brussels) and Mons area [29, 37]. In the early '80s, a new MenB strain (B:4:P1.4) was later first isolated in the Netherlands, where it was most prevalent in the Southwestern part (Rotterdam, Breda) causing significant disease [29, 30, 38]. The same strain, together with B:non-typeable:P1.4, entered Belgium in the early '90s through the province of Antwerp, spreading to other provinces [29, 30]. In 1994, Wallonia was reached and the phenotypes became prevalent in all Belgian provinces by 1995 [30, 38].

Towards 2000, the overall IMD incidence in Flanders rose. Particularly, in the province of Antwerp, IMD increased from 3.9 to 9.1 per 100 000 population because of a MenC disease outbreak in 2001 [39]. Phenotype C:2a:P1.2,5 was most prominent with 40% of isolates in 2001, and was previously also documented in England, Wales and the Netherlands [40-42]. Incidence rates in other provinces remained relatively unchanged [39]. Following the outbreak, a large routine and catch-up MenC vaccination programme was initiated. This led to an overall 88% reduction in MenC disease from 2001 to 2004, with a sharper decrease in the province of Antwerp (92%) [31, 39].

In late 2006, geographical cluster of MenB, non-serotypeable (B:NT:P1.14, cc-269) was identified in Flanders [43].

More recently in 2019, MenY and MenW have become more prominent in Flanders with 8 and 18 cases respectively, together accounting for 53% of all Flemish cases (personal communication, Wesley Mattheus, Sciensano database, 2020). MenW cases in Flanders were mainly linked to the hypervirulent cc11 (UK 2013 clone) [27]. Very little changes were observed in serogroup distribution in Wallonia and Brussels where MenB remained by far the most prevalent serogroup up till 2018 [24, 25]. However, an increase of MenW was observed in 2019, mainly due to the ST-9316 clone [27] also observed in Northern France [44].

## Available vaccines against IMD

Monovalent and polyvalent polysaccharide and conjugated vaccines that provide protection against 4 of the 6 major disease-causing meningococcal serogroups (A, C, W, and Y) have been available for many years [45]. However, low immunogenicity of MenB polysaccharides and potential cross-reactivity due to the similarity with human tissue antigens has hampered the development of a polysaccharide conjugate vaccine against MenB [46]. Focus for development therefore shifted to the use of surface-exposed (subcapsular) proteins. Using a new "reverse vaccinology" technique, specific antigen targets were identified through whole-genome sequencing[47]. In March 2017, 4CMenB became available in Belgium for infant vaccination as of the age of 2 months [21], followed by MenB-FHbp in September 2019, approved for use in individuals 10 years of age and older [20]. Specific proteins expressed at the surface of the bacteria were identified. Out of these proteins, three (factor H binding protein [fHbp], Neisserial adhesin A [NadA], and Neisserial heparin binding antigen [NHBA]) were selected for inclusion in 4CMenB, together with a 4th component, an outer membrane vesicle derived from an epidemic New Zealand strain. Together, these antigens can offer broad protection against the diverse disease-causing MenB strains [48, 49]. The three surface proteins, fHbp, NadA, and NHBA, are non-exclusive for MenB and preliminary data suggest that 4CMenB might also provide some level of cross-protection against other non-B serogroups [50-52]. MenB-FHbp on the other hand, includes two variants of the same surface-expressed fHbp protein, and elicited bactericidal responses above the correlate of protective level against non-MenB disease-causing serogroup isolates.[53] Although direct protection of subjects at risk is important, reducing meningococcal carriage and transmission can also be crucial for reducing IMD in a population setting. However, both MenB vaccines did not demonstrate an effect on carriage in adolescents nor indirect protection to unvaccinated adolescents through herd immunity [54-56]. Of note, no vaccine against MenX is available to date.

*Vaccines included in the Belgian vaccination calendar*

After a substantial increase in MenC disease incidence in the late '90s and early 2000, a conjugate vaccine against MenC was introduced in 2002 in the Belgian infant vaccine schedule at 15 months, together with a large-scale catch-up vaccination programme in 2001-2004. The widespread MenC vaccination campaign also generated important herd immunity amongst non-vaccinated individuals and significant decreases in overall MenC incidence [31]. The use of quadrivalent MenACWY vaccines was mainly restricted to travel medicine in case of travelling to endemic areas (e.g. for pilgrims of the Hajj) [57]. In response to

the rising number of MenY and hypervirulent MenW cases in Belgium and other European countries, and to the decline in protective antibodies against MenC in adolescents previously vaccinated, SHC recommendations are now in place to vaccinate against MenACWY at the age of 15 months and 15-16 years [20]. Thus far, these recommendations have not been implemented by the regional authorities and MenACWY vaccination remains at own cost for both age groups. The same applies to MenB vaccination, for which the recommendations are in place on an individual basis for children aged 2 months to 5 years, adolescents aged 15-19, and at-risk groups.

## Discussion

IMD is an acute and serious disease with relatively high mortality rates and long-term morbidity, often in otherwise healthy subjects. Recent Belgian epidemiology data show that IMD is endemic and that its overall incidence is currently low with around 1 case per 100 000 population per year. However, IMD incidence remains high in key age groups such as infants and children below 5 years of age. Outbreaks can also occur unpredictably as it happened in the past. Epidemiology of IMD is dynamic with changes that may be explained by secular trends, the emergence of hypervirulent strains or modifications of vaccination strategies, underlying the importance of epidemiological surveillance [17].

When comparing the most recent available data (2018) to other European countries, Belgium (1.0 per 100 000 population) was amongst the highest reported incidence rates for IMD (European average 0.6 per 100 000 population), following countries such as Ireland (1.8 per 100 000 population), the Netherlands (1.2 per 100 000 population), the United Kingdom (1.2 per 100 000 population), and Lithuania (1.1 per 100 000 population) [16]. All have updated their national recommendations for IMD vaccination [19, 58-61]. Ireland, the United Kingdom, and Lithuania have included MenB vaccination into their national calendar [58-60]. At the time of introduction (2015), the United Kingdom and Ireland reported MenB incidence rates of 16.1 and 16.9 per 100.000 population aged below 1 year [16] (9.7 per 100 000 in Belgium [25, 36]). Ireland, the United Kingdom, and the Netherlands have included MenACWY vaccination in adolescents [19, 58, 61]. The Netherlands also included MenACWY in young children at the age of 14 months [19]. Epidemiologic surveillance is important across countries to predict changes in epidemiology and to assess the impact of broader serogroup coverage. However, the decision to introduce a vaccine in a given country should not be based on epidemiology alone. Other factors such as vaccine immunogenicity, safety, cost-effectiveness, and ease of implementation should also be taken into account.

Despite its decline over the last two decades, MenB remains the leading cause of IMD in Belgium. Highest incidence rates are found in infants, who seem to be particularly at risk, making it an important health concern to paediatricians and parents. Therefore, MenB vaccination early in the first year of life could further reduce the overall burden of IMD, even before attending day-care. The most effective way to control MenB disease would be to interrupt transmission in all age groups by obtaining herd immunity, a strategy that has proven to be effective with MenC vaccination. However, data from a large randomized, controlled trial conducted among South Australian adolescents did not show any effect of 4CMenB on MenB carriage, suggesting that providing direct protection to those who are most at risk seems the best strategy to help prevent MenB disease [54]. MenB vaccines are now available through the private health sector for individual protection. Clinical studies with 4CMenB were conducted in infants, toddlers, adolescents, and adults [62], and the vaccine has been proven to be effective in national immunisation programmes. In 2015, the United Kingdom was the first country to implement 4CMenB into their routine, publicly-funded, national immunisation programme, as a reduced 2+1 dose schedule at 2, 4, and 12 months of age. The impact of the programme after 3 years shows a reduction of 75% of MenB disease in fully vaccine-eligible children irrespective of vaccination status or predicted MenB strain coverage, a good acceptance of the vaccine, and an acceptable safety profile [63]. Further real-world data is now rapidly accumulating, as other countries such as Italy [64], Ireland [58], Lithuania [60], Portugal [65], Andorra [66], and certain autonomous communities in Spain [67, 68], have also implemented universal mass vaccination programmes for infants against MenB. These data will also be crucial in determining the long-term protection of the MenB vaccines and their potential cross-protection against non-B serogroups. Both MenB vaccines, i.e. 4CMenB and MenB-FHbp, have been successfully used during university outbreaks [69]. Adolescents and young adults indeed represent the second peak in the distribution of IMD across age groups [16]. Cross-sectional surveys, conducted in conjunction with MenB vaccination campaigns in a US college where an outbreak occurred, evidenced that meningococcal bacteria carriage was 20 to 24% among student [55]. MenB was the most frequent (4% carriage), though the majority of the samples were non-groupable [55]. Meningococcal carriage in Dutch adolescents was also found to be 16% during a cross-sectional study conducted in 2013-2014 [70]. Even though Belgian data about bacterial carriage are limited [71], the Belgian SHC proposes to consider MenB vaccination for children from 2 months old to the age of 5 years, adolescents 15-19 years old and at-risk groups [20]. The reasons for not including MenB vaccination into the calendar include low MenB incidence, feasibility (the need to start early at the age of 2 months in co-administration with routine vaccines which would require 3 injections at the same time), the poor cost-effectiveness of the vaccine, and the lack of demonstrated herd immunity [20].

MenACWY vaccines have shown to have a significant impact on targeted serogroups [72]. In the United Kingdom, the introduction of MenC conjugate vaccine for infants in 1999 in the national programme has resulted in significant and sustained reduction of MenC disease through individual and herd protection [73]. The same drastic reduction in all age groups was also seen in Belgium when the vaccine was introduced in 2002 in the national calendar, although only children and adolescents were vaccinated [31]. Many countries, including the United Kingdom and Canada have meanwhile introduced booster vaccinations in adolescents, the main (asymptomatic) carriers of the bacteria, to maintain high antibody levels, preventing acquisition of carriage, and thus limiting spreading of MenC [74, 75]. In Belgium, few MenC cases still occur despite several years of routine vaccination. As a result, Belgium has now followed the same example by advising the administration of a MenC vaccine booster dose, recommended to be with the quadrivalent conjugate MenACWY vaccine, for adolescents [20]. The latter has the advantage of countering the increased incidence of MenY and MenW cases recently observed in Belgium and other European countries, by providing broad individual and herd protection against IMD, especially when combined with a temporary catch-up in 15-19-year-olds and vaccination in children aged 13-15 months. It should be noted that the effect of conjugate MenACWY vaccines on the carriage of MenW and the hypervirulent cc11 clone has not yet been demonstrated [76].

Though more common in older age groups, MenY and MenW cases also occur in young children. MenACWY vaccination at 15 months with one dose, as recommended by the SHC, can provide direct protection to young children as of 15 months of age, but preventing disease in the younger infants will require very high MenACWY coverage rates in adolescents to obtain herd immunity. Alternatively, multiple doses of MenACWY vaccine in a 1+1 or 2+1 schedule would be required for directly protecting those aged below 12 months of age [77]. As previously mentioned, 4CMenB contains four antigens that are shared with other *N. meningitidis* serogroups and has the potential to offer protection beyond MenB disease [50-52]. It has also shown to induce cross-protective bactericidal activity against MenW cc11 and MenX isolates from Africa [78]. Especially, the hypervirulent MenW ST-11, cc11 (UK2013) strain requires further attention as it is characterised by an atypical gastrointestinal presentation (with nausea, vomiting, and diarrhoea) and high mortality rates [79]. MenACWY vaccination in young children and adolescents, however, remains at own cost in Belgium.

Early diagnosis and chemoprophylaxis can help prevent severe sequelae and deaths due to IMD, and should be started as soon as the disease is suspected [80]. However, prevention through vaccination is the best defence against a disease that leaves little time to react. In a process of individual clinical decision-making, medical doctors need to discuss the availability of meningococcal vaccines with parents, based on unbiased and correct information, especially when prevention through vaccination remains optional and at own cost. Financial cost must be balanced against the risks for young children or adolescents, taking into account the possible life-long morbidity, as well as possible fatal outcome, that are not always included in economic cost-effectiveness models [81]. Parents need to be aware that there are different serogroups and that not all serogroups are covered by the actual national vaccination programme. In terms of timing, MenB vaccination needs to be discussed early in the first year of life in order to have sufficient protection before reaching the peak incidence around the age of 5 months. MenACWY vaccination follows later in life at the age of 13-15 months and in adolescence, according to recent SHC recommendations.

## Conclusion

IMD is a rare but severe disease. The epidemiology is dynamic and unpredictable. Shifts in epidemiology have led to reactive vaccination recommendations in several countries, including Belgium. This review highlights the changes in IMD epidemiology and meningococcal vaccination recommendations in Belgium. Vaccines are currently available for the five main disease-causing serogroups.

Healthcare professionals should be encouraged to inform parents on all available meningococcal vaccines, even on those not routinely recommended. Figure 3 summarizes the context, outcomes, and impact of this literature review for healthcare professionals.

## Trademark

Bexsero is a trademark owned by or licensed to the GSK group of companies.

Trumenba is a trademark owned by or licensed to Pfizer.

## Conflicts of interest

MR reports having received personal fees from the GSK group of companies for participation to scientific meetings and webinars, outside the submitted work. WM is employed by Sciensano, the Belgian Institute for health, which received grant from the Belgian Federal Government during the conduct of this work. FS and SK are employed by the GSK group of companies. FS holds shares in the GSK group of companies. The authors declare no other financial and non-financial relationships and activities.


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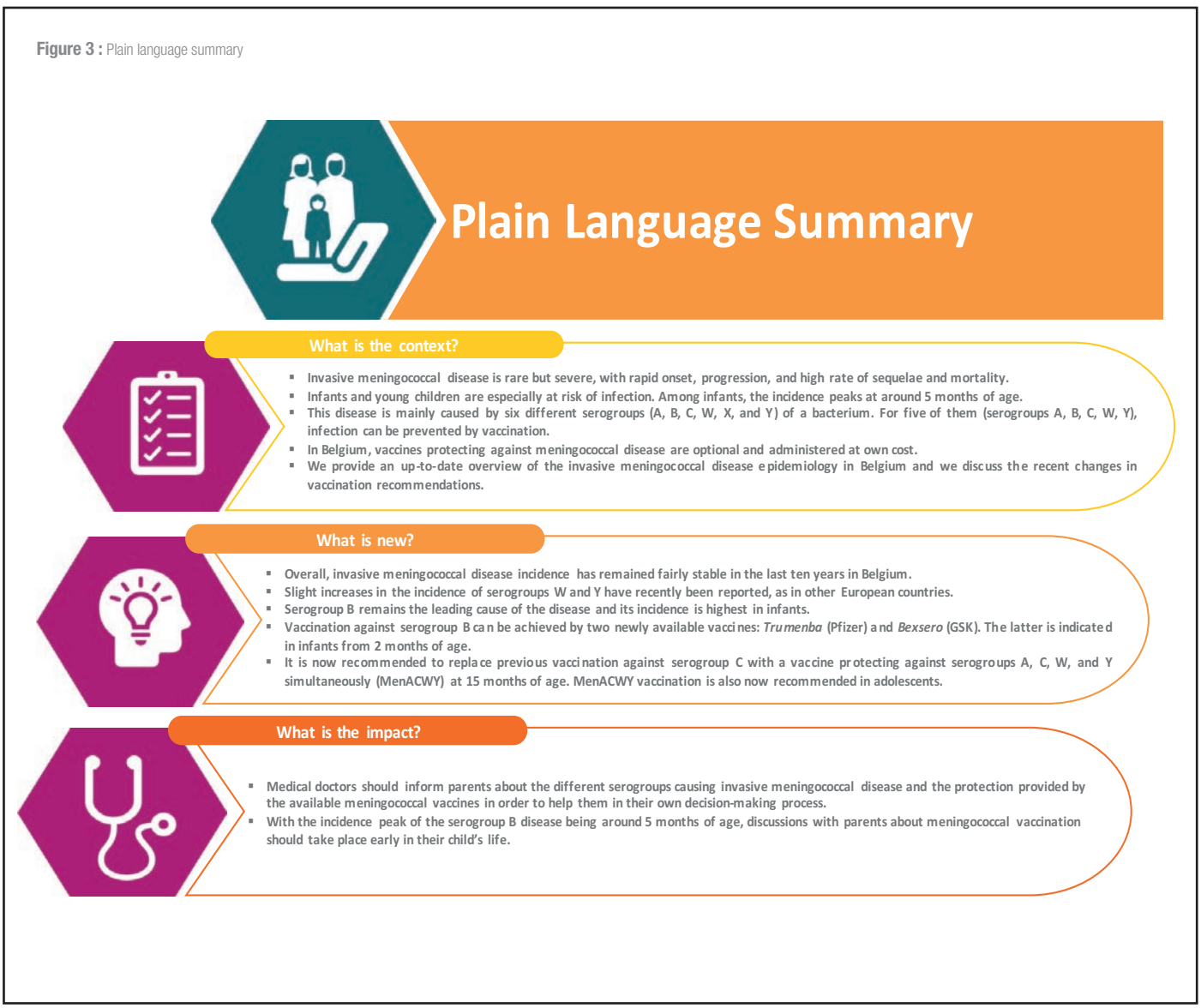
**Figure 3 :** Plain language summary



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# The analgesic effect of Virtual Reality in paediatric procedural pain: a systematic review.

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## Keywords

virtual reality, procedural pain, distraction, analgesia

## Abstract

Procedural pain is an important source of fear and distress for children. Distraction is a widely used non-pharmacological approach to manage paediatric pain. A new distraction method is Virtual Reality (VR) technology; it combines multiple senses to provide a feeling of immersion into a virtual world. Most reviews so far assessed the effect of VR distraction in adults. This systematic review of randomised controlled trials aims to evaluate the analgesic effect of VR distraction in procedural pain in children. A systematic search was conducted using MEDLINE (through PubMed), Embase, CENTRAL and Web of Science from the earliest date until January 2020. By determining a set of inclusion and exclusion criteria, 30 trials were retrieved. Selected studies were grouped by type of procedure. Children distracted by VR during painful procedures had overall less pain when compared to standard of care. The analgesic effect is better using active VR distraction than passive VR distraction. Mainly for minor procedures (e.g. wound care, phlebotomy), VR technology seems to be an appropriate technique to redirect children's attention away from the painful stimulus. However, most included evidence has low quality and is sensitive to bias resulting in uncertainty about the reliability and validity of the results. This paper provides support for further implementation of VR technology in daily medical practice on the children's ward, but more work is needed to determine which children might benefit from VR and how VR can play a role within a comprehensive policy for procedural comfort in sick children.

## Introduction

Pain is a personal, unpleasant experience involving both physical and emotional aspects of the body. A lot of the diagnostic and therapeutic tools we have at our disposal nowadays invoke a certain degree of pain. Especially for children, these procedures are a source of fear and distress. Chronically ill children have to undergo a large number of painful experiences as part of the diagnosis, monitoring and treatment of their condition. For young children with cancer, repetitive procedural pain often causes more distress than the disease itself[1]. Adverse emotional experiences arising from this pain do not decrease with time, they may even get worse if pain is not adequately managed[2] and they cause acute stress symptoms or profound psychological consequences at adult age[3,4].

Managing procedural pain is one of the important aims of modern clinical care. Multiple approaches can be used either in monotherapy or in combination therapy. First of all, there is the pharmacological pain approach. This ranges from local anaesthetics (e.g. EMLA cream (Eutectic Mixture Lidocaïne and Prilocaïne)) to systemic medications to procedural sedation. Another option is the non-pharmacologic approach; this subject has been extensively studied during the last decade. Non-pharmacologic interventions can be divided into non-psychological interventions (e.g. acupuncture, cold application) and psychological interventions. Psychological interventions can be cognitive (converting negative or unrealistic thoughts (cognitions) into more positive ones) or behavioral (replacing negative or maladaptive behaviour with positive behaviour)[5]. Techniques include hypnosis, deep breathing, positive reinforcement, relaxation training, distraction… Distraction can be adapted by any person in the room and can be done using visual, auditory or kinaesthetic distractors, or a combination of these. Commonly used techniques are talking to the child, watching television[6] or a movie on the smartphone or tablet[7]often causing substantial pain and distress. Distraction has been shown to reduce child-reported pain, but there is currently little published about the effects of using iPad technology as a distraction tool. Our primary objective was to compare the reduction of pain and distress using iPad distraction (games, movies, books of the child's choice, listening to music[8], playing with a doll… Cognitive behavioral therapy uses a combination or variation of strategies targeting cognitions (thoughts) or behaviors, or both. CBT for pain management aims to help children cope with their pain and distress caused by painful procedures. A wide variety of techniques to perform CBT is available. Which approach is desirable and most suitable, depends on multiple factors; the age and mental state of the child, the type of procedure to be performed and underlying conditions.

A more recent technique to distract children from painful procedures is Virtual Reality (VR). There are 2 types of VR application; non-immersive and immersive VR. In non-immersive VR, the user watches the virtual world on a computer screen and communicates through a keyboard and a mouse. By using immersive VR technology, the user is wearing a head-mounted 3D display (HMD) through which he or she can interact dynamically with a computer-generated environment. There is a motion sensing system enabling users to see their movements reflected into the virtual world. By using a HMD, there are limited visual and auditory cues from the world outside the computer generated environment so there is a real sense of immersion into this virtual world. "Immersion" in this context is often described as the subjective sensation that the user is connected with the world outside his or her physical body and is able to interact with it. This is lacking in the non-immersive type of VR, since the user still receives stimuli from the outside (real) world. It is exactly this sense of immersive attention that sets immersive VR apart from other distraction methods such as watching a movie[9]. The stimuli used for VR vary from passively watching virtual environments, to actively engaging in a video game.

Some studies already assessed the effect of VR technology in chronic and acute pain, in adults and children[10,11]. In this study, the aim is to systematically assess the analgesic effect of immersive VR technology in procedural pain in children.

## Materials and methods

### Information sources and search strategy

A systematic review of the literature on the analgesic effect of Virtual Reality in acute procedural pain in children was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[12]. This search was conducted using four electronic databases: MEDLINE (through PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. ISRCTN registry and ClinicalTrials.gov were searched for the identification of ongoing trials. Additional articles were obtained by manually

checking the reference lists of the included studies and related articles search. Duplicates were identified and eliminated using the Mendeley software. Search terms included the following Medical Subject Headings (MeSH) terms and free text terms*: 'virtual reality', 'paediatric', 'children', 'pain', 'distraction', 'analgesia'*. No language or time restrictions were placed on these searches.

### Selection criteria

A set of inclusion and exclusion criteria was established.

#### *Inclusion criteria*

Inclusion criteria are based on the 'PICO'-framework (Population, Intervention, Comparison, Outcome). Only studies with the following requirements were included:

- Type of participants: children and adolescents (3-21 years old) undergoing an acute painful procedure.
- Type of intervention: distraction by VR technology (immersive type).
- Comparison: Standard of Care (SOC); standard analgesic care, passive distraction or no distraction.
- Outcome: all measures of self-reported pain and observer-rated pain, physiological measures.

- Study design: Randomised Controlled clinical Trials (RCTs) and pilot and feasibility studies with a minimum sample size of 20 participants.

#### *Exclusion criteria*

Studies that met one or more of the following criteria were excluded for selection.

Only published articles were considered; unpublished data, ongoing trials, preliminary results and abstracts were not implemented in this paper.

### Study selection

We used three steps to select the appropriate articles. First, the literature was searched using a high sensitivity-low specificity assessment. All identified studies were imported into the Mendeley software. Duplicates were detected and removed. In a second step, title and abstract were screened according to the predefined set of inclusion and exclusion criteria. The third and final step was to analyse the full text of the eligible works. Records were excluded if no full text was available.

### Data extraction

A predefined set of data was extracted from each of the 30 included trials. The following elements were retrieved: authors, year of publication, study design (within- or between-subject design), patient characteristics (sample size, age range), underlying medical condition, inclusion criteria, exclusion criteria, type of acute procedure, form of VR application, virtual environment, comparison, outcome measures, results. When data were missing the study authors were contacted to provide the necessary information.

## Results

### Study selection

The search was conducted on the 14th of January 2020. Using the literature search strategy as described above 444 publications were identified. After duplicate removal by Mendeley, 295 titles were retrieved. By screening title and abstract, 246 studies were excluded for several reasons. Manual reference tracking and related article search added another 2 studies. Eventually 49 studies were selected for full-text review. Subsequently another 19 were excluded for a variety of reasons; a sample size of less than 20 participants (n=11), non-immersive type of virtual reality (n=4), a control other than SOC (n=3), only preliminary results (n=1). Finally, 30 articles were included. The PRISMA flow diagram -shown in figure 1- gives a summary of the process of study selection.

In this review the 29 included trials were divided into six groups according to the type of procedural pain. This makes a comparison more useful, since different procedures may have different clinical implications and pain levels.

### Key findings

In the following section, the main findings of the 30 trials included will be listed.

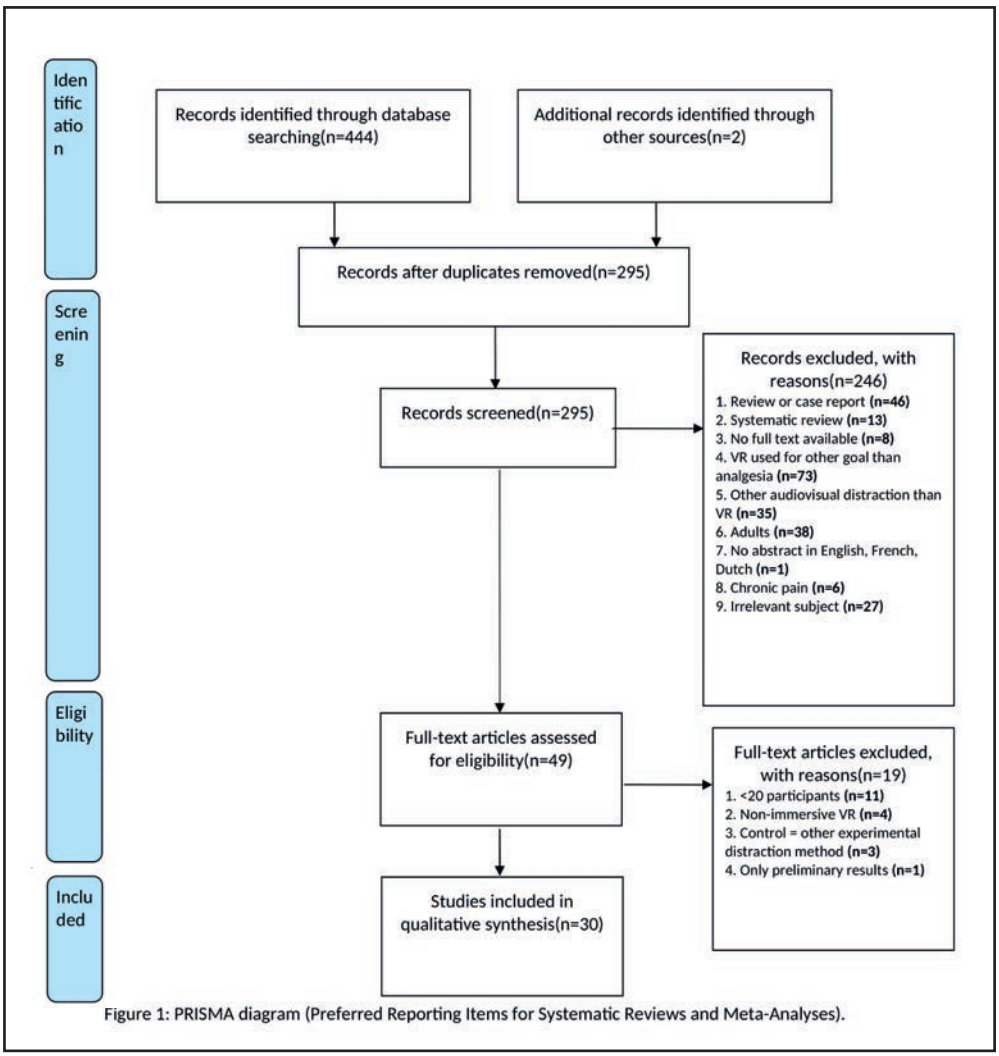

Figure 1: PRISMA diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

#### *Cold Pressor Trials*

A cold pressor trial is a test in which the hand of the participant is immersed into ice cold water. The participant is told to keep it there as long as possible and give a sign to the experimenter when it starts to hurt. This is considered as the 'pain threshold'. When the pain gets unbearable, the participant can remove the hand from the water. This is called the 'maximum pain tolerance' time point. These two measures are useful in the research of pain and analgesia. All five cold pressor trials included in this paper conducted one baseline trial during which pain tolerance and pain threshold were measured (table 1). To assess the effect of repeated exposure and habituation, a control subgroup underwent a second baseline trial. After this, the two interventional trials were conducted in counterbalanced order. Two of the trials compared an active VR game with passive VR distraction (this is watching the same game through the same VR Head Mounted Display (HMD), but without game-based interaction). Three other trials compared an interactive VR game with the same game on television or computer screen, without VR technology. In all trials, VR technology significantly improves pain threshold and maximum pain tolerance compared to baseline. Interactive VR distraction is significantly better than passive VR distraction, as concluded by Law et al.[13] and Dahlquist et al.[14]. Especially maximum pain tolerance improved significantly compared to baseline and passive VR

distraction. On the other hand, no unambiguous advantage of VR distraction over computer game distraction is found in any of the trials. Dahlquist et al.[15] found that the effect on pain tolerance is higher in older children than in younger ones. Only in older children, VR is significantly better than a videogame. Pain threshold is significantly higher in videogame distraction than in VR distraction, in all age groups. Also Dahlquist et al.[16] and Sil et al.[17] showed significant advantages of VR compared to baseline, but no difference between VR distraction and playing a videogame.

### *Venipuncture*

Eleven recent studies and one older, small study (Gold et al.[18]) have compared VR distraction to standard of care in venipuncture on children (table 2). In addition, 3 studies made a comparison with other means of analgesia or distraction: application of external cold and vibration (Gerçeker et al.[19]), using a kaleidoscope (Koç Özkan et al.[20]) or watching television (Dumoulin et al.[21]). In 8 studies there was a positive effect of using virtual reality on pain and/or anxiety. 3 smaller studies (Gold et al.[18], Dumoulin et al.[21], Dunn et al.[22]) and 1 larger study (Caruso et al.[23]) did not find a difference between virtual reality and SOC. In Gold et al.[18], there was a significantly lower affective pain (unpleasantness of pain) increase between pre- and post-procedure in the VR group compared to the control group. However, no significant absolute differences in pain intensity or affective pain were observed between both groups. Compared with other means of distraction, VR was better than kaleidoscope, but not better than external cold and vibration or watching television (this study also did not demonstrate a difference with SOC). Toledo del Castillo et al.[24] compared VR with topical analgesic cream and VR without topical analgesic cream. The VR + topical cream group had significantly lower self-reported, parent-reported and health provider-reported pain scores. For anxiety, there was only a significant difference in health provider-reported measures. Secondary analyses in Gold et al.[25] showed that patients with a higher 'anxiety sensitivity' benefit more from VR intervention than others.

### *Wound care*

Five trials included in this paper assessed the analgesic effect of VR in the treatment of burn wounds or other chronic wounds (table 3). Treatment of burn wounds includes dressing changes (Kipping et al.[31], Jeffs et al.[32], Hoffman et al.[33]) and physical therapy to counter the decreased range of motion and contractions associated with severe burns (Schmitt et al.[34]). Treatment of chronic wounds on lower limbs (Hua et al.[35]) is grouped with burn wounds, given the same repetitive character of painful dressing procedures. The results of these studies show mostly the advantage of VR distraction. Hua et al. detected an overall significant reduction in pain in the VR group compared to control. Pain measures were both reported by the children and the caregivers, and were taken before, during and after dressing changes. The most prominent analgesic effect of VR was found during dressing changes. Also duration of dressing change was significantly reduced in the VR group, as well as heartrate during the procedure. In Jeffs et al., children undergoing burn wound care were distracted by the "SnowWorld" virtual environment. They did not experience significantly less pain than SOC control group, although there was a trend towards the advantage of VR technology. Compared to passive distraction however, VR technology gave significantly better results. Only in the VR group there was a decrease from pre-procedural pain to procedural pain. Hoffman et al. also used the "SnowWorld" virtual environment. In this pilot study, VR reduced worst pain rating, pain unpleasantness and time spent thinking about pain, although pain ratings remained high. Kipping et al. showed a lower trend for the mean pain scores in the VR-group but this difference did not reach significance. Also physiological measures and duration of dressing change did not significantly improve using VR technology. Only the FLACC (Face, Legs, Activity, Cry, Consolability) pain scale had a lower score during dressing removal, which is generally considered to be more painful than dressing application. Also the amount of rescue doses of nitrous oxide was significantly lower in the VR-group. Concerning physical therapy, Schmitt et al proved significantly lower cognitive, affective and sensory pain on the first study day. On the other 4 study days the results were less consistent. On these days, an attrition bias was introduced as there were 23 subjects who did not continue beyond the initial study day, as a result of changes in their clinical care regimen. VR did not result in a significant increase in joint range-of-motion compared to control group.

### *Port access*

Two trials in this review assessed the analgesic effect of VR technology during port access procedure (table 4). Gershon et al.[36] compared VR technology with a computer game and SOC for distraction from pain during this port access-procedure. Only heartrate and nurse-reported VAS (visual analogue scale) were significantly reduced in VR group compared to SOC. Also nonverbal indices of distress measured by the behavioural pain assessment scale CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) indicated that children in the VR group had significantly less torso and leg muscle tension than the SOC group. No significant difference was found in the overall CHEOPS score. In general, all self-reported scores on the VAS were relatively low, ranging from 0 to approximately 30. Younger children did experience more distress with this procedure than older ones. Wolitzky et al.[37] found a significant difference regarding CHEOPS and pulse rate during port access, in favour of VR technology compared with no distraction. Retrospective distress rating (self-report of pain and anxiety) was not significantly reduced in the VR group.

### *Dental treatment*

Four RCT's examined the analgesic effect of VR distraction during dental treatment (more specifically Inferior Alveolar Nerve (IAN) block) (table 5). Three of the studies (Aminabadi et al.[38], Niharika et al.[39] and Koticha et al.[40]) used the split mouth study design. In the split mouth study design, there are two study treatments that are randomly assigned to left or right dentition sites. In Aminabadi et al.[38] and Niharika et al.[39], a statistically significant difference was detected between the two treatment sessions; children distracted by VR technology experienced less pain and less anxiety, regardless of the order of treatments. Koticha et al.[40] did not demonstrate a difference in anxiety between VR and no VR, pain was not considered in this study. There was a significant difference in physiologic measures (lower pulse rate) in favour of VR. Al-Habadi et al.[41] divided 102 children in 3 groups; the passive VR group, the non-VR distraction group and a control group which did not receive any form of distraction. Children first received a topical anaesthetic gel, after which distraction was started and IAN block was administered. No advantage of VR technology over both other groups was found. Watching a movie on a tablet resulted in significantly less pain compared to control. The two studies that could not demonstrate an effect in favour of VR, both included children with higher scores on the Frankl behaviour rating scale (i.e. showed more positive behaviour towards the dentist). Niharika et al. included children with a lower score on the Frankl behaviour scale, Aminabadi et al. did not mention this score.

### *Lumbar puncture*

Only one trial examined the effect of VR distraction during lumbar puncture (table 6). A pilot study of Wint et al[42] selected 30 adolescents undergoing lumbar puncture. A comparison was made between passive VR distraction combined with SOC, or SOC only. SOC in this trial consisted of topical EMLA cream, parents at bedside and procedural sedation. No statistical difference was found on the VAS pain scores between the control and experimental groups.

## Discussion

Pain can be experienced in a spectrum; minor medical procedures (e.g. venipuncture) are considered to be less painful than more invasive procedures (e.g. surgery, the manipulation of a displaced fracture). Obviously, for the latter, appropriate pharmacologic analgesia is necessary and several guidelines and recommendations describe the best techniques to do so. However, the degree of expected pain should not be a consideration in the context of pain reduction. Regardless of the level of pain, the primary aim is to enhance periprocedural comfort and sense of control by the optimal reduction of pain and distress, in order to allow a successful and time-effective medical procedure without the use of physical or psychological restraint.

Distraction is a successful and commonly used method to prevent pain. Especially for mild pain in minor medical procedures well-applied distraction may reduce distress to an acceptable level. Virtual reality is a recent distraction method in which multiple senses are involved to provide full immersion into a virtual world.

Using functional MRI (fMRI) researchers have discovered that cortical areas associated with attentional processes and pain modulation are more active during distraction, while areas associated with pain perception show less activity[43]. In a fMRI study specifically for VR distraction, pain is reduced by modulating the brain's response to a painful stimulation[44]. All five pain regions in the brain showed significant reductions in brain activity using VR distraction, compared to no distraction. Both sensory and emotional aspects of pain processing are involved.

Current neurocognitive and cognitive-affective models of attention and pain propose that pain is evolutionarily predisposed to have an alarm function. It interrupts and captures our attention, to form a motivation for action and escape certain behaviours[45]. The theory of 'attentional modulation of pain' has been demonstrated in behavioural studies using the primary task paradigms.

**Table 1:** overview of cold pressor trials. HMD: head mounted device; RCT: randomized controlled trial; VR: virtual reality.

| Author | Study design | Participants | Inclusion criteria | Exclusion criteria | Intervention | Control | Outcomes | Results |
|---|---|---|---|---|---|---|---|---|
| Law et al., 2010[13] | RCT (within-subjects design) | N=79, 6-15 years old | Age 6-15 years old | - Contra-indication to exposure to cold temperatures<br>- Mental retardation<br>- Hearing/vision impairments<br>- Impaired language | - Interactive VR HMD distraction with Nintendo Wii game (Aqua garden® game), verbal commands<br>- Passive VR distraction (watching pre-recorded footage from same game through VR helmet) | Wearing VR helmet without distraction | Pain tolerance | Significantly higher pain tolerance in VR group. Passive distraction is better than baseline (p=0.001) and interactive distraction is better than passive distraction (p=0.001) and baseline (p=0.001). |
| Dahlquist et al., 2007[14] | RCT (within-subjects design) | N=40, 5-13 years old | Age 5-13 years old | Not mentioned. | - VR HMD helmet with joystick (active; playing Finding Nemo® game)<br>- VR HMD helmet (passive; watching Finding Nemo® game) | No distraction | - Pain threshold<br>- Pain tolerance | Pain threshold and mainly pain tolerance are higher with distraction, and the highest during interactive VR distraction (p<0.01). |
| Sil et al., 2014[17] | RCT (within-subjects design) | N=62, 6-13 years old | Age 6-13 years old | - Contra-indication to exposure to cold temperatures<br>- Open wounds on hands<br>- Mental retardation<br>- Hearing/vision impairments<br>- Motor disability | VR HMD interactive distraction: Secret rings® game through Nintendo Wii®<br>- Same videogame on television (non-VR) | No distraction | - Pain tolerance | Significantly higher pain tolerance during VR and non-VR distraction compared to baseline (p<0.001). No significant advantage of VR distraction over videogame distraction (p=0.73). |
| Dahlquist et al., 2009[15] | RCT (within-subjects design) | N=41, 6–14 years old | Age 6-14 years old | - Contra-indication to cold exposure<br>- Mental retardation<br>- Hearing/vision impairments<br>- Vestibular difficulties<br>- Motor disability | - VR HMD helmet with joystick (active: playing Free Dive® game)<br>- Free Dive® videogame on computer screen with joystick | No distraction | - Pain threshold<br>- Pain tolerance | - Higher pain tolerance and pain threshold with VR compared to no distraction (p<0.001), this effect is larger in older children (p<0.05)<br>- No benefit of VR over computer game in pain tolerance (p>0.30)<br>- Pain threshold is higher with computer game than with VR (p<0.01) |
| Dahlquist et al., 2010[16] | RCT (within-subjects design) | N=50, 6-10 years old | Age 6-10 years old | - Contra-indication to cold exposure<br>- Mental retardation<br>- Hearing/vision impairments<br>- Vestibular difficulties<br>- Motor disability | - VR HMD helmet with joystick (active: playing Ice Age 2® game)<br>- Ice Age 2® videogame on computer screen with joystick | No distraction | - Pain threshold<br>- Pain tolerance | - Higher pain tolerance (p<0.001) and pain threshold (p<0.002) with VR compared to no distraction<br>- No significant difference between VR HMD distraction and computer game in pain tolerance (p>0.91) and pain threshold (p>0.05). |

Here, participants are instructed to perform a cognitive task while being exposed to a task-irrelevant pain stimulus. Task performance clearly diminishes during pain, because attention is diverted to the painful sensation[46]. To prevent this "bottom-up" mechanism of pain being in the centre of our attention, a "top-down" system is needed to deliberately use central cognitive resources to redirect attention away from this pain. This is how proper distraction could provide analgesia during painful procedures. Researchers found that the more demanding this distraction task is, the better its analgesic effect[47]. Evidence cited here is based on research in adults.

In line with this theory, one can predict that active distraction, which involves more central executive functioning, is better than passive distraction. This hypothesis is supported by multiple trials which compared the analgesic effect of active distraction to passive distraction[48].

### Type of VR

The hypothesis that active distraction is better than passive, is supported in this review of paediatric procedural analgesia. In two of the cold pressor trials included in this paper, active VR was compared to passive VR[13,14], and in 3 other trials active VR was compared to an active videogame[15-17]aged 6-14 years, underwent one or two baseline cold pressor trials followed by two distraction trials in which they played the same videogame with and without the helmet in counterbalanced order. Pain threshold (elapsed time until the child reported pain. There is a significant difference in analgesia between passive VR distraction and active VR distraction, while no difference is found between playing an interactive video- or VR game. These five trials corroborate the theory that the most important element of distraction is the interactivity of the distraction and not the form in which it is presented. Also secondary analyses of other trials included in this paper show that engagement in the distraction and procedural pain were inversely related.

The way VR is presented to the participant is mostly through goggles on a head-mounted device, with or without headphones. In this manner real-world visual and/or auditory stimuli are blocked and full immersion in the virtual world is obtained. Instead of using a head-mounted device, Jeffs et al.[31] made use of VR goggles mounted on a tripod device and Hoffman et al.[33] made use of VR goggles on an arm holder to allow patients with head burns to participate in the study. This type of device is less immersive, because the participant has the ability to move his view away from the virtual environment. Also here, the VR group had significantly better results than passive non-VR distraction.

An important observation is that technical aspects which increase the level of immersion (e.g. better quality of display, sound through headphones) lead to a significant difference in level of analgesia[49–51].

In the studies discussed here, a wide variety of VR devices and apps were used. Some are specifically designed for analgesia (e.g. SnowWorld), others use existing games or movies. No comparison between these was made.

### Types of procedural pain

It is important to determine the range of pain intensity in which VR distraction can be useful to provide analgesia. For example, the results of both trials about port access are not consistent. A possible explanation for this result is low pain stimulus of the port access procedure. For many patients the VAS-score ratings were only between 20 to 30 out of 100[36], suggesting that they did not experience a lot of pain during the procedure. A topical anaesthetic was used during the procedure, that may additionally have limited the distress experienced by participants, so VR distraction may provide limited no to additional value.

In contrast, venipuncture is a very common and low invasive procedure that can nonetheless be a source of significant distress for children. For this intervention, VR is a successful form of distraction. Most of the trials included in this paper found that procedural pain is significantly reduced while being distracted by VR technology. However, the study of Walther-Larsen[30] didn't find a difference when compared to adequate standard care.

For some of the most invasive procedures - like treatment and rehabilitation of burn wounds - significant advantages of VR over SOC or non-VR distraction have been shown[32-35]. Both for painful dressing changes or physical therapy, VR can be an adjunctive tool to provide analgesia. Standard of care for procedural

pain caused by burn wounds typically involves systemic acetaminophen, opioids and/or benzodiazepines, yet burn patients still report severe pain during burn wound care[52]. Overall, data included in this review suggest that VR is likely an effective way to reduce pain in children for dressing changes and physical therapy, but like we discuss below, adequate standard of care should be applied first..

Cold pressor trials included in this paper show that VR successfully reduces pain in children in an artificial setting. However, generalizability of these trials is limited. Procedural pain differs from pain induced in these trials regarding perceived controllability. In cold pressor trials, children can stop an experimental procedure at any time. There are also differences in terms of the level of anxiety that is associated with the pain stimulus and the clinical environment.

### Age effect and comparison to effects in adults

Two of the trials included in this paper[13,15] study if age was an important predictor in the analgesic effect of VR distraction in children. In both trials, older children demonstrated a greater response to interactive VR distraction than did younger children. A possible explanation might be that older children further developed their attention regulation abilities, so they can more selectively focus their attention to the goals of the videogame. It is also possible that older children obtained greater benefit of VR distraction because of their more mature expressive language skills. Dahlquist et al. stated that the VR HMD they used was designed for adults, and that the helmet may not have blocked the sound and visual field of the surrounding environment in younger children. More research is needed to draw conclusions about the effect of age in VR technology.

When the effect of VR analgesia in children is compared to the effect in adults, multiple trials suggest that children report a greater sense of presence into the virtual environments compared with adults[53,54]. This is because children process virtual experiences differently than adults[55]; the prefrontal cortex is not yet fully developed, and by consequence children may be more inclined to believe that the virtual experiences are 'real'. This is why virtual environments should be carefully selected and contextualized, and adapted to the age of the child. This difference in immersion however, does not automatically translate into a difference in VR analgesic effect. Multiple trials have shown that also in adults, VR might be a safe, non-pharmacologic adjunctive analgesic treatment. Most clinical trials about the analgesic effect of VR technology in procedural pain in adults are in the context of artificially evoked painful stimuli[49] or burn wounds[56].

Aside from age, individual differences and other personal traits appear to influence the effect of VR on pain perception in certain individuals. Future research should focus on matching certain types of VR content with age, coping styles and preferences by the use of qualitative or inductive approaches to understand the complex phenomenon of individual health care experiences in its natural context[57].

### Practical implications

In the context of using VR in the clinic it is important to consider if VR technology is worth the cost and the effort by nurses and medical staff. Possible disadvantages to take into consideration are the extra time needed to install the equipment and explain the game to the child or older patient. Also hygienic implications are possible challenges for this technology; the equipment is shared by numerous patients so infection control measures are imperative. As a possible solution, some consumer systems have washable covers to protect the parts of the headset that come into contact with patients' skin. A recent study evaluating the usability of VR technology in children with cancer concludes that its use is acceptable and safe in the context of nosocomial spread of infectious agents[5]acceptability[8].

The most common adverse effect of VR technology is nausea. In this paper, 10 of 30 trials reported possible side effects. Only in 3 of the trials, a small percentage of participants experienced mild nausea[25, 27, 34]. By using modern VR systems with higher frame rates, VR motion sickness has become an uncommon side effect.

Cost price of VR technology varies with the system that is used. There are phone-

**Table 2:** overview of venipuncture trials. CAS: coloured analogue scale; CCLS: certified child life specialist; ED: emergency department; FAS: Facial Affective Scale; FPSR: Faces Pain Scale-Revised; HMD: head mounted device; RCT: randomized controlled trial; SOC: standard of care; VAS: visual analogue scale; VR: virtual reality; WBFPS: Wong Baker faces pain scale.

| Author | Study design | Participants | Inclusion criteria | Exclusion criteria | Intervention | Comparison | Outcomes | Results |
|---|---|---|---|---|---|---|---|---|
| Gold et al., 2017[25] | RCT (between-subjects design) | N=143, 10-21 years old | 10-21 years old | - Cognitive disability<br>- History of seizure<br>- Certain medication<br>- Infection<br>- Visual/auditory impairment | VR distraction (n=70) (active: playing Bear Blast (appliedVR™) using the Samsung Galaxy S6 mobile-based Gear VR goggles (ages 13–21 years) or the Google Pixel mobile-based Merge VR goggles (ages 10–12 years) + SOC. | SOC: interaction with phlebotomist and television (n=73) | -Pain: VAS, CAS, FPSR<br>-Anxiety: VAS, FAS | Less procedural pain (FPSR) ($p<0.05$), less procedural anxiety (VAS) ($p<0.01$), better affect (FAS) ($p<0.001$). VAS and CAS not significantly different between conditions. |
| Gerçeker et al., 2018[19] | RCT (between-subjects design) | N=121, 7-12 years old | 7-12 years old | Chronic or congenital disease. | - VR distraction; Samsung headset with Samsung Galaxy S5 Note phone (passive; watching movie by choice) (n=40)<br>- External cold and vibration (plastic bee) (n=41) | SOC (n=40) | Pain: FACES | No significant difference between intervention groups ($p>0.05$). |
| Aydin et al., 2019[26] | RCT (between-subjects design) | N=120, 9-12 years old | Venipuncture at antecubital site | - Developmental problems that prevent communication<br>- Wearing glasses<br>- Pain before the intervention<br>- Chronic disease that causes pain | VR distraction (n=60): headset (passive: watching 3D 'Aquarium') | No distraction (n=60) | Pain: VAS, WBFPS | Less pain (VAS $p < 0.05$; WBFPS $p < 0.01$) in the experimental group |
| Chan et al., 2019[27] | RCT (between-subjects design) | N=123 (emergency department) and N=131 (outpatient), 4-11 years old | Sufficient English ability to complete study instruments | - Critical medical illness or deteriorating clinical status<br>- Medical conditions that preclude VR use<br>- Inability to consent/assent | VR distraction (ED: n=64, pathology: n=63): Google Pixel XL/Google Daydream (active: underwater adventure)<br>+/- systemic and/or topical analgesia | SOC: child-life therapy, toys, books, electronic devices, systemic and/or topical analgesia (ED: n=59; pathology: n=68) | - Change in baseline pain (FPS-R)<br>- Anxiety (visual analogue thermometer) | - ED: baseline pain was moderate (4, maximum score 10); VR produced significant reduction in pain and anxiety, SOC not<br>- Outpatient: no baseline pain; less increase in pain in VR group; reduction in anxiety in VR group, not in SOC group |
| Gerçeker et al., 2019[28] | RCT (between-subjects design) | N=136, 5-12 years old | 5-12 years old | - Chronic or genetic disease<br>- Visual problem- | VR distraction: Samsung Gear Oculus headset connected to Samsung Galaxy S5 Note mobile phone (passive: watching rollercoaster (n=45) or ocean rift (n=45)) | No distraction (n=46) | - Pain after the procedure: WBFPS<br>- Fear before and after the procedure: Child Fear Scale<br>- Anxiety before and after the procedure: Children's Anxiety Meter | - Lower pain scores in VR groups ($p<0.05$)<br>- Lower fear and anxiety scores after the procedure in VR groups ($p<0.05$)<br>- Reduction in fear and anxiety in VR groups, increase in fear and anxiety in control group |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Özkan et al., 2019[20] | RCT (between-subjects design) | N=139, 4-10 years old | - Routine health checkup<br>- No chronic, neurological and mental disease<br>- Body temperature between 36.5 and 37.1 °C<br>- No pain before the venipuncture<br>- Able to speak and understand Turkish | No exclusion criteria described | - VR distraction (n=46) through goggles compatible with iPhone 6 plus (passive: watching a video)<br>- Kaleidoscope (n=46) | No distraction (n=43) | - Pain: VAS, WBFPS<br>- Anxiety: Children's Fear Scale | - Lower pain scores in kaleidoscope and VR groups compared to control (p=0.000)<br>- Lower pain scores in VR group compared to kaleidoscope group (p<0.05)<br>- Lower anxiety scores in kaleidoscope and VR groups compared to control (p=0.000)<br>- Lower anxiety scores in VR group compared to kaleidoscope group (p=0.000) |
| Toledo del Castillo et al., 2019[24] | Cohort study | N=58, 4-15 years old | Able to use VR and validated scales | - Clinically unstable<br>- Receiving other types of analgesia during procedure<br>- Cognitive impairment<br>- Not possible to use the scales | VR distraction (n=38) with Woxter Neo VR1 glasses fitted with a mobile device (passive: watching a video) | SOC, not specified (n=20) | - Pain (WBFPS 4-6 y and VAS 7-15 y)<br>- Anxiety: Children's fear Scale | - Less pain (p<0.001) and anxiety (p=0.001) in VR group<br>- Lower pain scores in VR + analgesic cream group compared to VR - analgesic cream group |
| Chen et al., 2020[29] | RCT (between-subjects design) | N=136, 7-12 years old | - Conscious<br>- Needing intravenous injection<br>- Able to communicate in mandarin or Taiwanese<br>- Caregivers able to read Chinese | - Developmental delay, epilepsy or heart disease<br>- Undergoing chemotherapy<br>- Visually or hearing impaired<br>- Nearsighted more than 8.0 dioptres or farsighted more than 5.0 dioptres<br>- Head trauma in the past month<br>- Obese children<br>- Children who required blood transfusions<br>- Children who received two or more intravenous injections and had their blood drawn only one time | VR distraction (n=68): Xiaozhai V4 HMD using iPhone (passive: watching 1 of 4 virtual environments (roller coasters, space exploration, wildlife park, travel destinations)) | SOC (not specified) (n=68) | - Pain: WBFPS<br>- Fear: Children's Fear Scale | Significantly less pain and fear in VR group (p<0.05) |
| Dumoulin et al., 2019[21] | RCT (between-subjects design) | N=59, 8-17 years old | 8-17 years old | - Cognitive impairment<br>- No good command of English or French<br>- Epilepsy or migraine<br>- Vomiting at the time of the procedure | - VR distraction (n=20): eMagin z800 HMD using a PC running on Windows XP (active: shooting flies, game developed by UQO Cyberpsychology Lab using Virtools 4) +/- anaesthetic cream or Paineze spray<br>- Watching television (n=24): Looney Tunes or Animal Planet's Funniest Animals) +/- anaesthetic cream or Paineze spray | Distraction by the Child Life Program (n=15): nonprocedural talk, I-Spy book or 20Q ball +/- anaesthetic cream or Paineze spray | - Change in pain: VAS<br>- Change in fear of pain | - Comparable reduction in pain intensity in all 3 groups<br>- Larger reduction in fear of pain in VR group |
| Dunn et al., 2019[22] | Pilot study (between-subjects design) | N=26, 6-18 years old | Severe haemophilia | Visual, cognitive or hearing impairment | Active VR distraction (n=16) through HMD, not further specified | SOC (smart devices, bubbles and videos) (n=9) | Pain and anxiety: modified VAS/FACES pain scale | No significant difference in procedural pain and anxiety between VR and SOC groups |
| Walther-Larsen et al., 2019[30] | RCT (between-subjects design) | N=64, 7-16 years old | - Venous cannulation before planned IV induction at anesthetic department<br>- Danish speaking | - ASA score > 2<br>- Children on analgesia or sedatives<br>- Cognitive impairment<br>- Psychiatric diagnosis<br>- Headache, dizziness, recent head injury, epilepsy and other conditions in which application of VR goggles was judged to be potentially harmful<br>- When a topical anesthetic was not properly applied before the invasive procedure | Active VR distraction: playing Seagull Splash (n=28) through Samsung Galaxy S6 mobile-based Gear VR goggles + SOC | SOC (topical numbing cream, positioning and distraction by playing a 2-dimensional game on a smartphone, led by an experienced specialized pediatric pain nurse) (n=31) | - Patient satisfaction (0-100 scale)<br>- Pain (VAS) | No significant difference in pain scores, greater patient satisfaction in VR group (p = 0.05) |

based VR systems such as Gear VR or Google Cardboard, which consist of a smartphone wrapped in an inexpensive case with lenses. In more powerful VR systems, such as Oculus Rift, the content displayed on the headset is generated by a desktop or by a video game console instead of a smartphone[59]sometimes severely limiting their physical capacities. With the advent of affordable consumer-grade equipment, clinicians have access to a promising and engaging intervention for pediatric pain, both acute and chronic. In addition to providing relief from acute and procedural pain, virtual reality (VR. These systems are more expensive than the phone-based systems. If the current trends in price reduction, increase in portability, and practicality in use continue, VR systems are likely to become increasingly better adapted for the regular clinical use in paediatric patients. Design of apps specifically can raise costs, while it is not proven that this is more effective than using existing apps.

VR technology can't replace other measures in pain control such as topical numbing cream, positioning, sucrose feeding or breastfeeding (children aged < 1 year) and distraction. Therefore, it's important to have and adhere to high-quality evidence-based local protocols for pain management. More studies should be done that compare VR technology with optimal standard care, which was not the case in most of the studies described here. Also, studies that compare distraction by VR technology and other digital and non-digital distraction are needed[60].

Other questions that have to be answered is how long the effect of VR distraction persists (e.g. with longer or repeated procedures) and whether it should be used primarily or secondarily (once procedural distress has arisen). As we know little to nothing on the long term effects of immersive VR with possible manipulation of the immature brain, it could be, for now, safer to use it secondarily rather than primarily.

Medical devices don't have to adhere to the strict regulations for medication; but also in this field, it's important only to use VR devices and apps that have proven to be effective and safe in high-quality trials and for which safety is permanently followed. This applies the more for young children with developing brains and vision. Occulus, one of the companies that produce VR headsets, disclaim that young children should not use the technology as "improper sizing in children younger than 13 can lead to discomfort or adverse health effects, and younger children are in a critical period of visual development". As always, we should adhere to the principle of 'primum non nocere'.

### Limitations

This systematic review has some limitations. First, the methodologic quality of most of the trials was moderate and of some of the trials rather low. Complete blinding of participants and personnel is not possible given the type of intervention. Allocation concealment and blinding of outcome assessment was in most studies insufficient. Also, a minimum amount of 20 participants was an inclusion criteria for a trial in this review. Even then, most trials in this context were rather small. This limits the generalizability of the results.

All of the trials included used self-reported pain measurement to assess the pain experienced during intervention. To account for recollection bias, most of the trials combined self-reported measures with other measures, such as behavioural observation and physiologic measures (e.g. pulse rate, $O_2$ saturation). Unfortunately there are no absolute biomarkers or clinical signs that form a comprehensive measurement of the procedural pain experience.

'Standard of care' is interpreted differently in trials. This might be due to cultural differences. For example, in Kipping et al.[31], children in the control group who received SOC for burn wound treatment had access to TV, stories, music, caregivers or no distraction. In Jeffs et al.[32], SOC was the typical care and communication provided by the staff nurses during burn wound care, without an alternative type of distraction. Especially in the wound care trials, none of the control groups had adequate procedural pain management. Before

**Table 3:** overview of wound care trials. APTT: adolescent pediatric pain tool; FLACC: face, legs, activity, cry, consolability; HMD: head mounted device; RCT: randomized controlled trial; ROM: range of motion; SOC: standard of care; VAS: visual analogue scale; VR: virtual reality.

| Author | Study design | Participants | Inclusion criteria | Exclusion criteria | Intervention | Comparison | Outcomes | Results |
|---|---|---|---|---|---|---|---|---|
| Hua et al., 2015[34] | RCT (between-subjects design) | N=65, 4-16 years old | Chronic wounds on lower limbs requiring active dressing changes | - Non-Chinese speaking<br>- Visual or auditory disability<br>- Comorbidity<br>- Sedative medication<br>- Requiring surgery | VR HMD with joystick (active; playing Ice Age 2® game) (n=33) | Standard distraction: toys, television, books, parental comfort (n=32) | - Pain: FLACC scale, FACES, VAS<br>- Pulse rate, O2 saturation<br>- Length of dressing changes | - Both FACES pain score and VAS-score show significantly less pain in VR group before, during and after dressing change. FLACC-score was lower in VR group during and after dressing change.<br>- Time length of dressing was significantly reduced in VR-group (p=0.003).<br>- Lower pulse rates (p=0.013) in VR group but no difference in O2 between groups. |
| Schmitt et al., 2010[33] | RCT (within-subjects design) | N=54, 6-19 years old | - Burn wounds<br>- Requiring physical therapy | - Susceptibility to motion sickness<br>- Burns on head<br>- History of seizures | VR distraction through HMD (SnowWorld® pain control virtual environment) + standard analgesic care | Standard analgesic care alone : opioid +/- benzodiazepine | - Pain: 0-100 graphic rating scale<br>- Subjective assessments<br>- Maximum ROM | - Significantly less cognitive, affective and sensory pain (p<0.05) on first study day. Less consistent results on other 4 study days.<br>- No significant increase in maximum joint range-of-motion (p=0.21). |
| Jeffs et al., 2014[31] | RCT (between-subjects design) | N=28, 10-17 years old | - Speaking English<br>- Undergoing burn wound care for the first time (without sedation) | - History of motion sickness<br>- History of seizure<br>- Incarcerated minors/ foster care<br>- Cognitive disability | - VR distraction through goggles on mounted device; SnowWorld® pain control virtual environment (n=8)<br>- Passive non-VR distraction : watching video on television (n=10) | SOC: typical care and communication by the staff (n=10) | Pain : APTT | VR group had less pain than passive distraction group (p=0.029) but not less than SOC group (p=0.32). Only in the VR group there was a decrease from preprocedural pain to wound care procedural pain. |
| Hoffman et al., 2012[93] | Pilot study (within-subjects, within-wound care design) | N=48, 6-17 years old | - Compliant and able to complete evaluations<br>- No history of psychiatric disorders<br>- No delirium, psychosis or organic brain disorder<br>- Able to communicate in English or Spanish<br>- Moderate or higher worst pain during wound care | - Burn size < 10% TBSA<br>- Not capable of completing the study measures<br>- No wound cleaning sessions required<br>- History of significant cardiac, endocrine, neurologic, metabolic, respiratory, gastrointestinal or genitourinary impairment<br>- Receiving prophylaxis for alcohol or drug withdrawal<br>- Burns of eyes, eyelids or face so severe the burns precluded use of VR equipment<br>- History of severe motion sickness | VR distraction through MX90 VR goggles (NVIS.com) on a goggle arm holder (active: playing 'Snow World' with a wireless mouse), undergoing burn wound care + usual pain medications | SOC (usual pain medications) | Worst pain, pain unpleasantness and time spent thinking about pain using graphic rating scales | - VR reduced 'worst pain' ratings (p<0.001)<br>- VR reduced pain unpleasantness and time spent thinking about pain |
| Kipping et al., 2011[30] | RCT (between-subjects design) | N=41, 11-17 years old | - Burn wounds<br>- Requiring first conscious dressing change<br>- Total Burn Surface Area of >1%. | - Cognitive impairment<br>- Burn locations that impact use of VR<br>- Visual or hearing impairment<br>- Non-English speaking<br>- Child safety and protection issues | VR HMD with joystick playing Chicken Little® or Need for Speed® game (n=20) | Standard distraction by choice: TV, stories, no distraction… (n=21) | - Pain: VAS, FLACC scale<br>- Pulse rate, O2 saturation<br>- Length of procedure | - No significant difference in VAS-score between VR group and control during dressing removal (p=0.16) and application (p=0.40), significantly less pain (FLACC score) in VR group during dressing removal (p=0.02) but not during dressing application (p=0.23).<br>- No significant difference in length of procedure, O2 or pulse rate. |

implementing VR, procedural pain management should be optimized. In the study of Walther-Larsen et al.[30], the control group followed a protocol with topical numbing cream, positioning and distraction by a specialized nurse. No difference between this group and the VR group was observed; on the other hand, VR wasn't worse than the time- and staff-consuming intervention in the control group. VR could be an alternative on moments where less staff is available e.g. weekends or night-shifts.

There is a wide variety of pain assessment tools and scores which can be used as an outcome measure in interventional studies about pain.

The differences between trials and the inadequate pain management in control groups greatly influence the comparison. Moreover, the studies included here comprise different procedures, wide age range and different types of VR experiences. In our opinion, this makes a formal meta-analysis impossible. Eilers et al. did make a formal meta-analysis but mention high heterogeneity[61]. In the future, it will be important to answer the question for who VR might work during which procedure.

## Conclusion

This systematic review provides evidence that immersive VR technology might be a promising distraction method to improve procedural experience in some children. Especially wound care and IV access could be proper indications for VR distraction. The effect of active VR distraction is better than passive VR distraction. More large trials of good methodologic quality are needed to further investigate its analgesic effect and to draw conclusions about which type and content of VR are the most suited for which types of patients in which indications. Hard evidence for wide application within the pediatric population is still lacking.

**Table 4:** overview of port access trials. CHEOPS: Children's Hospital of Eastern Ontario pain scale; HMD: head mounted device; RCT: randomized clinical trial; VAS: visual analogue scale; VR: virtual reality.

| Author | Study design | Participants | Inclusion criteria | Exclusion criteria | Intervention | Comparison | Outcomes | Results |
|---|---|---|---|---|---|---|---|---|
| Gershon et al., 2004[35] | Pilot and feasibility Study (between-subjects design) | N= 59, 7-19 years old | - Having cancer<br>- Undergoing port access procedure | - Non-English speaking<br>- Not with their legal guardian | - VR HMD with joystick (active: Virtual Gorilla program) (n=22)<br>- Virtual Gorilla program displayed on computer screen with joystick (n=15) | No distraction (n=22) | - Pain: VAS, CHEOPS<br>- Pulse rate | - No significant difference in child-reported pain.<br>- Significant difference in nurse-reported VAS and pulse-rate (both $p<0.05$) between VR and no distraction.<br>- No significant difference in overall CHEOPS score.<br>- No significant difference between VR distraction and computer display distraction. |
| Wolitzky et al., 2005[36] | RCT (between-subjects design) | N=20, 7-14 years old | - Cancer<br>- Undergoing port access procedure | Not mentioned | VR distraction (HMD) with joystick (Gorilla® environment) (n=10) | No distraction (n=10) | - Pain (VAS, CHEOPS)<br>- Pulse rate | CHEOPS score and pulse rate were lower in VR group ($p<0.01$ and $p<0.05$), VAS-score was not ($p=0.10$). |

**Table 5:** overview of dental treatment trials. FLACC: face, legs, activity, cry, consolability; HMD: head mounted device; IAN: inferior alveolar nerve; LA: local anesthesia; MCDAS: Modified Child Dental Anxiety Scale; RCT: randomized controlled trial; VR: virtual reality; WBFPS: Wong Baker Faces Pain Scale.

| Author | Study design | Participants | Inclusion criteria | Exclusion criteria | Intervention | Comparison | Outcomes | Results |
|---|---|---|---|---|---|---|---|---|
| Aminabadi et al., 2012[37] | RCT (within-subjects design) | N=120, 4-6 years old | - Routine dental care<br>- Requiring restorative treatment | - Anxiety disorders<br>- Previous invasive painful medical or dental history | VR eyeglasses (passive; watching Tom and Jerry® episode) + topical and local anaesthesia | No distraction, with topical and local anaesthesia | - Pain: FACES<br>- Anxiety: Faces version of the Modified Child Dental Anxiety Scale (MCDAS) | Significant advantage in both groups of VR over no VR ($p<0.001$). |
| Niharika et al., 2018[38] | RCT (within-subjects design) | N=40, 4-8 years old | - No anxiety disorder at the first visit according to SCARED questionnaire<br>- First attendance<br>- Presence of at least 2 carious primary molars requiring pulp therapy<br>- Frankl behavior rating 2 | - Visual or auditory deficits | - VR distraction using Anti Tank Virtual Reality 3D glasses and Google VR box (passive: watching cartoon "doreman") + tell-show-do technique + topical and local anaesthesia | - Tell-show-do technique of behavioral management+ topical and local anaesthesia | - Pain: WBFPS<br>- Anxiety: faces version of the modified child dental anxiety scale (MCDAS)<br>- Oxygen saturation and pulse rate | - Decrease in pain and anxiety scores when using VR ($p<0.001$)<br>- Lower pulse rate with VR in group A ($p<0.05$), not in group B<br>- No difference in oxygen saturation levels |
| Al-Halabi et al. 2018[40] | RCT (between-subjects design) | N=102, 6-10 years old | - No previous dental experience<br>- Categorized under positive ratings of Frankl scale 5 who required LA administration in the mandibular arch (IAN block) | Systemic or mental disorders | - Passive VR distraction through 'VR box' HMD watching cartoon episode + local anaesthesia<br>- Watching cartoon episode on tablet + local anaesthesia | Basic behavior guidance techniques without distraction + local anaesthesia | - Pain: FACES, FLACC<br>- Pulse rate | No advantage of VR distraction over tablet or control ($p=0.67$ and $p=0.62$). |
| Koticha et al., 2019[39] | RCT (within-subjects design) | N=30, 6-10 years old, undergoing extraction of bilateral primary molars | - Bilateral nonrestorable primary molars<br>- Frankl behavior rating 3-4 | - Medically compromised children<br>- Children with special health care needs<br>- Patients who had a bad experience with dentist<br>- Frankl behavior rating 1-2 | VR distraction using BlackBug Virtual Reality Glasses on an Apple iPhone 6 (passive: watching cartoon "chotta bheem or doremon") + topical and local anaesthesia | No VR glasses, with topical and local anaesthesia | - Anxiety: Venham's picture test<br>- Pulse rate<br>- Oxygen saturation | - Increase in anxiety in VR group ($p=0.03$), no difference in anxiety before and after the procedure in control group<br>- No difference between groups for anxiety and oxygen saturation<br>- Pulse rate after extraction significantly less in VR group ($p<0.03$) (108.4 vs 112.2/min)<br>- No difference in pulse rate before and after the procedure in VR group, increase in pulse rate in control group<br>- No difference in oxygen saturation before and after the procedure |

**Table 6:** overview of lumbar puncture trials. VAS: visual analogue scale; VR: virtual reality.

| Author | Study design | Participants | Inclusion criteria | Exclusion criteria | Intervention | Comparison | Outcomes | Results |
|---|---|---|---|---|---|---|---|---|
| Wint et al., 2002[41] | Pilot study (between-subjects design) | N=30, 10-19 years old | - Having cancer<br>- Undergoing at least a second LP<br>- Any ethnic origin | - Non-English speaking<br>- Auditory or visual impairment | VR glasses; passive distraction (watching video Escape®) + SOC (n=17) | SOC: procedural sedation with fentanyl and midazolam, topical anaesthesia, full explanation and parental presence (n=13) | Pain: VAS | No statistical difference was found between VR and control group (p=0.77). |

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# How to position impedance-pH probes in pediatric patients: a pilot trial

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## Keywords

electrode positioning, equation, multiple intraluminal impedance, pH-impedance monitoring, pH metry, probe, gastro-esophageal reflux

## Abstract

**Background:** Multichannel intraluminal -impedance (MII) - pH recording is frequently used for the diagnosis of gastroesophageal reflux disease in children. The location of the probe is essential to obtain a reliable recording.

**Objective:** Positioning of the electrode through radiologic or fluoroscopic control is recommended as the standard. In order to decrease radiation, different attempts have been made to develop equations to obtain a correct positioning of the probe without radiation.

**Methods:** We prospectively compared the location of the MII-pH probe in 30 children according to i) the location according to fluoroscopy, which is considered the gold standard; ii) the location according to a formula developed by our nurses, and iii) the location according to another equation which was recently developed.

**Results:** According to the global results, both equations adequately predict the correct location of the probe. However, probably due to inadequate measurements, significant differences are observed in a few individual patients.

**Conclusions:** The equation developed in our unit is easy to apply and predicts in the majority of cases the correct location of the MII-pH electrode, resulting in decreased manipulations and less radiation exposure. As a consequence, radiologic control of the exact position of the probe remains recommended.

## Introduction

Oesophageal pH monitoring has been for years the standard to measure gastro-oesophageal reflux. However, per definition, pH monitoring will detect only acid reflux. Multichannel intraluminal impedance (MII), the inverse measurement of intraluminal conductivity, detects the flow of luminal contents, and measures therefore reflux independent of pH (1). Nowadays, MII-pH recording is a recommended investigation for the diagnosis of gastro-oesophageal reflux disease since it will measure acid and non-acid reflux since impedance and pH recordings are combined (1). Impedance rings are 1.5 cm or 2 cm apart from each other in infant and pediatric catheters, respectively. The procedure can be performed in all age groups. The major indications for MII-pH recording are extra-oesophageal symptoms such as coughing, wheezing and failure of treatment. The symptom-association analysis allows to conclude if there is a time assication between a symptom and a reflux episode.

The correct location of the pH-monitoring and MII-pH probe is of major importance for an accurate interpretation of the result of the investigation (1). The catheter is inserted transnasally. The current guidelines of the European and North-American Societies of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN) recommend that the pH electrode must be placed at a distance of two vertebral bodies above the diaphragm, and that this position should be confirmed by radiology (X-Ray or fluoroscopy) (1).

The aim of this pilot study was to evaluate a method developed by the nurses of our proper team to anticipate a positioning of the probe as correct as possible when radiologically controlled, and compare our method to a recently developed, albeit unpublished, formula in another center. A correct placement of the probe without the need of radiologic control would be of benefit for the patient and nursing staff, and simplify the manipulations related to the investigation.

## Material and Methods

Thirty consecutive children referred for MII-pH recording because of extra-oesophageal symptoms possibly related to gastro-oesophageal reflux were included in this pilot study. Prior to the fluoroscopic control, the nursing staff located the probe at a distance calculated according to a simple equation developed by the KidZ Health Castle team: "distance (nose tip to ear canal) + (nose tip with head in neutral position to nipple line) in cm". Through years of experience and "try and error', the nurses developed this simple equation which was up to now not validated. Children with scoliosis or other anatomic problems were excluded.

The final location of the MII-pH probe was determined by the nursing staff under radiologic control by fluoroscopy, which should be two vertebral bodies above the left diaphragm in 30 consecutive patients (1).

Colleagues from another center developed the following equation (Equation 2): "5.6 + (height in cm * 0,12) + (sternal fork-xyphoid process length * 0.57)" (unpublished).

The formula developed by our team was compared to the outcome of the other equation, and both were compared to the correct location according to the radiologic correct location.

We did not calculate other statistical parameter than the correlation coefficients.

## Results:

Table 1 summarizes the findings for the 30 MII-pH recordings. The age of the children ranged between 2 months and 12 years.

The correlation coefficient between one of both equations and the fluoroscopic controlled location was above 0.90. According to the KidZ Health Castle equation, the probe was almost exactly located (a difference of maximal 1 cm between the distance according to the equation and according to fluoroscopy) in 18/30 children (60%). According to "equation 2", a difference of 0 to 1 cm was observed in 20/30 patients (66%). A difference of more than 2 cm was observed in 3/30 (10%) children for the KHC-equation and in 2/30 (7%) children according the Equation 2.

**Table 1.** Distances in cm from nose tip to exact location of the MII-pH probe.

| Patient n° | Weight / kg | Height / cm | Fluoroscopy | KHC Equation | Difference | Equation 2 | Difference |
|---|---|---|---|---|---|---|---|
| 1 | 9.75 | 75. | 20 | 21 | **1** | 20 | 0 |
| 2 | 8.19 | 70.9 | 21 | 231 | 2 | 21.5 | 0.5 |
| 3 | 5.30 | 59.0 | 18 | 18 | **0** | 17.5 | 0.5 |
| 4 | 5.00 | 57.5 | 18 | 18 | 0 | 18 | 0 |
| 5 | 4.50 | 54.4 | 15 | 17 | 2 | 16.5 | 1.5 |
| 6 | 5.98 | 59.0 | 17 | 17 | 0 | 18.5 | 1.5 |
| 7 | 38.25 | 149.0 | 30.5 | 30 | 0.5 | 30.5 | 0 |
| 8 | 5.05 | 58.7 | 17.5 | 17.5 | 0 | 17.5 | 0 |
| 9 | 10.0 | 80.5 | 20 | 21 | 1 | 21 | 0 |
| 10 | 7.2 | 66.5 | 18 | 23 | **5** | 20.5 | **2.5** |
| 11 | 7.0 | 61.5 | 17.5 | 20 | **2.5** | 17.5 | 0 |
| 12 | 5.02 | 54.0 | 17 | 17 | 0 | 17 | 0 |
| 13 | 4.18 | 56.0 | 17 | 19 | 2 | 17. | 0 |
| 14 | 6.60 | 64.5 | 19 | 16 | **3** | 19. | 0 |
| 15 | 40.80 | 146.5 | 33 | 32 | 1 | 32 | 1 |
| 16 | 36.50 | 138.0 | 34 | 33 | 1 | 32 | 2 |
| 17 | 8.34 | 71.0 | 20 | 20 | 0 | 20.5 | 0.5 |
| 18 | 9.28 | 72.0 | 21 | 20 | 1 | 19.0 | 2 |
| 19 | 7.81 | 68.0 | 16 | 17 | 1 | 20.5 | **4.5** |
| 20 | 7.85 | 73.0 | 19 | 19 | 0 | 20 | 1 |
| 21 | 47.40 | 145.0 | 34 | 35 | 1 | 32 | 2 |
| 22 | 12.15 | 82.8 | 21 | 21 | 0 | 22 | 1 |
| 23 | 10.6 | 83.5 | 21 | 22 | 1 | 20.5 | 0.5 |
| 24 | 6.05 | 61 | 18 | 18 | 0 | 18 | 0 |
| 25 | 8.96 | 71.6 | 18 | 20 | 2 | 19 | 1 |
| 26 | 13.8 | 97.4 | 23 | 23 | 0 | 23.5 | 0.5 |
| 27 | 9.75 | 75.0 | 20 | 22 | 2 | 21.5 | 1.5 |
| 28 | 8.19 | 70.9 | 22 | 24 | 2 | 23 | 1 |
| 29 | 5.00 | 57.5 | 17 | 19 | 2 | 19 | 2 |
| 30 | 5.3 | 59.0 | 18 | 18 | 0 | 18 | 0 |

**Legend.** KHC: KidZ Health Castle; Difference: difference in cm between distance according to equation and fluoroscopy.

## Discussion

Overall, both equations predicted a correct location, defined as a difference of 0 to maximal 1 cm, of the MII-electrode in the majority of the children (60 vs 66%). The formula scored equally well independent of the length of the children, since the age of the children included varied from 2 months to 12 years. However, depending on the equation used, in 3/30 (10%) or 2/30 (7%) children the probe needed to be relocated with more than 2 cm. Any alternative for radiologic control should result in an accurate placement of the probe. A difference of 1 centimeter or less was not considered as a clinically relevant difference because head movements and respiration cause a greater displacement. None of both equations provides satisfactory outcome in children with anatomic malformation such as scoliosis. Regarding the HKC equation, it is very important that the head is in neutral horizontal position.

Although the correlation coefficients with fluoroscopic distance are above 0.90 for both equations, we estimate that it cannot be excluded that a relocation of the probe with over 2 cm could possibly change the result of the investigation, and thus cause erroneous interpretation of the MII-pH recording what would have a significant clinical impact for the patient. Independent of the indication of the pH monitoring or MII-pH recording, interpretation of the data should be adequate, and therefore correct location of the pH measuring sensor is mandatory. As a consequence, radiologic control remains the gold standard.

Due to the increased radiation sensitivity of children, the potential risk of multiple radiographic examinations should be as much as possible minimalized. The guidelines of the European and North-American Societies of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN) recommend a radiography or fluoroscopy to determine the location of the MII-pH probe (1). Historically, different formulas to estimate the correct location of the probe were developed with the goal to avoid radiology and thus decrease exposure to radiation. The avoidance of the necessity for a radiologic control would also simplify the methodology of the MII-pH recording and decrease the burden for the patient and the health care professionals.

Several formulas can be found in the medical literature to estimate the correct MII-pH probe location. Most of them take into consideration the patients' height. Historically, the Strobel formula (0.252 × length in centimetre + 5) was the first attempt to avoid radiologic control and was developed more than 40 years ago (2). However, this formula was considered inadequate as it was shown to overestimate the oesophageal length: the taller the child, the greater the inaccuracy (2). Moreau et al developed a different formula based on 116 children (L = 0.216 (H) + 7.13) resulting in a correlation coefficient of 0.85 with the radiologic control (3).

In 1991, Staiano and Clouse evaluated in 213 children and adults if anthropometric variables could be used to accurately predict sphincter location across all age ranges (4). But once more, results were disappointing. The regression equation that best predicted the location in children younger than two years of age ("L = 0.22[H] + 4.92", where L is the location in centimetre from the nares and H is the height in centimetre) still resulted in an error of more than 1 cm in 10 % (4). In the older patient groups, the error of the predicted lower oesophageal sphincter location was greater than two cm in more than 25%, even when more age specific equations were used (4).

A Spanish group tested different formulas which were used in their institutions to estimate the best catheter positioning length in adults according to formulas used in children (5). The tested equations were: "9.31 + height in cm × 0.197" (Hospital de Navarra ) and "9.31 + height in cm × 0.179" (Hospital Infantil Vall d'Hebron, Barcelona) (5). The formula from Barcelona came out as the best, but differences up to 6 cm in adults were observed (5).

Colleagues from the Great Ormond Street Hospital developed a table (GOSH-Table) based on height intervals of 144 children and showed a correlation between desired catheter position ("approximately two vertebral bodies above the diaphragm") for the whole group of 0.95 (6). For the same group of children, these authors also calculated the correlation between desired catheter position and Strobel, which was 0.84, and Moreau, with a correlation of 0.85 (6).

A Polish group reported that according to observations from 353 children aged 0-18 years in whom the position of the pH sensor was determined radiographically, that the following mathematical formula ("3.2 + 0.2 × body length or height in centimetre") could guide to the best location of the probe (7). However, the desired location was only obtained in 71.7% of the patients (7).

Recently, a new equation was developed based on 45 paediatric patients (3 months -13 years old) : "5.6 + (height in cm * 0.12) + (sternal fork-xyphoid process length * 0.57)", which was reported to reach a correlation of 0.93 (unpublished data). The accuracy of this equation was also tested in our pilot trial.

The mean difference between the final length according to fluoroscopy and the distance estimated through the KHC equation was 0.63 cm and according to Equation 2 was 0.45 cm. As a mean, this difference is likely to lack any clinical significance if we consider the change in position of the electrode caused by changes induced by head movements or respiration by the patient. However, according to both equations, the observed difference with fluoroscopy was more than 4 cm in 1/30 patients. This was likely due to inaccurate measurements by the health care professionals, but it does reflect clinical reality.

A major limitation of this pilot trial is the small sample size. We suggest future research including larger samples in order to evidence the influence of this or other variables in the insertion length.

## Conclusions

Both equations that were evaluated in this study estimate the appropriate insertion length of a MII-pH-impedance catheter in a more precise way than the equations that were previously proposed. Up to now, radiologic control remains the gold standard, and thus required in order to obtain an accurate interpretation of the investigation. However, the more correct the estimated distance can be predicted, the less subsequent re-location of the probe that will be needed during fluoroscopy. Both equations provided a comparable predictive adequacy, but the KidZ Health Castle equation is easier to calculate. This will result in a decreased radiation exposure, and decrease the discomfort and burden for patient and health care provider. However, as of today, fluoroscopic or radiologic control remains the gold standard for appropriate probe location for oesophageal pH or MII-pH recording.

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# SPA® REINE
## water en het microbioom van de baby

Tijdens de eerste levensmaanden speelt het darmmicrobioom een belangrijke rol. **Gesprek met adviseur menselijke voeding Jean-Pierre Mans,** die uitleg geeft over de rol van het microbioom en over de noodzaak om de rijkdom ervan te behouden om op termijn de ontwikkeling van infecties of van ziektes zoals diabetes of obesitas te voorkomen[1].

### HET BELANG VAN HET MICROBIOOM BIJ DE GEBOORTE

**JP MANS** *Het microbioom van de baby wordt vanaf de geboorte gevormd door het contact met de vaginale flora na een bevalling via de natuurlijke weg. De kolonisatie met bacteriën gebeurt geleidelijk aan en in een welbepaalde volgorde. De eerste darmbacteriën hebben zuurstof nodig om zich te vermenigvuldigen (enterokokken, stafylokokken,...). Vervolgens is het de beurt aan de bacteriën die zich zonder dit gas ontwikkelen (bacteroïden, clostridium, bifidobacterium...)[2]. Onder invloed van borstvoeding, meer variatie in de voeding, medische behandelingen en de omgeving gaat de samenstelling van het microbioom evolueren. Omstreeks de leeftijd van 3 jaar stabiliseert het zich.*

### EEN GOEDE HYDRATATIE VOOR EEN GOED MICROBIOOM

**JP MANS** *Bij het jonge kind speelt hydratatie een belangrijke rol omdat het lichaam van de zuigeling voor bijna 80% uit water bestaat, tegenover 60% op volwassen leeftijd[3]. De baby heeft dus zeer veel water nodig: 150ml/kg/j[4]. Licht gemineraliseerd water en vooral borstvoeding vervullen heel wat functies, waaronder het transport van de voedingsstoffen, de vitamines en de mineralen die nodig zijn om de opname ervan te vergemakkelijken.*

### EEN GEWIJZIGD MICROBIOOM HERSTELLEN

**JP MANS** *Eén van de risico's bij diarree of gastro-enteritis bij de baby is dehydratatie (tot 15% van het gewicht van de baby, vooral vóór de leeftijd van zes maanden). In dit geval, en als het kind borstvoeding krijgt, moet de moeder daarmee doorgaan. Er moet trouwens een rehydratatieoplossing worden toegediend die gereconstitueerd is met een licht gemineraliseerd water. Als er bovendien een antibioticakuur werd opgestart, moet het darmmicrobioom opnieuw worden gekoloniseerd[5]. 80% van de immuuncellen van het menselijk lichaam bevinden zich immers in het spijsverteringskanaal. Een gewijzigd darmmicrobioom verhoogt het risico dat de baby later infecties of ziekten ontwikkelt[1]. In deze context kan men zijn toevlucht nemen tot probiotica, waarvan bepaalde stammen hun nut hebben bewezen.*


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# An interesting case "out of paper" with celiac disease leading to xylophagia: case report and review of literature

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## Keywords

Pica, xylophagia, failure to thrive, celiac disease

## Abstract

We describe a young girl presenting with the intriguing symptom of xylophagia, subsequently being diagnosed with celiac disease. Our goal is to review literature on prevalence and etiology of pica and to raise awareness on the less obvious presentations of celiac disease and its possible consequences. In this case, diagnosis was established and treatment was initiated rapidly after first atypical presentation on consultation, with good clinical outcome. We want to stress the need for further population-based re-search on pica, given the potential and dangerous consequences of ingestion of nonnutritive substances.

## Introduction

Celiac disease is a well-known auto-immune disease caused by intolerance to gliadin, a component of gluten. It causes a chronic inflammation in the small bowel, and most patients develop typical symptoms such as diarrhea, abdominal pain and distention, failure to thrive and sometimes nutritional deficiencies. Diagnosis in children can nowadays be made through blood analysis and specific genetic HLA-testing. In doubtful cases, small bowel biopsies are necessary (1). As pediatricians, we are familiar with these common symptoms of celiac disease and its treatment; however, this case underscores the need to consider its possibility in less familiar complaints. We present a six-year-old girl with pica behavior, consequently being diagnosed with celiac disease.

## Case report

A six year old girl was seen in the outpatient clinic because of the excessive intake of paper. There were no important problems in her medical history. The familial history learned that her father was known with psoriasis. The ingestion of paper (known as "pica" in literature, more specifically "xylophagia") started six months before, and increased since then. The parents were most concerned about the failure of intake of normal nutrition and secondary weight loss. Other complaints were abdominal pain and fatigue.

At the consultation, no immediate triggering (psychological) factors could be withheld. Clinical examination, including an extensive neurological examination, did not reveal anything except a tired-appearing young girl with manifest weight loss of 2 kg. She was diagnosed with pica. Blood analysis showed an important iron deficiency anemia with a hemoglobin of 7,2 g/dL. [Table 1] This anemia could provoke pica, yet why would this girl have such an important iron deficiency?

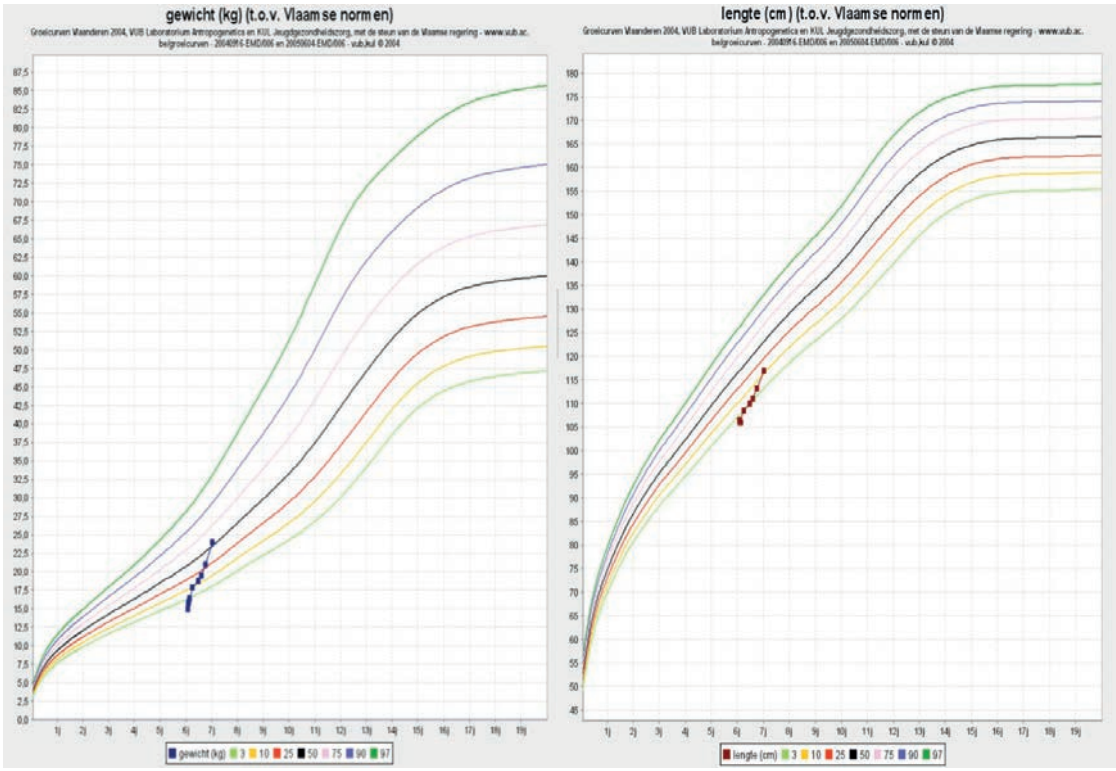
Iron supplementation was started, yet one week later more blood results were known and screening for celiac disease showed an immeasurably high titer of anti-tissue transglutaminase antibodies (>128U/ml) with normal total IgA. In 2012, ESPGHAN (the European Society for Paediatric Gastroenterology Hepatology and Nutrition) guidelines were adjusted to permit omission of duodenal biopsies in selected cases.(1) However, in Belgium intestinal biopsies are still necessary to qualify for a medical reimbursement by the national health insurance and therefore gastroscopic evaluation was planned on short-term. This confirmed the diagnosis of celiac disease (chronic duodenitis with severe villous atrophy, Marsh classification 3C). The girl was put on a rigorous gluten free diet.

Clinical checkup one month later showed a child in good clinical condition, with a favorable weight gain [Figure 1] and most of all: almost disappearance of xylopaghia. Biochemically there was a slowly increasing hemoglobin with still low iron stores. Anti-tissue transglutaminase antibodies however remained immeasurably high.

**Table 1**

| Parameter | Reference range | 30/08/2019 | 24/05/2019 | 27/03/2019 | 12/02/2019 | 20/11/2018 | 11/10/2018 |
|---|---|---|---|---|---|---|---|
| Hemoglobin (g/dl) | 11,5-14,5 | 12,6 | 12,3 | 10,2 | 7,9 | 8,1 | 7,2 |
| MCV (Fl) | 75-87 | 75,6 | 66,4 | 57,7 | 49,7 | 51 | 48 |
| MCH (pg) | 25-31 | 25,5 | 23,5 | 17,2 | 15 | 14,8 | 13,1 |
| Serum iron (mcg/dL) | 37-145 | 62 | 76 | 67 | 19 | 14 | 13 |
| Ferritin (mcg/L) | 15-150 | 180 | 253 | 194 | 3 | 2 | 5 |
| Transferrin saturation (%) | 20-50 | 22 | 29 | 19 | 4 | 3 | 3 |
| Anti-gliadin IgG (U/mL) | | 26 | 17 | | 51 | 35 | |
| Anti-tissue transglutaminase antibodies (TGA-IgA) (U/mL) | 0-7 | 123 | 144 | 627 | > 128 (absolute value of 1310 after dilution) | > 128 (absolute value of 654 after dilution) | > 128 (absolute value of 1405 after dilution) |
| IgA (g/L) | 0,34-3,05 | 0,76 | 0,89 | 0,93 | 1,21 | 1,01 | |

Figure 1




The clinical biologists were asked to determine the absolute value of antibodies. This revealed - after dilution - a meaningful decrease (1405 U/ml before diet, 654 U/ml on gluten-free diet). A further slow recovery of the intestinal mucosa is expected (when continuing a rigorous diet), with secondary resolution of the iron deficiency and no come back of pica. In the following months, there was a biochemical recovery and total disappearance of the xylophagia.

## Discussion

### Definition

Pica has been an intriguing symptom for over centuries, being firstly described by Hippocrates in 400 BCE (2-6). Its name is derived from the animal world in which a magpie - with scientific name 'pica pica' - is a bird with peculiar eating habits since it is an opportunistic omnivore (7). Consequently, "pica" is used to describe a disorder that makes people crave for nonnutritive substances (5-7).

Considering the DSM-V criteria (Diagnostic and Statistical Manual of Mental Disorders), pica is a feeding disorder (next to rumination disorder and avoidant/restrictive food intake disorder,) more than an eating disorder (anorexia nervosa, bulimia nervosa, binge eating disorder and other specified disorders) (8-10). To be diagnosed with pica, a patient must display (a) persistent eating of non-nutritive substances for a period of at least one month, (b) which is inappropriate to the developmental level of the individual, (c) which is not part of a culturally supported of socially normative practice and (d) if it is occurring in the presence of another mental disorder (e.g. autism, schizophrenia) or during a medical condition (e.g. pregnancy), it is severe enough to warrant independent clinical attention (9, 11, 12).

Pica covers different types of cravings, from pagophagia (snow, iced substances) and hyalophagy (glass) over geophagia (earth or soil-like substrates), xylophaghia (paper or wood) and trichophagia (hair) (7, 8, 12).

Most patients are rather selective in their cravings for only one or a couple of nonnutritive substances (13).

### Epidemiology

Review of literature mostly confirms how little is known about this condition and even though widely spread prevalence rates are mentioned within particular populations, most authors agree that prevalence rates are severely underestimated (7, 14).

First of all: in the absence of complications mentioned below, diagnoses depends on self-reportage which is likely to be limited by a sense of shame (7, 12). Secondly, in some cultures pica is accepted as a normal behavior (see below) and standardized criteria (e.g. DSM V criteria) and definitions for pica are not consequently used (4, 7). Thirdly, as pica is under-researched, we lack population-based prevalence rates and etiological models, with consequently only few evidence-based diagnostic and therapeutic options (7, 8).

What is agreed on in literature is that women (and most specifically during pregnancy), children and mentally-retarded patients are most susceptible, as are people living in low socioeconomic and underdeveloped areas (5, 7, 9, 11, 14). As the DSM V criteria state, pica is considered normal in young age given the developmental stage and the normal phase of oral exploration, yet one expects a decrease with age. Frequency ranges between 6,7 and 18,5 percent in children, yet go as high as 58 percent in adults with iron deficiency anemia and even 68 percent in pregnant women (4, 6, 8, 11, 15-17). Male or female predominance differs in literature (2, 7, 8, 11, 17).

### Clinical signs and complications

In the majority of cases, patients will show no abnormalities on physical examination. Nevertheless, some children are malnourished and might present with abdominal complaints as did our patient. Other possible clinical manifestations depend on type of craving and its potential evolution to complications (13).

The necessity of more knowledge is in fact driven mostly by these potential and dangerous consequences that can be divided into five distinct categories: toxicity as a result of ingestion (e.g. encephalopathy, peripheral neuropathy, cognitive impairment), gastro-intestinal obstruction (e.g. vomiting, abdominal distention), excessive intake of calories, nutritional deficits (e.g. pallor, tachycardia when anemic) given the altered 'normal' intake and infectious risks (e.g. parasitic infection, toxoplasmosis) (7, 8, 11-14).

### Etiology

Regarding the etiology of pica, controversy persists. Possible etiological factors can be divided in four categories: (a) developmental abnormalities, (b) sociocultural habits, (c) psychosocial and (d) nutritional factors (7, 11, 12, 18).

Considering developmental abnormalities, it has to be acknowledged that up to the age of three, pica is acceptable if the behavior of the child is not compulsive. Mentally retarded patients are more susceptible to develop pica as are patients with an autism spectrum disorder (11). On the other hand, in some countries and ethnic groups, the eating of certain substances is considered normal (e.g. eating of clay as part of a cleansing ritual in some African tribes) (9). Pica is more prevalent in households with low socioeconomic status (7, 11, 12, 19, 20).

In otherwise healthy children, psychological factors can contribute to the development of pica (e.g. traumatic experiences, parental neglect, bullying, maternal deprivation). Lastly, nutritional deficits and a diet lacking iron, zinc and calcium are described in literature in association with a higher prevalence of pica (4, 11, 14).

In our patient, we did not have immediate indications of psychosocial difficulties, there were no sociocultural particularities and we noted a normal development. Therefore, nutritional abnormalities seemed most likely and worthy of further investigation.

Literature gives distinct opinions on a link between pica and nutritional deficiencies (17). Most authors describe an association between iron-deficiency (with or without anemia) and pica, however with uncertainty about pica as a consequence or as a cause of this iron-deficiency ("chicken or the egg") (2, 4, 5, 7, 11, 21). Interestingly, in the nineties two comparable case reports - celiac disease in childhood in association with iron deficiency and pica - were published (7, 22, 23). Korman et al. describe three children with geophagia and iron deficiency with consequent diagnosis of celiac disease. In these cases, pica was assumed to result from iron deficiency secondary to malabsorption. After introduction of a gluten-free diet, all children showed a rapid resolution of pica and a significant weight gain, growth spurt and correction of anemia. The author states that iron deficiency in celiac disease is multifactorial: anorexia is common and may result in diminished iron intake, impaired absorption of iron was observed in some patients and iron may be lost because of rapid turnover of epithelial cells as well as because of occult intestinal blood loss. Inhibition of intestinal absorption of iron after ingestion of non-nutritive ingredients with secondary low iron status, was described by other authors (4, 14, 21, 24, 25).

The strength of the relationship between pica and iron deficiency was studied by Miao et al, given previous studies lacking controls and rigorous blinding.(4) This recent meta-analysis, including over 6.000 individuals with pica behavior, did confirm a significant increased risk for anemia and low hemoglobin, hematocrit and plasma zinc in the presence of pica (4). As there is a rapid resolution of pica when iron supplementation is started, even before normalization of the iron status itself, pica might rather be a consequence than a cause of iron deficiency (4, 14). A possible explanation is a decrease in dopaminergic transmission in presence of an iron-deficiency, leading to pica. This is suggested by an exacerbation of pica under therapy with neuroleptics (14, 24, 26).

Despite the direction of this relationship, it is important for physicians to be aware of the possibility of pica in a child being diagnosed with an unexplained iron-deficiency of iron-deficient anemia, especially in a high-risk population: children with underlying developmental disorders and children growing up in families with low socioeconomic status.

Little is known about a possible relationship between pica and blood levels of calcium and zinc (5, 7).

## Conclusion

In this case, the diagnosis of celiac disease with secondary deficient absorption of nutrients with the onset of iron deficiency anemia and presumably a subsequent presentation with xylopaghia, was made within one month after presentation, with a minimum of examinations. After confirmation of celiac disease with intestinal biopsies, the patient was put on a gluten free diet with good clinical evolution and resolution of pica.

Take home message: as pediatricians (in training), we are familiar with the common symptoms of celiac disease. However, this case underscores the need to consider the possibility of this disease in more vague physical complaints since it remains a fascinating yet little understood entity in which a high index of suspicion is necessary for diagnosis.

The authors have no conflict of interest to declare.

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# Case report: Plastic bronchitis in a previously healthy child

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## Keywords

Plastic bronchitis, pediatrics, pneumology, bronchoscopy, dyspnea

## Abstract

In endobranchial plastic bronchitis, firm casts develop in the bronchial tree, causing respiratory obstruction. It presents with unspecific symptoms and imaging, but can evolve into life-threatening respiratory distress. Although most often seen after cardiac surgery, previously healthy children are also at risk. Cast removal by urgent bronchoscopy is necessary to treat plastic bronchitis. There is currently no standard treatment strategy. Therapy includes cast removal by bronchoscopy, together with inhaled or instilled mucolytics and fibrinolytics for cast disruption when removal is difficult. We present the case of a two-year-old, healthy boy, who presented with symptoms of pneumonia. Rapid respiratory deterioration developed with need of high pressure ventilation. Chest X-ray initially showed an infiltrate rapidly evolving into complete obliteration of the left lung. Plastic bronchitis was diagnosed with an urgent bronchoscopy.

## Introduction

In plastic bronchitis (PB) firm and cohesive "plastic-like" branching casts develop in the tracheobronchial tree, hereby leading to potentially life-threatening respiratory obstruction. PB is a rare disease, developing in 4% of patients post Fontan surgery but with no known incidence or prevalence in non-cardiac surgery patients[1]. It occurs predominantly in patients after cardiac surgery or with underlying respiratory diseases.

Histologically two types of casts are seen: type I casts containing inflammatory cells and fibrin and type II casts which are hypocellular with predominantly mucin. Type I casts are most often seen in inflammatory lung disease, where type II casts are more often associated with congenital heart disease [2].

Initial presentation is often unspecific, mimicking other causes of respiratory distress like pneumonia or an asthmatic exacerbation. The most frequent symptoms are cough, dyspnea and wheezing. Life threatening respiratory distress can arise very quickly. Due to the rarity of the disease and the unspecific symptoms and radiological imaging, diagnosis is often missed.

In this case report, we present a previously healthy 2-year-old boy with PB which rapidly evolved into a medical emergency. Due to the high morbidity and mortality of PB, it is important to raise awareness of this rare condition.

## Case report

A two-year-old boy presented with mild cough and fever for four days and progressive dyspnea for two days. Medical history revealed neonatal early onset sepsis and a ventricular septum defect with spontaneous closure at follow up. He was otherwise healthy without respiratory pathology such as asthma. On examination a moderately sick child was seen with a fever of 39°C, tachypnea, a grunting breathing pattern and crepitations over the left lung on auscultation. His vital functions were stable with oxygen saturation of 100%. Community acquired pneumonia was suspected and IV antibiotics were prescribed. While placing the intravenous access, rapid respiratory deterioration developed in the course of minutes. Bag-valve-mask ventilation was started, followed by intubation which was hindered due to thick mucus obstructing the view and passage of the tube. After intubation, high pressures and $FiO_2$ were needed to ensure adequate oxygenation and ventilation. Chest X-ray showed an infiltrate in the left lung with correct tube placement (Figure 1A). On arrival at the pediatric intensive care unit two hours later saturation was only 88% despite $FiO_2$ of 1.0. X-ray showed a complete left lung atelectasis (Figure 1B) which persisted after endotracheal instillation with NaCl 0.9% and aspiration, and subsequent stepwise recruitment with PEEP (positive end expiratory pressure) up to 15 mmHg. Urgent flexible bronchoscopy (Olympus® BF type 3c40, Tokyo, Japan) was performed trough the endotracheal tube. A large viscous atelectatic plug which could not be aspirated was seen in the left main bronchus. In suspicion of plastic bronchitis, saline solution and 300 mg of acetylcysteine was installed: some firm casts were aspirated which showed the typical appearance of casts shaped in the pattern of bronchi (Figure 2). Instillation of 2500 units of the mucolytic dornase alfa into the left main bronchus was used to reduce mucosal viscoelasticity which facilitated removal of most of the bronchial casts. After additional instillation of 5 mg tissue plasminogen activator (tPA) in the left main bronchus, the remaining peripherally located casts were also removed. Control bronchoscopy showed mild edema of the bronchi, subsequent X-rays showed resolution of the atelectasis. The following hours were characterized by the development of ARDS (acute respiratory distress syndrome) possibly triggered by a combination of hypoxia, infection and inflammation. The child was sedated, paralyzed and ventilated with lung protective ventilation in prone position. Physiotherapy was performed twice daily. Inhalation therapy with 5 mg tPA four times daily was continued for 4 days. Intravenous clindamycin and cefotaxim were started. After 3 days clindamycin was stopped, cefotaxim was continued for 7 days. No bacterial neither viral pathogen could be isolated from repeated endotracheal cultures or nasopharyngeal aspirates. Cardiac ultrasound was normal, screening for immunological disorders or cystic fibrosis was negative. Pathological examination of the casts showed large amounts of inflammatory cells, mostly eosinophils. After 9 days he was successfully extubated. The child recovered completely without any complications. Our diagnosis was pneumonia complicated by type I PB.

## Discussion

PB is characterized by the formation of endobronchial casts, diagnosed when patients cough up cast material or when casts are found during bronchoscopy, as was the case in our patient. The casts are histologically classified as either inflammatory (type I) seen most often in inflammatory or infectious lung disease, or non-inflammatory (type II), the latter being more commonly found in children with underlying cardiac defects. Etiology remains unclear: in type 2 abnormal lymphatic drainage or elevated pulmonary venous pressure may lead to lymph fluid accumulation in the airways forming rubbery or caulk-like plugs. Dysregulated mucous secretion caused by inflammation might play a role in type 1 cast formation, especially in asthmatic or infectious patients [2].

Initial signs of PB are usually unspecific with cough, dyspnea and wheezing. The rapid development of severe respiratory distress should prompt further investigation. The condition might be mistaken for pneumonia, foreign body aspiration or status asthmaticus. In our case the moderately sick child presenting at the consultation room without marked respiratory distress developed life threatening respiratory collapse in a course of minutes. Although chest X-ray often shows the affected lung not expanding normally, this is not a diagnostic finding by itself. Imaging can show lung infiltrates, atelectasis or hyperinflation of the contralateral lung. As in our patient, initial radiological images can also show limited or no changes.

Most clinicians consider PB when respiratory symptoms are seen in children after cardiac surgery, mostly Fontan procedure. Structural heart disease and cardiac surgery are associated with an increased risk of PB (4-14%) [1]. Sickle cell anemia and asthma are other common underlying pathologies [3]. It can be triggered by (viral) infections, with influenza A being the most frequent pathogen. However, as shown in our case report, previously healthy children might also develop PB and evolve from being moderately sick to a life-threatening condition in a matter of hours. Prognosis is generally good except in cases associated with cardiac diseases in which mortality rates are up to 29% [4].

Currently there is no standardized treatment. Acute treatment is focused on either facilitating expectoration or removal of the casts to guarantee adequate ventilation and oxygenation. In some cases this can be achieved by physiotherapy with inhaled bronchodilators, corticosteroids or mucolytics to try to disrupt the cast formation. Due to its rarity and aspecific symptoms PB is often underdiagnosed in children, leading to a life threatening emergency when the casts obstruct the mayor airways. Urgent bronchoscopy by an experienced pediatric pulmonologist is essential, but often challenging due to the consistency of the casts which makes them too tick for suctioning and too soft to be taken out by forceps. Instilled or inhaled mucolytics such as acetylcysteine of dornase alfa can be used for disruption of the casts [2,5]. Inhalation of heparin or tPA can have a fibrinolytic action on the fibrin containing casts [6]. If unsuccessful direct administration of tPA in the airways might be helpful in disrupting the plastic like casts, making it possible to remove them [7]. Acetylcysteine, dornase alfa and tPA were subsequently installed in our patient to finally remove all casts. Multiple fibroscopic attempts are often needed, as was also the case in our patient.

Following the acute removal, further therapy depends on the underlying condition. Inhalation of hypertonic salt and use of low-dose oral azithromycin could reduce mortality by anti-inflammatory action [8]. In cardiac patients dynamic contrast magnetic resonance lymphangiography might visualize lymphatic abnormalities. In those cases targeted lymphatic duct embolization can be performed preserving the thoracic duct [10]. Sometimes heart transplantation is used to avoid repetitive cast formation and risk of asphyxia [9].

## Conclusion

PB is a rare disease with high morbidity and mortality, sometimes secondary to underlying diseases but often without predisposing factors. The non-specificity of its symptoms could lead to wrongful diagnosis of more common diseases as asthmatic exacerbation or pneumonia, further complicating its management. Any rapid respiratory deterioration, even in previously healthy children, should prompt the clinician to consider the diagnosis of PB. Initial unimpressive thoracic X-rays do not exclude it, as seen in our case. Urgent bronchoscopic removal of the casts is paramount, both diagnostically as therapeutically. To facilitate removal, inhaled mucolytics or fibrinolytics, or instillation of tPA might be necessary to disrupt the casts.

**Figure 1 :** Chest X-ray: A) after intubation and B) two hours later

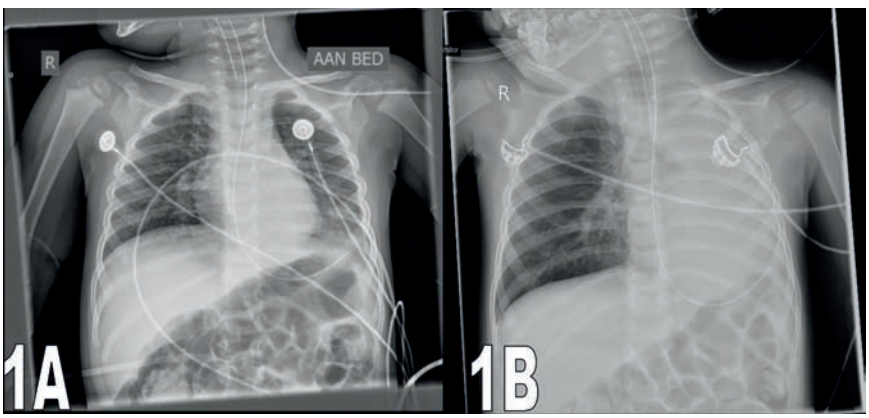
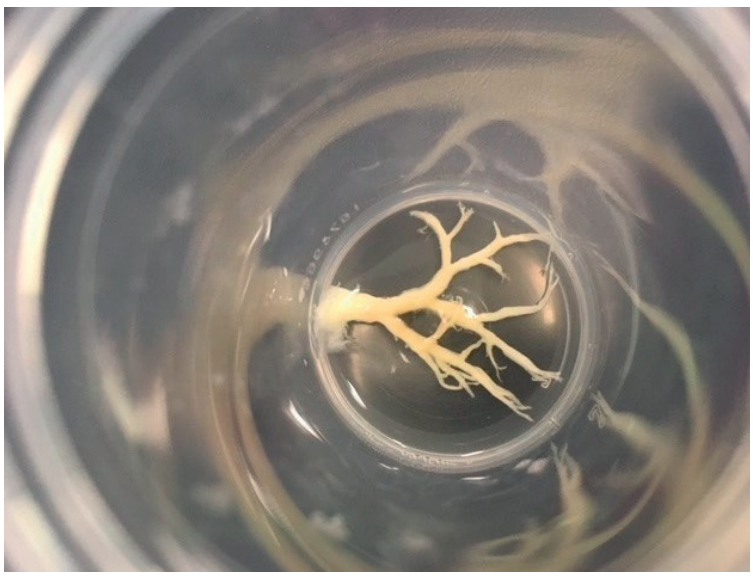



**Figure 2 :** One of the bronchial casts

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# Lenticulostriate infarction presenting as a central facial nerve palsy, caused by post-varicella arteriopathy in a 5-year-old girl

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## Keywords

Arterial stroke, post-varicella arteriopathy, facial nerve palsy

## Abstract

Cerebral vasculopathy leading to arterial stroke is a serious but uncommon complication of varicella-zoster-virus (VZV) infection. Diagnosis is based on a recent (less than one year) history of varicella infection, signs and symptoms of transient ischemic attack or stroke, and typical vascular anomalies on neuroimaging.

We report a case of post-varicella arteriopathy in a 5-year-old girl, who presented with a left-sided central facial nerve palsy and discrete hemiparesis after a brief period of occipital headache. Brain magnetic resonance imaging (MRI) showed an acute lenticulostriatal infarction on the right side, and magnetic resonance angiography revealed vasculitis of the right middle cerebral artery (M1) territory. Cerebrospinal fluid examination showed a positive PCR for varicella zoster.

Based on the diagnosis of VZV vasculopathy, methylprednisolone and acyclovir were administered, in addition to antithrombotic therapy using aspirin. In the weeks after this treatment there was a clinical improvement, and no new strokes occurred.

In addition to this case report, a short review of the literature was performed.

## Inleiding

Varicella is een frequent voorkomende kinderziekte die wordt veroorzaakt door het Varicella Zostervirus (VZV) en kent over het algemeen een mild verloop met typische vesiculaire rash. Ondanks het meestal benigne en zelflimiterende verloop kan deze infectie verantwoordelijk zijn voor heel wat complicaties, gaande van secundaire bacteriële huidinfecties tot ernstige respiratoire en neurologische sequelen.

Hoewel zeldzaam, wordt varicella geassocieerd met een breed spectrum aan neurologische complicaties waaronder ataxie, encefalitis, meningitis, transverse myelitis en ischemische cerebrovasculaire incidenten.

Deze acute ischemische incidenten zouden enerzijds het gevolg kunnen zijn van een tijdelijke trombofilie in kader van veralgemeende infectie, doch lijken voornamelijk te worden veroorzaakt door vasculopathie ten gevolge van de varicella zoster infectie.

Wij beschrijven een casus van een ischemisch herseninfarct ten gevolge van een postvaricella arteriopathie bij een 5-jarig meisje met als aanmeldingsklacht een discrete centrale nervus facialisparese links voorafgegaan door een kortdurend moment van occipitale hoofdpijn.

## Casusbeschrijving

Een 5-jarig meisje zonder relevante medische voorgeschiedenis wordt naar spoed doorverwezen door de huisarts omwille van een acuut ontstane afhangende mondhoek links. Enkele uren voorafgaand aan het opmerken van de afhangende mondhoek maakte zij een kortdurende episode van occipitale hoofdpijn door, welke spontaan verdween. Tijdens deze episode zou zij één maal hebben gebraakt. Ongeveer drie weken voordien had ze een varicella primo-infectie.

Bij klinisch nazicht wordt motorische uitval van de linker onderste gelaatshelft weerhouden, passend bij een centrale nervus facialisparese. Tevens wordt een zeer discreet hemibeeld links vastgesteld. Urgente CT-scan (computed tomography) van de hersenen zonder contrast in de eerste uren na onset van de symptomen is normaal. Bloedcontrole toont geen stijging van de inflammatoire parameters, normaal hemogram, normaal ionogram, normale nier- en leverfunctie. Lumbaalvocht toont geen leucorachie, protidorachie, noch glucorachie. Borrelia serologie is negatief. Varicella PCR (polymerase chain reaction) op cerebrospinaal vocht is positief.

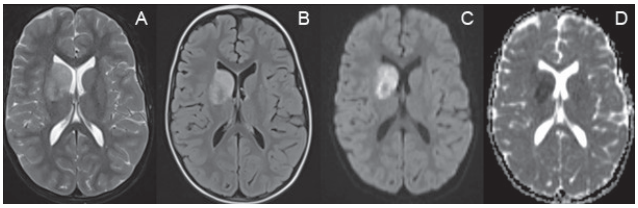
MRI (Magnetic resonance imaging) van de hersenen, uitgevoerd 72 uur na opname, toont significant oedeem met beperkt massa-effect ter hoogte van de nucleus caudatus, putamen, globus pallidus en crus anterior van de capsula interna, passend bij een lenticulostriataal infarct rechts (Figuur 1), waarvoor doorverwijzing naar een universitair centrum voor verdere diagnostiek en behandeling.

Daar wordt aanvullend een MRA (Magnetic Resonance Angiography) uitgevoerd die een onregelmatige aflijning van het M1 segment van de arteria cerebri media rechts toont, verdacht voor vasculitis (Figuur 2). Gezien de lokalisatie van het letsel en de positieve varicella PCR, meest waarschijnlijk passend bij post-varicella arteriopathie.

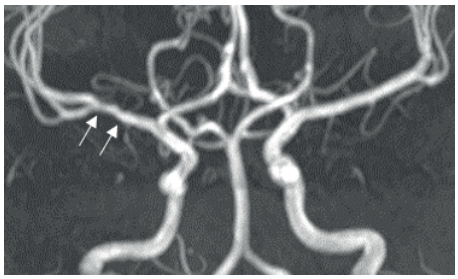
Een anti-inflammatoire behandeling onder de vorm van stootdosissen methylprednisolone 20 mg/kg intraveneus gedurende 5 dagen wordt gestart. De behandeling wordt verdergezet met prednisolone oraal aan een dosis van 2 mg/kg/d in 2 giften gedurende 1 maand, met nadien traag afbouwschema. Tevens werd behandeld met intraveneus aciclovir aan een dosis van 1500 mg/m2 per dag in 3 giften gedurende 2 weken, en werd als antitrombotische behandeling aspirine geassocieerd aan 3 mg/kg per dag. Controle beeldvorming na stopzetten van prednisolone toont afname van het oedeem en de zwelling in de geïnfarceerde zone regio met sequelaire gliose en volumeverlies (Figuur 3). Er is echter een persisterende onregelmatige aflijning van het M1 segment van de arteria cerebri media rechts, waarop de behandeling met aspirine wordt gecontinueerd.

Tevens werd een intensief, multidisciplinair revalidatieschema opgestart. Onder de ingestelde therapie doen zich geen nieuwe ischemische events voor en er is een gunstige klinische evolutie van de nervus facialisparese en het hemibeeld. Ook op herhaalde beeldvorming (na 1 en 3 maanden) wordt een gunstige evolutie gezien. Verdere controle beeldvorming wordt voorzien 5, 9, 15 en 27 maanden na de initiële presentatie.

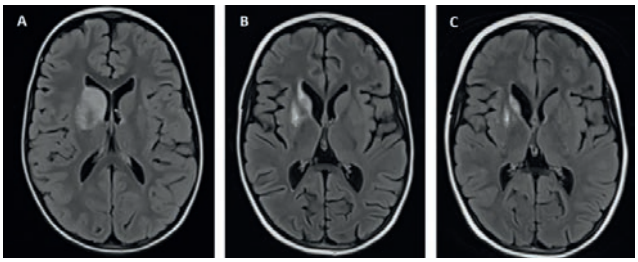
**Figuur 1 :** MRI, uitgevoerd 72 uur na opname, toont een uitgebreide infarctzone lenticulostriataal rechts, zichtbaar als een hyperintense zone op T2 fatsat (A) en FLAIR (B), en als zones van difussierestrictie op de diffusie gewogen opnames (B1000 (C) en ADCmap (D)).




**Figuur 2 :** Digitale MR substractie angiografie met onregelmatige aflijning van het M1 segment van de rechter arteria cerebri media.



**Figuur 3 :** Evolutie van de hyperintense zone op FLAIR beelden bij opname (A), na 1 maand (B) en na 3 maanden (C).




## Bespreking

Ischemische cerebrovasculaire incidenten:

Acute ischemische cerebrovasculaire incidenten (CVA) komen zelden voor bij kinderen. De incidentie wordt geschat op 1,3 tot 1,6/100.000 [1, 2] met een onverklaarde mannelijke predominantie, waarvan het grootste deel zich presenteert voor de leeftijd van 2 jaar. De meest frequente vorm van presentatie is focaal neurologische uitval (met voornamelijk hemiparese), doch ook convulsies en eerder diffuse neurologische afwijkingen zoals verminderd bewustzijn of non-specifieke symptomen zoals apneus, hoofdpijn en braken, komen voor [2].

De onderliggende etiologie verschilt sterk van deze bij volwassenen. Daar waar bij volwassen voornamelijk arteriosclerose als meest voorkomende oorzaak wordt gezien, lijkt bij kinderen een onderliggende arteriopathie de belangrijkste etiologische factor te zijn. Deze wordt bij ongeveer de helft (49%) van de kinderen met een acuut arterieel ischemisch incident op beeldvorming vastgesteld. De meest voorkomende arteriopathieën zijn dissecties (13%), post-varicella arteriopathie (12%), transiënte cerebrale arteriopathie (8%) en Moya-Moya disease (8%) [1].

Andere, minder frequent voorkomende etiologieën omvatten (congenitale) cardiale aandoeningen, waarbij de cerebrovasculaire incidenten vaak procedure gerelateerd zijn, protrombotische aandoeningen en ernstige acute ziektes zoals meningitis, sepsis en asfyxie [1, 2].

Varicella en post-varicella arteriopathie (PVA)

Het Varicella Zostervirus (VZV) behoort tot de Herpesviridae, een groep van neurotrope dubbelstrengige DNA (Deoxyribonucleic acid) virussen welke zeer frequent voorkomen en waartegen bij ongeveer 80-90% van de volwassenen antistoffen worden teruggevonden. De subgroep van de α-herpesvirussen (waaronder onder meer het herpes simplex type 1 en 2, maar ook het varicella zostervirus) heeft de uitzonderlijke eigenschap om naast het veroorzaken van een acute infectie, tevens nadien latent aanwezig te blijven in het zenuwweefsel en van daar uit te reactiveren [3, 4]. Het VZV is het enige gekende humane virus met de mogelijkheid tot replicatie in de arteriële bloedvaten, waarna het zich zowel via de sensoriële zenuwbanen als de bloedvaten kan verspreiden [5].

Varicella primo-infectie is een zeer frequent voorkomende en uiterst besmettelijke aandoening binnen de pediatrische populatie met een piekincidentie rond de leeftijd van 4-5 jaar. De primo-infectie veroorzaakt een typisch papulovesiculair exantheem dat spontaan geneest binnen de 7-10 dagen. Over het algemeen kent de primo-infectie een eerder mild en zelflimiterend verloop, doch ernstige complicaties kunnen, voornamelijk (maar niet uitsluitend) binnen hoog risicogroepen zoals neonaten, immuungecompromiteerden en adolescenten, voorkomen. De meest frequent voorkomende complicaties zijn ernstige bacteriële surinfecties van de huidletsels en (pleura)pneumonieën, maar ook minder gekende neurologische complicaties zoals meningo-encefalitis en cerebellitis kunnen voorkomen [3, 4].

Varicella is tevens geassocieerd met een verhoogd risico op ischemische cerebrovasculaire accidenten bij kinderen. In de eerste zes maanden na het doormaken van een varicella infectie zou het risico op een ischemisch CVA 4-6 maal hoger liggen dan in de standaard populatie [6-8]. Ondanks deze risicostijging blijft het absolute risico uiteraard beperkt, gezien de lage baseline prevalentie in de pediatrische populatie. De feitelijke incidentie van deze ernstige complicatie is daarom moeilijk te bepalen, doch wordt geschat op ongeveer 1/15.000 pediatrische varicella patiënten [6, 9]. Post-varicella ischemische CVA's kunnen enerzijds worden veroorzaakt door veralgemeende infectie met geassocieerde trombofilie, doch lijken voornamelijk gerelateerd te zijn aan een VZV geassocieerde arteriopathie, ook post-varicella arteriopathie (PVA) genoemd.

Mogelijks wordt de feitelijke incidentie van PVA onderschat, en dit door een aantal diagnostische problemen en afwezigheid van eenzijdige diagnostische criteria. Enerzijds wordt, in geval van een CVA, vaak geen varicella serologie of PCR bepaald op cerebrospinaal vocht [8] en zijn er meerdere arteriopathieën die het klinisch beeld, met de typische vasculitislocalisaties van een PVA kunnen nabootsen. Anderzijds zijn de bevindingen op cerebrospinaal vocht niet steeds conclusief. Zo is er, bij ongeveer 1/3 van de PVA patiënten [10], geen pleiocytose aanwezig, kan het virus slechts zeer zelden worden gekweekt en is virale PCR op cerebrospinaal vocht onvoldoende sensitief met negatieve resultaten bij tot 70% van de patiënten met sterk klinisch vermoeden van PVA [8]. Dit komt vermoedelijk door het laattijdig optreden van neurologische symptomen (soms maanden na de primo-infectie), waarbij men weet dat de PCR voor viraal DNA reeds 1-3 weken na het optreden van de acute infectie negativeert [6]. Antilichaam diagnostiek met detectie van intrathecale productie van VZV IgG (Immunoglobuline G) is betrouwbaarder in geval van laattijdige diagnostiek en vasculopathieën, en is tot 100% sensitief gebleken in studies bij volwassen, hoewel er nog onvoldoende data ter beschikking zijn voor de pediatrische populatie [6, 10].

PVA komt over het algemeen voor bij jonge, voorheen gezonde kinderen binnen het eerste jaar na doormaken van een varicella-infectie, met het grootste risico binnen de eerste zes maanden [9]. De meest typische klinische presentatie bestaat uit hemiparese, doch een breed spectrum aan neurologische afwijkingen is mogelijk en is uiteraard afhankelijk van de plaats van de stenose [8, 9, 11].

Arteriële stenoses ten gevolge van post-varicella arteriopathie zijn meestal unilateraal en komen typisch voor in de supraclinoïdale arteria cerebri interna (ICA), het A1 of A2 segment van de a. cerebri anterior en het M1 en M2 segment van de arteria cerebri media [4, 9, 11, 12]. De infarctzones worden voornamelijk gezien in de gebieden die worden bevloeid door de lenticulostriatale takken van de hiervoor vermelde arterieën, zoals de basale ganglia en capsula interna [8, 9, 11, 12]. Een arterieel infarct in één van bovenstaande gebieden, in combinatie met een recent (minder dan twaalf maanden geleden) doorgemaakte varicella-infectie en in afwezigheid van andere risicofactoren voor trombose, is sterk suggestief voor PVA.

Normale radiologische bevindingen bij initiële presentatie lijken de diagnose van post-varicella arteriopathie echter niet uit te sluiten. Zo werden in een retrospectieve studie bij 23 kinderen met typische PVA, bij 1 patiënt geen afwijkingen vastgesteld op de initiële MRI, en was de angiografie bij 4 anderen eveneens normaal. Het is daarom aangewezen om, bij verdenking van PVA met normale initiële beeldvorming, deze te herhalen aangezien

progressie van de stenose een verhoogd risico geeft op recurrente CVA of TIA's (Transient Ischemic Attack) [12].

De onderliggende pathogenese van deze VZV geassocieerde arteriopathie is tot op heden nog niet volledig uitgeklaard. Hoewel het aantonen van varicella zoster virus in de wand van de aangetaste arteriën bij patiënten die zijn overleden aan de gevolgen van PVA meest waarschijnlijk wijst op een transaxonale migratie van het virus vanuit de craniale ganglia naar de grotere arteriën, waar virusreplicatie zorgt voor inflammatie met endotheliale schade en bijgevolg trombose [4, 7, 9, 12]. Deze hypothese wordt ondersteund door histologische studies waarbij virale partikels en een lymfocytair infiltraat met destructie van de lamina elastica interna werden aangetoond [8].

Varicella zoster virusstammen vertonen onderling weinig verschil in virulentie, wat suggereert dat een onderliggend defect in het immuunsysteem van de patiënten vermoedelijk een rol speelt in het ontwikkelen van ernstige ziekte en sequelen. Hoewel het reeds gekend is dat patiënten met een onderliggende immuundeficiëntie een verhoogd risico hebben op het ontwikkelen van een ernstige varicella-infectie, lijken de eerder beschreven sequelen echter vaak voor te komen bij overigens gezonde kinderen. Dit leidt tot de hypothese dat een specifieke afwijking van de VZV immuniteit betrokken is bij het ziekte proces. Zo werd in een recente studie een mogelijks verband aangetoond met onderliggende mutaties in het POLR3A en POLR3C gen, welke coderen voor RNA polymerase III en zo leiden tot een verstoorde interferonproductie met invloed op de virusreplicatie in geval van een VZV infectie [13].

Bij de meeste kinderen met typische PVA kent de vasculaire stenose een monofasisch verloop, met occasionele progressie tot zes maanden na de eerste presentatie, gevolgd door een regressie over een periode van ongeveer twee jaar zonder restenose bij follow-up [12]. De snelle progressie en reversibiliteit van de arteriële stenose wordt onderlijnd door de afwezigheid van collaterale bloedvatvorming [12], doch in de literatuur wordt ook klinische beterschap in afwezigheid van, of met incomplete radiologische regressie, beschreven [8]. Aangezien verdere progressie van de arteriële stenose, meer dan zes maanden na de initiële presentatie atypisch is voor PVA, dient in dat geval een alternatieve diagnose (zoals onderliggende vasculopathie (vb moyamoya syndroom, dissecties, Transiënte focale cerebrale arteriopathie …), hematologische maligniteit, coagulopathie, cardiale of metabole aandoeningen) te worden overwogen [9].

Bij ongeveer 1/3 van de patiënten treden echter, gedurende de eerste maanden na initiële presentatie, recurrente CVA/TIA op, ondanks antitrombotische therapie. Dit heeft vermoedelijk te maken met acute arteriële beschadiging en progressie van de stenose gedurende de eerste maanden [8, 9, 12]. Eenmaal de periode van regressie van de vasculaire stenose zich inzet, wat kan worden opgevolgd via herhaalde beeldvorming, doen zich slechts zeer zelden nog TIA's of CVA's voor.

Tot op heden is er geen eenduidig therapieprotocol voor de behandeling van VZV geassocieerd CVA bij kinderen. Corticoïden, met als achterliggende rationale onderdrukking van de inflammatie ten gevolge van virale replicatie in de bloedvatwand, worden frequent voorgesteld. In deze casus werd gekozen voor behandeling met corticoïden gezien de acute presentatie van de klachten, het duidelijk aanwezige oedeem op beeldvorming en de (nog) positieve PCR op het cerebrospinal vocht. Tot op heden zijn er echter geen studies die het gunstige effect van hoge dosissen corticoïden op de uiteindelijke outcome kunnen aantonen [9, 11]. Bovendien is het mogelijk dat, gezien het immunosuppressief effect, toediening van corticoïden de virale replicatie net zou kunnen bevorderen. Vaak wordt een antivirale behandeling onder de vorm van aciclovir opgestart, doch gezien het vaak lange interval tussen infectie en optreden van de neurologische symptomen is het effect van deze behandeling vermoedelijk ook eerder beperkt [8].

Verschillende studies tonen bovendien een spontaan gunstig verloop van de vasculaire letsels en neurologische symptomen, ongeacht de therapie [5, 9].

Antitrombotische therapie onder de vorm van acetylsalicylzuur lijkt, gezien het risico op recurrente CVA, aangewezen. Recente studies tonen namelijk een daling van het risico op recurrente ischemische cerebrovasculaire accidenten ten gevolge van een arteriopathie bij kinderen onder behandeling met acetylsalicylzuur. De optimale duur van de antitrombotische behandeling is nog onduidelijk, hoewel het aannemelijk lijkt om de behandeling verder te zetten tot regressie of stabilisatie van de vasculaire letsels [8, 11]. Tot op heden zijn er geen eenduidige richtlijnen beschikbaar omtrent de optimale frequentie van beeldvormig gedurende de follow-periode. In bovenstaande casus werd ervoor gekozen om, in de eerste opvolgingsfase, frequent beeldvorming (per 2 maanden) onder de vorm van MR hersenen te voorzien teneinde vroegtijdige complicaties en respons op de initiële behandeling te kunnen evalueren. Nadien kan dit interval worden uitgebreid tot een 6-tal maanden (of uiteraard sneller bij kliniek), om de evolutie van de bloedvatwandafwijkingen op te volgen en daarop de duur van de antitrombotische behandeling te baseren. Bij een gunstige evolutie met verdwijnen van de typische vasculitisletsels zal verder jaarlijkse opvolging worden voorzien.

De neurologische outcome van PVA is over het algemeen gunstig. Toch worden bij tot 70% van de patiënten, na een gemiddelde follow-up van twee jaar, persisterende neurologische uitvalsverschijnselen gerapporteerd [9, 11]. Deze zijn meestal mild en bestaan voornamelijk uit persisterende, meestal discrete hemiparese, maar ook gedragsproblematiek zou voorkomen bij tot ongeveer 1/3 van de patiënten [9]. Andere, meer uitgesproken neurologische complicaties zoals bijvoorbeeld progressieve hemidystonie ten gevolge van infarctering in de basale ganglia kunnen echter ook voorkomen, dus follow-up op langere termijn in een aangepaste revalidatiesetting is noodzakelijk.

## Besluit

Een ischemisch cerebrovasculair accident ten gevolge van arteriopathie is een zeldzame, doch welbeschreven complicatie na het doormaken van een varicella-infectie. Verschillende studies tonen een 4 tot 6 maal hoger risico op ischemisch CVA bij kinderen in de eerste zes maanden na het doormaken van een varicella primo-infectie.

De diagnose van PVA dient te worden overwogen bij alle, voorheen gezonde kinderen, die zich presenteren met een acuut ischemisch accident binnen het jaar na doormaken van een acute varicella infectie, en in het bijzonder bij infarctering ter hoogte van de basale ganglia en stenose van de supraclinoïdale arteria cerebri interna (ICA), het A1 of A2 segment van de arteria cerebri anterior of het M1 en M2 segment van de arteria cerebri media.

Idealiter bestaat de diagnostische work-up uit MRI, MRA en analyse van het cerebrospinaal vocht voor detectie van VZV antistoffen en, hoewel minder sensitief, VZV DNA.

Verdere uitwerking met opsporen van andere, mogelijks behandelbare risicofactoren voor arteriële stroke (zoals cardiale afwijkingen, auto-immune- of protrombogene aandoeningen) is steeds noodzakelijk, gezien de diagnose van PVA vooralsnog eerder een uitsluitingsdiagnose blijft.

De pathogenese van PVA is tot op heden onvoldoende duidelijk, doch zou vermoedelijk berusten op een combinatie van zowel infectieuze als inflammatoire mechanismen. Het effect van behandeling met corticoïden of antivirale therapie op de uiteindelijke uitkomst werd nog niet aangetoond en dient verder te worden onderzocht. Antitrombotische behandeling door middel van acetylsalicylzuur lijkt effectief in de preventie van recurrente CVA, doch de optimale duur van de behandeling blijft ter discussie staan.

Gezien het monofasisch verloop met spontane regressie over een periode van twee jaar en minimaal risico op recurrente stroke eenmaal de regressie van de vasculaire stenose zich instelt, zou herhaalde beeldvorming niet mogen ontbreken in de follow-up, waardoor de duur van de antitrombotische therapie eventueel kan worden afgestemd op de radiologische bevindingen.

**Conflicts of interest:**

Er zijn geen conflicts of interest voor elk van de hierboven vermelde auteurs.

**Tabel**

**Differentiaal diagnose in geval van arteriële (en recurrente) stroke bij kinderen.**

Hematologische aandoeningen*

- Protrombotische aandoeningen (Gestoorde APC resistentie, factor V Leiden, hyperlipoproteïnemie(a), proteïne C/S deficiëntie, antitrombine III deficiëntie, antifosfolipiden syndroom, diffuse intravasculaire coagulatie)
- Ferriprieve anemie, polycythemie, thrombocytose
- Hemoglobinopathieën (sikkelcelanemie)
- Hematologische maligniteit

Cardiale afwijkingen*

- Congenitale cardiopathie
- Iatrogeen
- Endocarditis/myocarditis
- Ritmestoornissen

Vasculopathie

- Transiënte focale cerebrale arteriopathie (FCA/TCA)*
- Post-varicella arteriopathie
- Vasculitis (Primaire angiitis van het centraal zenuwstelsel (PACNS), Systeemlijden)*
- Moyamoya vasculopathie*
- Fibromusculaire dysplasie *

Metabole en bindweefselaandoening*

- Mitochondriale aandoeningen (MELAS)
- Bindweefselziekten zoals syndroom van Marfan of Ehler-Danlos
- Lysosomale afwijkingen zoals ziekte van Fabry
- Stoornissen in ureumcyclus (OTC deficiëntie)
- Aminoacidurie, glutaaracidemie type I

Infectie

- Pharyngitis, sinusitis, otitis media, mastoiditis
- Meningitis
- Sepsis
- Varicella zoster virus, parvovirus, neuroborreliose, …

Aandoeningen van hoofd en hals

- Trauma
- Maligniteit
- Intracraniële arterioveneuze malformities*
- Neurochirurgie
- Carotisdissectie*

*Verhoogd risico op recurrente strokes.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# Case report of a boy with autism who refuses to eat

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## Keywords

scurvy, vitamin C, autism, restrictive diet, pediatric

## Abstract

Scurvy is caused by prolonged vitamin C deficiency. It has a variable disease spectrum with bone, dental, gingival, hematological, dermatological and systemic manifestations. Pediatric scurvy is rare and therefore seldom suspected. We report a case of a 3 year old boy with autism, presenting with refusal to walk, fatigue and bleeding symptoms. A broad differential diagnosis was considered, including non-accidental injury. Diagnosis was finally made based on diet history, radiological findings and symptoms resolution with vitamin C substitution. Awareness of the disease, especially in certain risk groups, can facilitate early diagnosis, avoiding invasive diagnostic exams and hospitalization.

## Introduction

A prolonged vitamin C (ascorbic acid) deficiency results in scurvy, which is characterized by a variety of hematological (bleeding symptoms, anemia), dermatological (hyperkeratosis, petechiae, ecchymosis), dental (gingival bleeding, swelling), bone (osteopenia, epiphyseal bone destruction, subperiosteal hemorrhage, bone pain), muscle (myalgia, muscle weakness) and systemic symptoms (fever, lethargy). It was described as early as in ancient Egypt and has long been the main cause of death in sailors [1–4]. Since the link between dietary intake of vitamin C and scurvy was discovered by Sir James Lind in 1753, prevalence has decreased importantly and the disease became relatively unknown, especially in developed countries [4,5].

As the presenting clinical picture is heterogeneous, a broad differential diagnosis has to be ruled out, leading to a delay in diagnosis and treatment.

By presenting a case of pediatric scurvy in a boy with autism spectrum disorder, we want to raise awareness for risk groups, highlight the importance of a thorough history record and enhance recognition of symptoms to facilitate early diagnosis and management.

## Case Report

A 3-year old boy was referred to our hospital, for the evaluation of progressive walking difficulties since 3 weeks. He had been treated with non-steroidal anti-inflammatory drugs for several days, because of working diagnosis of muscle strain, without positive effect.

He presented to our emergency department with muscle weakness, fatigue and a tendency to fall. There was no history of trauma or infection. At the age of 2.5 years, he had been diagnosed with autism spectrum disorder, after being referred for delayed motor and language development and a progressive selective eating pattern. He did not receive any vitamins or food supplements.

Clinically, he had normal tendon reflexes and a subtle symmetrical muscle weakness of the lower limbs (4/5). He was unable to walk and stand up from a seated position. His weight was 15.2kg (-1.0 SD) and length was 106 cm (-0,1SD). On further examination, an anal fissure and a sacral hematoma were seen. Upon these clinical findings, parents reported him to have severe constipation.

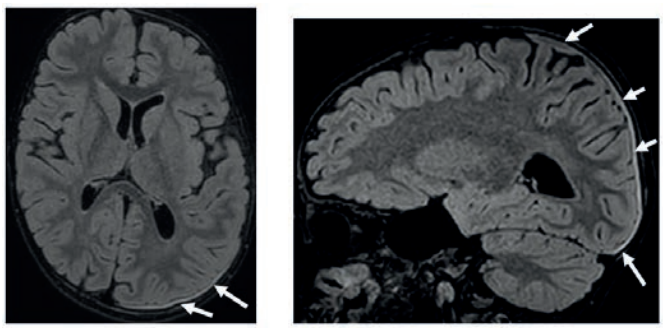
Investigations prior to hospital admission, including radiological imaging of the lower extremities, ultrasound of the hip and CT of the skull, all were reported negative. Complete blood count, ionogram, creatine kinase and markers of inflammation were evaluated. The sedimentation rate was elevated (40 mm/h [≥ 1 - ≤ 10mm/h]) and an iron deficiency anemia (Hemoglobin 8.0g/dl [11.5 - 13.5g/dl], mean corpuscular volume 57.7 fL [75.0 - 87.0], iron 17µg/dl [65 – 165 µg/l], ferritin 15µg/l [30 – 400µg/l],) was found.

He was admitted for further investigations. Because of elevated inflammatory parameters, a central inflammatory or auto-immune disease had to be excluded. Cerebrospinal fluid was negative, including antibodies against Mycoplasma, Epstein Barr, Cytomegalovirus and Borrelia. Antiganglioside and paraneoplastic antibodies came back negative as well.

Whereas an MRI (Magnetic Resonance Imaging) of the spine was normal, MRI of the brain showed a subacute subdural hematoma (figure 1). The latter finding together with the anal fissure, sacral hematoma and unexplained neurologic presentation, led to a suspicion of non-accidental craniocerebral trauma, which was further investigated.

Fundoscopy was normal. A full body radiological examination showed fractures of the right humerus and distal radius, but also multiple metaphysic abnormalities were seen. Following expert radiological advice, this atypical radiological image, described as alternating dense metaphyseal lines and metaphyseal lucencies, led to an extensive further diagnostic work-up, as described in Table 1. The abnormalities were already visible on the radiological images prior to admission, but were all described as normal. Gum bleeding

**Figure 1 :** MRI of the brain showing the subacute subdural hematoma



was noted during admission, after which it became clear that the boy was known to have frequent gum and nose bleeds over the past months.

Dietary history revealed that the patient's diet had consisted of milk, chocolate paste, bread and cookies over the last several months (see table 2). Dietary work-up showed an insufficient intake of vitamin E, C, D, A, B6 and zinc. Substitution of vitamin C (150mg/day) and vitamin D (2000IU/day) was started. He was also treated with 6mg/kg/day elementary iron.

Biochemical evaluation revealed a severe vitamin C deficiency (undetectable [0.5 - 1.5 mg/dl]), low levels of vitamin A (275µg/l [300 – 650µg/L]) and a vitamin D deficiency (25-OH-vitamin D 6.7µg/l [11.0-60.0 µg/l]). At that point, partial recovery of muscle strength was already seen. The patient was discharged from the hospital and followed up by a multidisciplinary team, comprising a hematologist, a neurologist and a nutritional team for diet adjustment. Complete resolution of symptoms was seen after 2 months. Plasma vitamin C level was normalized at that point (1.4mg/dl).

**Table 1:** Work up of the differential diagnosis in our case, based on the atypical radiological image of multiple metaphysic abnormalities.

| DIFFERENTIAL DIAGNOSIS | PERFORMED EXAMINATION | RESULTS |
|---|---|---|
| Non accidental injury | Full body radiography<br>Ophthalmologic exam<br>MRI brain | Multiple fractures<br>Normal<br>Sub acute subdural hematoma |
| Rickets | PTH, Calcium, phosphate, alkaline phosphatase<br>Vitamin D | Normal<br><br>Low 25-OH-vitamin D |
| Leukemia | Blood smear<br>Peripheral blood count | Normal<br>Microcytic anemia<br>Normal platelets<br>Normal white blood cells |
| Nutritional problems | | |
| Copper deficiency | Serum level copper | normal |
| Hypervitaminosis A | Serum level vitamin A | low |
| Scurvy | Serum level vitamin C | Undetectable |
| Multifocal osteomyelitis | Inflammation<br><br>Bone scintigraphy | Low CRP and sedimentation ratio<br>Normal |
| Menkes syndrome (intermediate form) | Genetics<br>Lactate<br>Copper metabolism | Not performed<br>Normal<br>Normal copper, high ceruloplasmin |
| Prostaglandin therapy | | Did not receive prostaglandins. |
| Metabolic disease (metaphysic dysplasia)<br>Organic aciduria<br>MPS, oligosacharidose mucolipidose<br>Wilson disease<br>Osteogenesis imperfecta | Expert metabolic advice<br><br>Urine organic acid<br>Normal metabolic tests<br><br>Ceruloplasmin<br>Genetics | <br><br>Normal<br><br><br>Normal<br>Not performed |

Abbrevations: CRP c-reactive protein ; MPS Mucopolysacharidose; PTH parathyroid hormone

**Table 2:** Summary of the dietary anamnesis.

Calculated energy intake showed a daily intake of 1433 kcal per day (recommendation: 1175kcal per day). The dietary history revealed an insufficient intake of vitamin E, D, C, A, B6 and zinc.

| Meal | Products | Quantity |
|---|---|---|
| Breakfast | Semi skimmed chocolate milk<br>White or brown bread<br>Chocolate paste | 600 ml<br>3 or 4 slices |
| Snack | Nic nac cookies or other | 1 portion, not always |
| Lunch | Semi skimmed chocolate milk | 330 ml |
| Snack | Nic nac cookies or other<br>Semi skimmed chocolate milk | 1 portion, not always<br>330ml |
| Diner | White or brown bread<br>Vegetable soup<br>Chocolate paste or minced meat | 1 or 2 slices<br>2 or 3 times a week |
| Bedtime | Semi skimmed chocolate milk | 330ml |

## Discussion

This case report emphasizes the risks of a restricted diet, which can be seen in children with autism spectrum disorder and possibly lead to nutritional deficiencies. Meta-analysis of eating patterns in this clinical population showed that 48-89% of these children have feeding problems mainly characterized by a restricted diet[6]. Multiple cases of autistic children with scurvy have been described in the literature[2,3,5,7]. In this group of patients, regression in behavior as an effect of scurvy have been described, as was also seen in our case.

Whereas Golriz et al published a series of 32 children with scurvy, who all had an underlying medical condition, cases of dietary deficiency in otherwise healthy children have been described[3,5]. Combined nutritional deficits are commonly seen (thiamine, pyridoxine, cobalamin and vitamin D)[1,3].

Due to poor knowledge of the condition and significant overlap of symptoms with more frequent illnesses such as osteomyelitis, septic arthritis, leukemia, etc., several cases have been published with a delayed diagnosis, after many unnecessary and often invasive investigations. It therefore remains necessary to call for attention to this disease and to ask for a precise dietary history especially in the known risk groups (table 3)[1,7].

**Table 3:** Pediatric risk groups, prone to develop scurvy.

| Reduced intake of vitamin C | Poor absorption |
|---|---|
| Neurodevelopmental delay [5] | Severe gastritis/enteritis (ex. Inflammatory bowel disease, NEC)[8] |
| Autism spectrum disorder [5] | Intestinal GVHD[8] |
| Obesity [3] | Gastric bypass surgery [3] |
| Multiple food allergy[9] | Drug interactions: Phenobarbital [3,8] |
| Fructose intolerance[5] | Chemotherapy (nausea and vomiting)[1,5] |
| Low socioeconomic status [3] | |
| Eating disorders [3] | |
| Chemotherapy [5] | |
| Very picky eaters [3] | |
| Diet of sole boiled milk as infant [8] | |
| Tube feeding as sole nutritional source – when not properly stored (decrease of vitamin C content) [3] | |
| Dysfagia [5] | |
| | |
| Iron overload due to multiple transfusion (sickle cell disease or thalassemia) – causes acceleration of vitamin C catabolism[5] | |

Abbrevations: NEC necrotizing enterocolitis; GVHD graft versus host disease

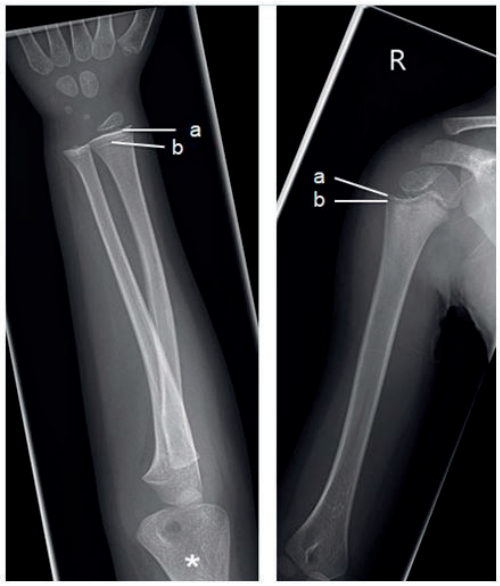
Standardised diagnostic criteria for scurvy are lacking. Diagnosis is based on a clinical suspicion, dietary history and treatment response. A low serum vitamin C level is diagnostic, however, serum levels do not reflect body storage well and are influenced by recent ingestion of ascorbic acid[1,8]. Mild signs of inflammation with an elevated sedimentation rate can be seen, as well as iron deficiency anemia (by reduced absorption of iron, hemorrhage and coexistent hematopoietic nutrient deficiencies)[2,7].

In case of prolonged insufficient vitamin C intake, there is a period of several weeks to months before symptoms occur. Early symptoms include fatigue, anorexia, failure to thrive, irritability, mood changes, follicular hyperkeratosis, bone pain, weakness, bruising, gingival swelling and bleeding[2]. Advanced and more severe symptoms include subperiosteal and cerebral hemorrhage, pseudoparalysis, infection and convulsions. Diffuse spontaneous bleeding and heart failure can eventually lead to death[1,8].

Musculoskeletal manifestations as the presenting symptom are common in children, as was also the case in our patient[2]. The involvement is typically symmetrical[1]. Subperiostal hemorrhages cause bone pain with limping and refusal to walk[3]. Although typical radiologic findings are well defined in literature (see figure 2), early subtle radiological signs such as osteopenic bone are non-specific and often overlooked. Underdiagnosis of the disease due to radiologists' unfamiliarity with the imaging findings of the disease has been reported[2,3,5]. Since abnormal metaphyseal findings that are described in scurvy, can simulate metaphyseal fractures, non-accidental trauma has to be ruled out.

**Figure 2 :** Radiologic characteristics described in scurvy 1 Signs that were seen in our case are marked on the picture.

- Ground glass appearance of the bone / osteopenia (*)
- Pencil-thin cortices
- Fraenkel's Line – White dense line of metaphyseal calcification (a)
- Trummerfeld zone – adjacent radiolucent band (b)
- Pelkan spur – lateral metaphyseal breaking/fracture
- Wimberger sign – central rarefaction with peripheral calcification of epiphyses




This heterogeneous clinical picture can be explained by the multiple biochemical reactions in which vitamin C plays a role[1]. Its main function is the synthesis and stabilization of collagen and connective tissues in skin, cartilage, bone, dentine and blood vessels[1]. Deficiency leads to fragility of these tissues which results in diffuse bleeding symptoms, frizzy hair, poor wound healing and bone deformation[3]. Furthermore, vitamin C is involved in the metabolism of neurotransmitters (dopamine, norephinephrine), cholesterol (formation of steroid hormones and bile acids) and prostaglandins and acts as a co-factor in de synthesis of carnitine, important in the energy metabolism and muscle function[1,3,7,8]. Important anemia in scurvy patients is seen because vitamin C is used in the conversion of folic acid to folinic acid, which enhances formation of red blood cells and it also reduces iron to its better absorbable ferrous state[1,3].

Humans depend on the nutritional intake of vitamin C as they lack the enzyme l-gulonolactone oxidase to convert glucose into ascorbic acid[1,3]. The daily recommended intake of vitamin C is 15-45 mg for children of 1 to 13 years old and 65-75mg for children of 14 to 18 years old[7]. Fruits (citrus fruits, currants) and vegetables are the main sources. Importantly, dietary products can lose their vitamin C content because of storage or cooking[3].

In case of nutritional deficiency, vitamin C stores have to be quickly replenished in order to prevent further clinical deterioration. However, treatment regimens are not standardized. Therapeutic dosages described in the literature range from 100-300mg/day for children[1,2]. The rate of absorption when orally ingested is dose-dependent: the lower the dose, the higher the absorption. Studies revealed that uptake is most efficient when 100mg per day of vitamin C is administered[3]. Recommendations for duration of therapy vary from 1 to 3 months or until clinical signs have resolved. In the meantime, adequate dietary intake of ascorbic acid is reintroduced. Rapid recovery of symptoms is typically seen once supplementation is started and this evolution can help to confirm the diagnosis. In the meantime, analgesics can be used to treat symptoms of pain. Complete resolution of symptoms is expected.

## Conclusion

Pediatric scurvy is currently an uncommon disease. In children with malabsorption or restricted diets, presenting with musculoskeletal symptoms, it should be kept in mind and a detailed clinical and dietary history needs to be performed before extensive investigations are done. Early recognition facilitates the simple treatment of this potentially life threatening disease and rapid recuperation once treatment has started is seen.

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# The outcome of posterior reversible encephalopathy syndrome (PRES) in children: a systematic review and case-report of a 16-year old girl with systemic lupus erythematosus and PRES

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## Keywords

PRES; children; clinical outcome; neurological outcome, sequelae

## Abstract

Background: Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical and radiological picture characterized by neurological symptoms and radiological abnormalities with a predominance in the posterior region of the brain. Case histories suggest persistent neurocognitive problems are possible, but the outcome in children has not yet been extensively described. Method: a systematic review of the literature with specific attention to the neurological and radiological outcome of PRES in children, supplemented with a case description from our own pediatric tertiary center. Results: A total of 410 children with PRES were reported. Full clinical recovery was seen in 78%. Neurocognitive problems were described in 5 children, but no one was formally tested. Regarding radiological outcome, normalization of the abnormalities was seen in most cases, but persistent lesions were seen in 22% with follow-up imaging between 2.5 days and 42 months after the acute event. Conclusion: Not all children fully recover after PRES. Detailed information on the neurocognitive outcome is lacking. Prospective studies will be needed in the future to assess the importance of minor sequels on neurocognitive level in more detail.

## Introductie

In 1996 werd Reversible Posterior Leukoencephalopathy Syndrome (RPLS) voor het eerst beschreven door Hinchey et al. als een reversibel klinisch-radiologisch beeld. Tegenwoordig is het beter gekend onder de naam Posterior Reversible Encephalopathy Syndrome of afgekort PRES[1]. Het ontstaat meestal acuut of in de loop van enkele uren en wordt klinisch gekenmerkt door neurologische symptomen, zoals hoofdpijn, visusstoornissen (bijvoorbeeld diplopie, gezichtsvelduitval of corticale blindheid), veranderingen in het bewustzijn (verwardheid tot coma) en epilepsie. De intensiteit en ernst van de klinische manifestaties varieert enorm en natuurlijk hoeven niet alle symptomen aanwezig te zijn; de aanwezigheid van één symptoom is echter wel zeldzaam en moet doen denken aan een andere diagnose[2-4]. Nucleaire Magnetische Resonantie (NMR) van de hersenen toont bij PRES typisch hyperintense letsels op FLAIR en T2-gewogen beelden. De afwijkingen zijn voornamelijk (sub)corticaal en gelokaliseerd in de pariëtale en occipitale cortex[5].

Zoals de naam PRES doet vermoeden, is het meestal een reversibele aandoening, doch niet zelden is er permanente neurologische schade en in een aantal gevallen kan het zelfs tot de dood leiden[6-9]. Door sommigen wordt dan ook geopteerd om de naam te veranderen naar 'Potential Reversible Encephalopathy Syndrome'[8].

De meeste studies omtrent outcome beschrijven echter resultaten bij volwassenen. Over kinderen wordt de laatste jaren stilaan meer gepubliceerd, maar vooral in case-reports en kleinere case-series met uiteenlopende settingen. Daarenboven is er zeer weinig gekend over het neurocognitief functioneren na PRES[6-9].

Hier beschrijven we een casus van een 16-jarig meisje dat normaal secundair onderwijs volgde en na het doormaken van PRES concentratie- en gedragsproblemen vertoonde. Aan de hand van een systematische review willen we de outcome van PRES bij kinderen beter in kaart brengen.

## Materialen en Methode

***Zoekresultaten*** – Op 22/11/2019 werd een systematische literatuurreview uitgevoerd. Volgende MeSH termen, gecombineerd door de Booleaanse operatoren AND en OR, werden gebruikt in de zoekmachines PubMed en Embase: "Child", "Children", "Infant", "Adolescent", "Posterior Reversible Encephalopathy Syndrome", "Clinical outcome", "Clinical patient outcome", "Clinical therapeutic outcome", "Clinical therapy outcome", "Clinical treatment outcome", "Neurologic outcome". We selecteerden case reports, case series en originele studies (retrospectief, prospectief, observationeel) over kinderen en adolescenten tot maximaal 18 jaar oud met PRES vanaf januari 2000 tot heden. Bovendien werd de referentielijst van reviewartikels nagekeken voor niet-gevonden referenties. Enkel artikels in het Engels of Nederlands waarvan de volledige tekst voor ons beschikbaar was, werden geïncludeerd. Artikels zonder gegevens over de outcome van PRES werden geëxcludeerd. De lijst van artikels werd door twee onafhankelijke auteurs gecontroleerd op relevantie. Na de initiële screening op basis van titel en abstract, werd de volledige tekst bestudeerd. Indien de studie ook over volwassenen rapporteerde, werd deze enkel geïncludeerd als de relevante data voor de kinderen/adolescenten apart geanalyseerd konden worden.

***Data extractie en analyse*** – Voor elke individuele patiënt werden gegevens verzameld over leeftijd, geslacht, onderliggende diagnose, symptomen bij presentatie van PRES en risicofactoren. Hypertensie werd gedefinieerd als een systolische en/of diastolische bloeddruk ≥ p95 + 12 mmHg of ≥ 130/80 mmHg (laagste waarde in rekening te nemen), volgens de definitie van de American Academy of Pediatrics (AAP) van 2017[10]. Daarnaast werd nagegaan wat de klinische (herstel, epilepsie, sequellen, mortaliteit en reden van overlijden) en radiologische outcome was, alsook de duur van opvolging.

## Resultaten

***Casusbeschrijving*** – Een meisje van 16 jaar werd binnengebracht met de MUG wegens een focale epilepsieaanval thuis (clonieën rechter hand) met secundaire generalisatie na hevige stekende hoofdpijn pariëtaal links in de ochtend. In de voorgeschiedenis weerhielden we lupus nefritis en pericarditis met hypertensie

waarvoor maandelijkse toediening van cyclofosfamide. Er was een normale neurologische ontwikkeling en ze volgde het normale secundair onderwijs. Klinisch onderzoek op spoedgevallen toonde een jongedame met Glasgow Coma Score (GCS) van 15/15 met een tongbeet en verder normaal systeemonderzoek. Er was forse hypertensie (bloeddruk = 229/132 mmHg), doch overige parameters waren normaal en ze was afebriel. Een CT-scan van de hersenen liet een kleine discrete hypodense zone links subcorticaal zien. Dringende NMR hersenen toonde multipele bilaterale T2/FLAIR hyperintense letsels pariëto-occipitaal verder uitbreidend naar frontaal (zie figuur 1A). De diagnose van PRES werd gesteld. Gezien ontwikkeling van status epilepticus onder ingestelde behandeling met benzodiazepines, fenytoïne en levetiracetam, werd ze gesedeerd met propofol en kunstmatig geventileerd. Tijdens de sedatie werden geen epilepsieaanvallen meer gedocumenteerd op een continu elektro-encefalogram (EEG). Twee dagen later kon ze geëxtubeerd worden. Er was een goede klinische recuperatie onder strikt antihypertensief beleid (calciumantagonisten intraveneus en per os, ACE-inhibitor, β-blokker, α-blokker en lisdiuretica) en anti-epileptische therapie (levetiracetam en valproaat).

Één week later ontwikkelde de patiënte een voos gevoel ter hoogte van haar linker onderbeen en voet. Aanvullende NMR van de wervelzuil was negatief. Cerebrale beeldvorming kon een neurolupus uitsluiten, maar toonde een subtotale regressie van de confluerende witte stofletsels beiderzijds (zie figuur 1B) én de aanwezigheid van talrijke microbloedingen bilateraal, voornamelijk fronto-pariëtaal gelokaliseerd (zie figuur 1D). De sensorische uitval werd gekaderd binnen een centrale origine ten gevolge van de regresserende witte stofletsels, dewelke een gunstige evolutie kende over de volgende maanden.

Bij een controle NMR 1 jaar later werd een volledige regressie van de witte stofletsels vastgesteld (zie figuur 1C), maar onveranderde aanwezigheid van de talrijke microbloedingen beiderzijds (zie figuur 1E). Anti-epileptica konden na 1 jaar gestaakt worden zonder recidief insult.

Over het verdere verloop ontwikkelde de patiënte echter cognitieve klachten, namelijk aspecifieke geheugenklachten en verandering van karakter. Neuropsychologisch onderzoek toonde meerdere deficits op audioverbaal- en visueel geheugen, aandachtsfuncties, executieve – en visuospatiale functies. Meer gedetailleerde gegevens hierover zijn beschikbaar in tabel 1.

**Figuur 1 :** Evolutie van de neurologische beeldvorming bij onze patiënt

Legenda:

A: MRI hersenen bij diagnose PRES

Multipele bilaterale T2/FLAIR hyperintense letsels, voornamelijk occipito-pariëtaal gelegen, maar ook frontaal.

B: MRI hersenen 2 weken na diagnose PRES

Subcorticaal gelocaliseerde confluerende T2/FLAIR hyperintense zones fronto-pariëtaal en beperkt rechts temporo-occipitaal: subtotale regressie.

C: MRI hersenen 1 jaar na diagnose PRES

Volledige regressie van de confluerende wittestofletsels beiderzijds.

D: Microbloedingen 2 weken na PRES

Talrijke hypo-intense spots corticaal en subcorticaal, voornamelijk fronto-pariëtaal.

E: Microbloedingen 1 jaar na diagnose PRES

Onveranderde aanwezigheid van de talrijke microbloedingen beiderzijds.

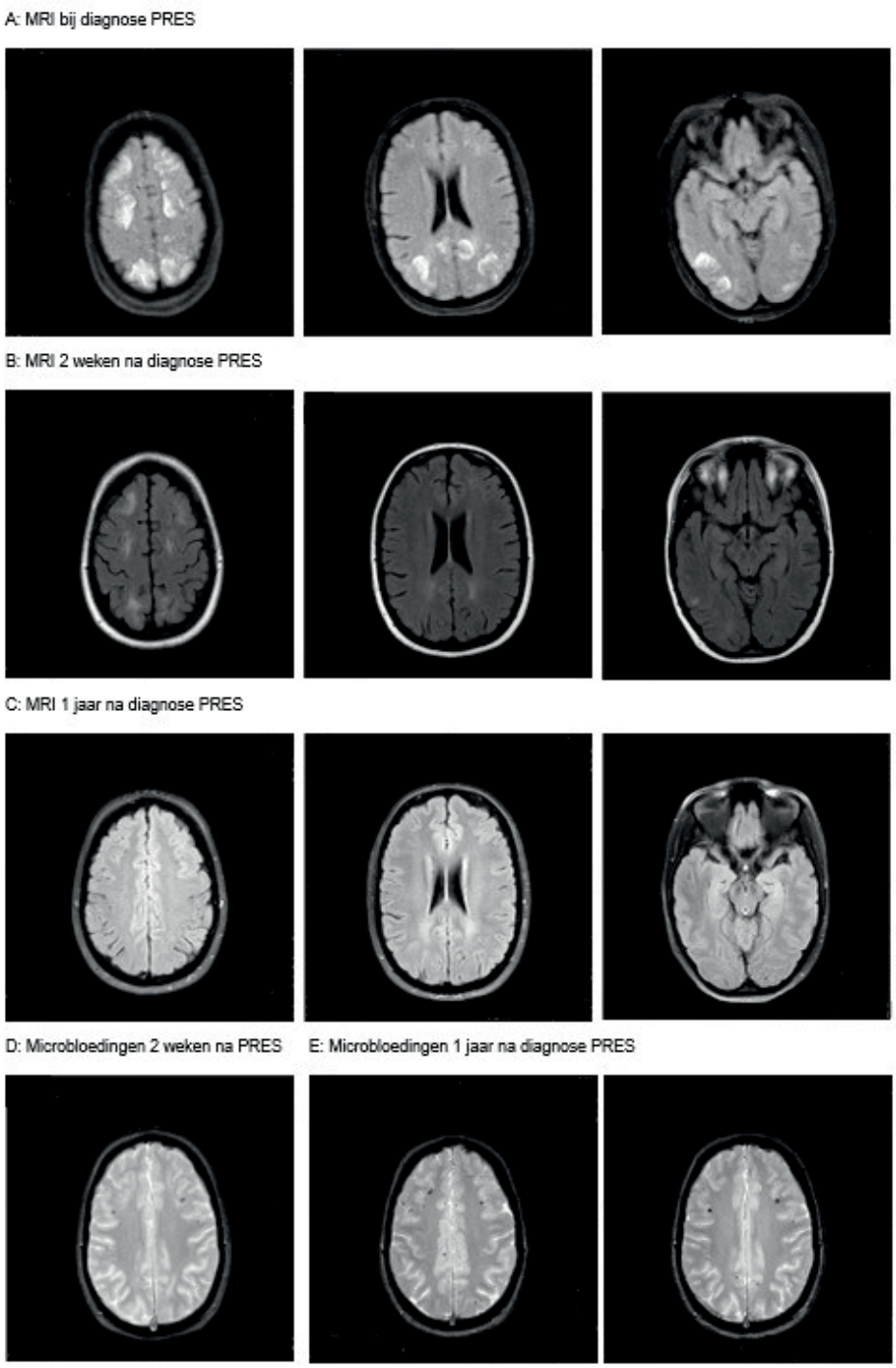


Table 1

| Geheugen | Score | Interpretatie |
|---|---|---|
| Minimental State Examination (MMSE) | 24/30<br>- Oriëntatie in tijd (-2)<br>- Oriëntatie in ruimte (-1)<br>- Delayed recall (-1)<br>- Herhalen (-1) | Verminderd |
| Auditory Verbal Learning Test (AVLT) | Prestatie op 5 trials<br>- Trial 1: 4 (< Pc 1)<br>- Trial 2: 6 (< Pc 1)<br>- Trial 3: 3 (< Pc 1)<br>- Trial 4: 7 (< Pc 1)<br>- Trial 5: 5 (< Pc 1)<br>Som: 25 (< Pc 1) | Ondermaats |
| Rey Visual Design Learning Test (RVDLT) | Prestatie op 5 trials<br>- Trial 1: 3 (Pc 7)<br>- Trial 2: 3 (< Pc 1)<br>- Trial 3: 4 (< Pc 1)<br>- Trial 4: 6 (< Pc 1)<br>- Trial 5: 7 (< Pc 1)<br>Som: 23 (< Pc 1) | Ondermaats |
| Logisch geheugen: Vlaamse Dementie Batterij (VDB-2) | Aantal elementen: 15/23<br>Betekenis: 5/5 | Gemiddeld |
| Rey Fifteen Item Memory Test (FIT) | 9/15 (= cut-off) | Cut-off |
| Aandacht en Executief Functioneren | Score | Interpretatie |
| Digit Span (Wechsler Memory Scale-Revised) | Voorwaarts: maximaal 3 (< Pc 1)<br>Achterwaarts: maximaal 2 (< Pc 1) | Ondermaats<br>Ingeperkte aandachtspanne, gerichte aandacht en werkgeheugen |
| Stroop Color Word Task | Woord: 48" (Pc 4)<br>Kleur: 76" (< Pc 1)<br>Interferentie: 127" (< Pc 1)<br>Interferentie factor (I.F.): 65 (< Pc 1)<br>Fouten: 14 | Vertraagd werktempo<br>Pathologische interferentiefactor<br>Verstoorde selectieve aandacht, cognitieve flexibiliteit en responsinhibitie |
| Trail Making Test (TMT) | a-versie: 42" (Pc 27)<br>b-versie: 94" (Pc 6)<br>b/a: 2.23 | Subtest A: gemiddeld<br>Verwerkingssnelheid: matig gemiddeld<br>Set –shifting en visueel alterneren: behouden |
| Bourdon-Wiersma Test | Gem. rijtijd: 10.56 (Pc 86)<br>Gem. rijafw: 2.27 (< Pc 1)<br>Weglatingen: 73 (< Pc 1)<br>Fouten: 8 | Regeltijd: gemiddeld<br>Regelafwijking: ondermaats<br>Onnauwkeurige werkhouding en verminderde volgehouden aandacht |
| Visual Elevator Task | Score: 7/10 (Pc 25)<br>Timing score: 3.74 (Pc 25-50) | Gemiddeld<br>Gemiddeld werktempo |
| Woordvloeiendheid | Letters: 28 (Pc 11)<br>Categorie: 21 (Pc 24) | Letterwoordvlotheid: discreet ingeperkt<br>Semantische woordvlotheid: behouden |
| Stemming | Score | Interpretatie |
| Beck Depression Inventory (BDI) | 6/63 | Geen depressieve kenmerken |
| Visuospatiale Perceptie | Score | Interpretatie |
| The Visual Object And Space Perception Battery (VOSP) | Objectdecisie: 14/20 | Verminderd |
| Intellectueel Functioneren | Score | |
| Nederlandse Leestest voor Volwassenen (NLV) | Score: 40<br>IQ-schatting: 76 (Pc 5-9) | Zwak begaafd intellectueel functioneren |
| Taal | Score | Interpretatie |
| Boston Naming Test (BNT) | Score: 52/60 (Pc 38) | Gemiddeld |
| Visuoconstructieve Praxis | Score | Interpretatie |
| Tekenen | Kubus: 0/1 | Verminderd in rekening brengen van perspectief bij tekenen van figuren |

***Resultaten zoekstrategie –*** Na de gecombineerde manuele en database zoektocht werden 85 artikels gevonden, waarvan 60 via PubMed, 21 via Embase en 4 via een referentielijst. Na eliminatie van duplicaten bleven in totaal 78 artikels over. Conform de exclusiecriteria werden nog eens 19 artikels verwijderd op basis van titel en abstract en 15 op basis van volledige tekst, zodat een totaal van 44 studies geïncludeerd werd in onze systematische review. Een overzicht van dit proces wordt weergegeven in figuur 2. We includeerden 25 case reports en/of case series en 19 retrospectieve studies.

***Patiënt karakteristieken –*** In totaal werden 410 kinderen geïncludeerd in deze review. Het betroffen 213 jongens en 197 meisjes, respectievelijk 52% en 48%. De leeftijden varieerden van 1 jaar tot 18 jaar. De onderliggende diagnoses waren uiteenlopend en kunnen ondergebracht worden in verschillende categorieën: (1) oncologisch (n = 273) waarvan 222 hematologische en 33 vaste tumoren; bij 18 kinderen werd het type tumor niet verder gespecifieerd; (2) hematopoïetische stamceltransplantatie (n = 106), waarvan bij 89 kinderen omwille van maligniteit; (3) orgaantransplantatie (n = 12); (4) auto-immune of reumatologische aandoening (n = 19); (5) nefrologische pathologie (n = 42) en (6) andere (n = 47). Figuur 3 geeft meer details hierover weer.

***Klinische manifestatie en neurologische beeldvorming –*** De kinderen presenteerden zich met verschillende symptomen: in 86% van de kinderen was er sprake van epilepsie (n = 353), bij 52% was er een verminderd bewustzijn (n = 211), hoofdpijnklachten traden op in 35% (n = 142) en visusstoornissen werden gezien in zo'n 30% (n = 123). De meeste kinderen vertoonden meer dan één symptoom: bij minstens 18 kinderen werd toch slechts 1 symptoom beschreven (≥ 4%).

De aan- of afwezigheid van risicofactoren werd bij 374 patiënten beschreven (91%). In 81% (n = 303) hiervan was hypertensie aanwezig op het moment van PRES. De toediening van corticosteroïden kwam voor in 43% (n = 161) en het gebruik van calcineurine-inhibitoren in 30% (n = 112). Resultaten van een NMR onderzoek waarop PRES bevestigd werd, waren beschikbaar in 98% van de kinderen (n = 400). Slechts voor 17% van de kinderen was duidelijk hoelang na het ontstaan van klinische symptomen beeldvorming uitgevoerd werd en dit varieerde van 1 uur tot 13 dagen.

***Klinische outcome –*** In totaal zijn 91 kinderen overleden, waarvan 9 ten gevolge van PRES (2%). Bij 19 kinderen (5%) werd herval van PRES beschreven. Gegevens over morbiditeit waren bij 69% van de kinderen beschikbaar (n = 284). De duur van opvolging liep echter ver uiteen van enkele dagen tot 9 jaar. In 78% van deze kinderen (n = 222) werd een gunstige klinische outcome beschreven zonder de aanwezigheid van enige restsymptomen. Persisterende afwijkingen werden gezien bij 53 kinderen (19%): diagnose van epilepsie of gebruik van anti-epileptica op moment van publicatie (n = 26; 9%), onvolledige recuperatie van klinisch beeld (n = 5; 2%), milde cognitieve beperking (n = 2; 0.7%), blijvende paraplegie (n = 2; 0.7%), visusstoornissen (n = 2; 0.7%), ADHD (n = 1; 0.4%), chronische vermoeidheid (n = 1; 0.4%) en niet verder gespecifieerde afwijkingen (n = 14; 5%). In een klein derde van de kinderen (n = 129; 31%) waren de beschikbare gegevens onvoldoende gedetailleerd om tot een gunstige of ongunstige uitkomst te kunnen besluiten.

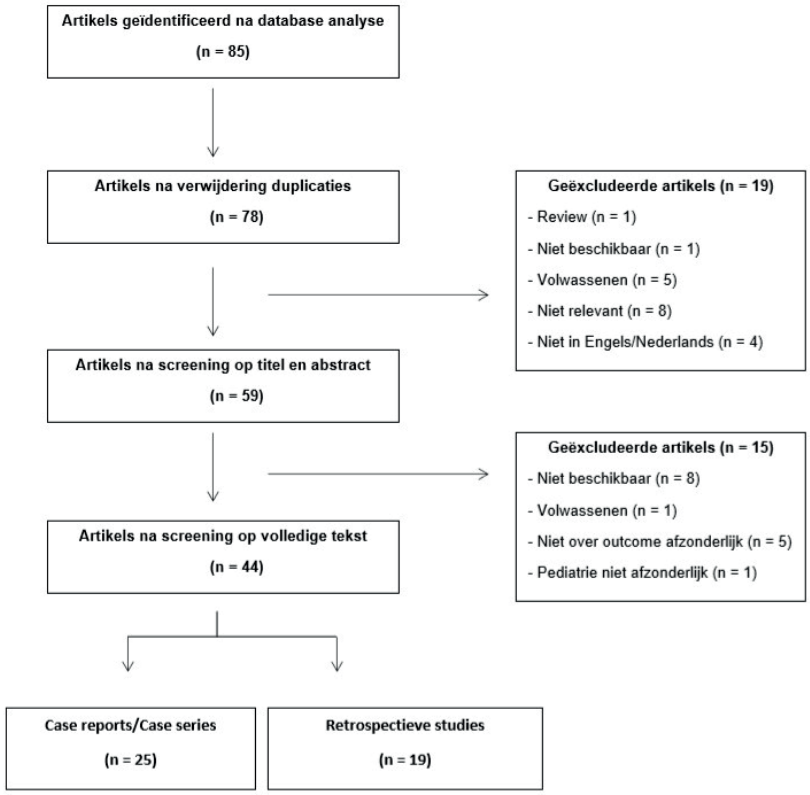
***Radiologische outcome –*** Follow-up beeldvorming was beschikbaar in 302 kinderen, wat overeenkomt met 74%. De tijd tot controle beeldvorming werd niet overal gedocumenteerd, maar was beschikbaar in 253 kinderen en liep uiteen van enkele dagen tot 42 maanden. In 23 kinderen werd beeldvorming meerdere keren herhaald en werd verdere regressie van de letsels over verloop van tijd aangetoond (range 3 – 126 maanden). In 78% (n = 236) van de 302 kinderen met minstens 1 controle NMR werden geen restletsels meer aangetoond, terwijl bij 22% (n = 66) nog persisterende afwijkingen op NMR gezien werden: verbetering, maar onvolledige resolutie van de hyperintensiteit (n = 17; 6%), bloeding (n = 12; 4%), corticale en laminaire necrose (n = 7; 2%), focale atrofie (n = 3; 1%), toename van bestaande lesies (n = 2; 0.7%), infarct (n = 1; 0.3%), gliose (n = 1; 0.3%) of niet nader omschreven (n = 26; 9%). Bij 3 kinderen werden meerdere afwijkingen genoteerd: necrose en bloeding in 2 patiënten; blijvende hyperintense letsels en bloeding in 1 patiënt.

## Discussie

Posterior Reversible Encephalopathy Syndrome (PRES) is een klinisch-radiologisch syndroom met een breed spectrum van (sub)acute neurologische symptomen in combinatie met tekenen van vasogeen oedeem in de (sub)corticale posterieure regio's van de hersenen op beeldvorming[1]. Het pathofysiologische mechanisme van PRES is nog niet volledig opgehelderd, maar waarschijnlijk spelen zowel hyper-en hypoperfusie als een direct cytotoxisch effect op het vasculaire endotheel een rol[3,7,11-12]. In de literatuur wordt bij kinderen epilepsie het meest beschreven naast een veranderd bewustzijn en hoofdpijn[4,13-16]. Visusstoornissen worden frequenter bij volwassenen gezien[14]. Ook in de casussen beschreven in deze review was epilepsie veruit het meest frequente symptoom in 86%, bewustzijnsveranderingen werden in de helft van de kinderen gezien (52%). Toch werd de diagnose bij onze casussen soms vrij laat gesteld (tot 13 dagen na begin van klachten), terwijl Roth et al. aantoonde dat snelle herkenning en behandeling door eliminatie van mogelijk uitlokkende factoren essentieel is voor een gunstige korte en lange termijn prognose[17].

Gegevens over outcome in de literatuur zijn vooral bij volwassenen gerapporteerd. Neurologisch herstel wordt beschreven in 70-90% van de gevallen[9,17-19]. In onze systematische review kunnen we een goede neurologische outcome bij 78% van de kinderen noteren. Toch verloopt PRES niet altijd even gunstig. Mortaliteit in de literatuur varieert tussen 5 en 19%, afhankelijk van de onderliggende

**Figuur 2 :** Studie selectie

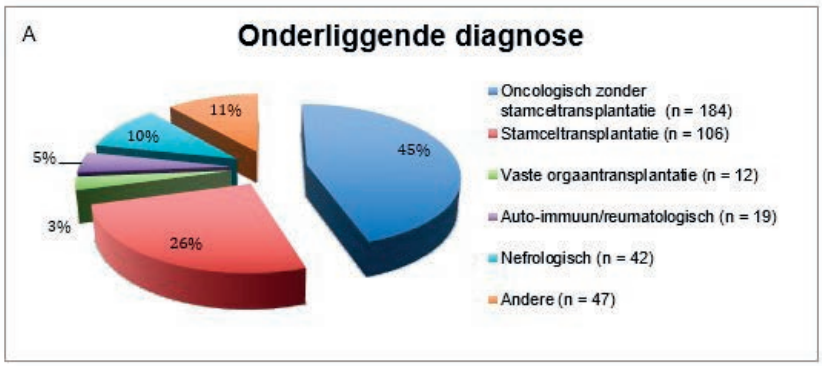


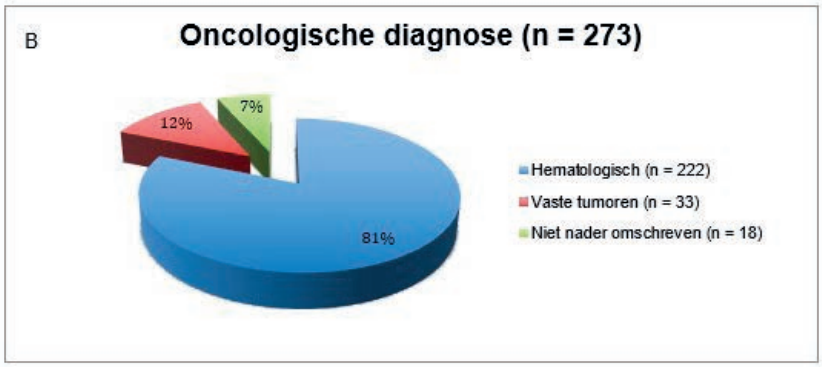

**Figuur 3 :** Overzicht van de patiëntkarakteristieken

Legenda:

A: Overzicht onderliggende diagnose

B: Overzicht type maligniteit



etiologie[9,20-22]. Epilepsie wordt in 1-4% gezien[23-24] en herval van PRES komt voor in 5-10%[17,25]. Wij weerhouden hier een mortaliteit ten gevolge van PRES van 2%, herval van 5% en een slechte neurologische outcome bij 19%. Daarnaast toonde onze eigen casus aan dat deze cijfers mogelijks de neurologische outcome onderschatten. Het meisje in kwestie vertoonde immers recuperatie van het klinisch neurologische beeld, kon anti-epileptica stoppen zonder recidief insult, maar ontwikkelde later neuropsychologische afwijkingen die aan de hand van testing beter in kaart gebracht konden worden (zie tabel 1). Natuurlijk kan niet met zekerheid gezegd worden dat deze afwijkingen volledig ten gevolge van PRES zijn, aangezien er geen voorgaande neuropsychologische toetsing beschikbaar is. Het feit dat ze voordien normaal secundair onderwijs gevolgd heeft, suggereert dit echter wel. Daarenboven beschrijven Stroescu et al. in 2011 twee volwassen patiënten met PRES bij wie neuropsychologische investigatie een gelijkaardig patroon vertoonde, namelijk vooral een beperking in de spatio-perceptuele en gerelateerde functies, naast de executieve functies[26].

Beeldvorming kon bij onze patiënt enkel talrijke microbloedingen in het licht stellen, wat als vermoedelijke verklaring van de neuropsychologische afwijkingen werd gezien. Dergelijke microbloedingen worden bij meer dan de helft van de volwassen patiënten met PRES beschreven (58%)[27], maar zijn mogelijks zeldzamer bij kinderen (13.5%)[28]. Bloeding (intraparenchymateus en/of subarachnoïdaal) werd in de literatuur reeds geassocieerd aan een slechte outcome (Odds Ratio 4.93)[29], maar er zijn geen gegevens over de gevolgen van microbloedingen. In onze literatuur search werden nog 5 andere kinderen met klinisch neurocognitieve stoornissen beschreven. Geen enkele hiervan werd onderzocht door middel van gestandaardiseerde neurocognitieve testen en het is ook onduidelijk of zij al dan niet afwijkingen vertoonden op controle beeldvorming. Anderzijds werden ook de andere patiënten niet neurocognitief getest, waardoor we niet kunnen inschatten of sommige patiënten subklinische neurocognitieve problemen vertoonden. Gezien er vooral retrospectieve studies gepubliceerd zijn, is het immers ook mogelijk dat er niet altijd controle beeldvorming plaatsvond bij (schijnbaar) volledige klinische recuperatie met een optimistisch inschatten van de outcome als gevolg.

De sterktes en beperkingen van deze review hangen uiteraard samen met de kwaliteit en rapportering van gegevens in de geïncludeerde studies. Eerst en vooral is er een zeer grote variabiliteit in de duur van klinische en radiologische opvolging. Gungor et al. toonde echter aan dat radiologisch herstel vaak pas na meer dan 1 maand optreedt, waardoor verdere regressie of zelfs volledige resolutie van de gerapporteerde letsels in de loop van de tijd nog zou opgetreden zijn bij patiënten met kortere opvolging[30]. Bovendien kan een bias in het al dan niet uitvoeren van controle beeldvorming op geleide van de kliniek de gegevens beïnvloeden. Tot slot maakten het ontbreken van data of onvoldoende details een juiste interpretatie en inschatting vaak moeilijk. Dit neemt echter niet weg dat deze systematische review aangeeft dat PRES bij kinderen zeker niet altijd reversibel is en dat ook neurocognitieve problemen aanwezig kunnen zijn, mogelijks zelfs zonder epilepsie of motorische sequellen.

## Conclusie

Er zijn hoegenaamd geen gegevens beschikbaar in de huidige literatuur omtrent de neurocognitieve outcome van PRES bij kinderen. In deze review wordt een gunstige klinische en radiologische outcome na PRES beschreven in slechts 78%, waaruit blijkt dat PRES niet zo onschuldig en reversibel is. In onze casus lijkt er daarenboven een verminderd cognitief functioneren te zijn. Het is dan ook van groot belang om een beter zicht te krijgen op de morbiditeit en neurocognitie na het doormaken van PRES. Als eerste stap hiertoe zou het nuttig kunnen zijn gegevens van alle Belgische patiënten samen te brengen, maar in de toekomst dienen best prospectieve follow-up studies met neurocognitieve testing opgezet te worden.

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# BEXSERO

**Vaccin tegen meningokokken van groep B (rDNA, component, geadsorbeerd)**

## Het **eerste** vaccin tegen meningokokken van **serogroep B**.[1]

## Het **enige** geïndiceerd vanaf **2 maanden**.[1,2]

## 2+1

voor zuigelingen vanaf de leeftijd van **2 maanden**.[1]

**VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN** Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL** Bexsero suspensie voor injectie in voorgevulde spuit Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd) - EU/1/12/812/001 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. coli*cellen door recombinantDNAtechnologie [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg $Al^{3+}$) [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit) **THERAPEUTISCHE INDICATIES** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **DOSERING EN WIJZE VAN TOEDIENING** Dosering

**Tabel 1. Samenvatting van de dosering**

| Leeftijd bij eerste dosis | Primaire immunisatie | Intervallen tussen primaire doses | Booster |
|---|---|---|---|
| Zuigelingen van 2 tot en met 5 maanden [a] | Drie doses, elk van 0,5 ml | Niet minder dan 1 maand | 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] |
| | Twee doses, elk van 0,5 ml | Niet minder dan 2 maanden | |
| Zuigelingen van 6 tot en met 11 maanden | Twee doses, elk van 0,5 ml | Niet minder dan 2 maanden | Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis [c] |
| Kinderen van 12 tot en met 23 maanden | Twee doses, elk van 0,5 ml | Niet minder dan 2 maanden | Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis [c] |
| Kinderen van 2 tot en met 10 jaar | Twee doses, elk van 0,5 ml | Niet minder dan 1 maand | Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen [d] |
| Adolescenten (11 jaar of ouder) en volwassenen* | | | |

[a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld [d] Zie rubriek 5.1 van de volledige SPK. *Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **CONTRAINDICATIES** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **BIJZONDERE WAARSCHUWINGEN EN VOORZORGEN BIJ GEBRUIK** Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen. Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuurstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Personen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van personen met complementdeficiëntie, asplenie of miltdisfuncties. Personen met familiale complementdeficiënties (bijvoorbeeld C3- of C5-deficiënties) en personen die behandelingen ondergaan die de terminale complementactivatie remmen (bijvoorbeeld eculizumab) hebben een hoger risico op een invasieve ziekte veroorzaakt door *Neisseria meningitidis* groep B, zelfs als deze personen antilichamen ontwikkelen na vaccinatie met Bexsero. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. Terugvinden herkomst Om het terugvinden van de herkomst van biologicals te verbeteren moeten de naam en het batchnummer van het toegediende product goed geregistreerd worden. **BIJWERKINGEN** Overzicht van het veiligheidsprofiel De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥1/10) Vaak: (≥1/100, <1/10) Soms: (≥1/1.000, <1/100) Zelden: (≥1/10.000, <1/1.000) Zeer zelden: (<1/10.000) Niet bekend: (kan met de beschikbare gegevens niet worden bepaald) De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar)** 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** 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 Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: myalgie, artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België** Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie Postbus 97 B-1000 Brussel Madou Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **Luxemburg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy – Hôpitaux de Brabois Rue du Morvan 54 511 VANDOEUVRE LES NANCY CEDEX Tél : (+33) 3 83 65 60 85 / 87 Fax : (+33) 3 83 65 61 33 E-mail : crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments Allée Marconi - Villa Louvigny L-2120 Luxembourg Tél. : (+352) 2478 5592 Fax : (+352) 2479 5615 E-mail : pharmacovigilance@ms.etat.lu Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië **DATUM VAN DE GOEDKEURING VAN DE TEKST** 04/2020 (v10) **AFLEVERINGSWIJZE** Op medisch voorschrift.

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# Traumatic brain injury or else?

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## Keywords

peroxisomal disorder, leukodystrophy, neurodegeneration, traumatic brain injury

## Abstract

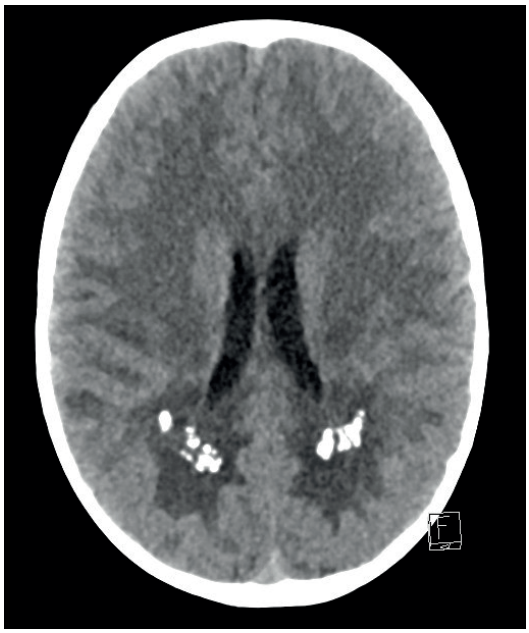
We discuss the case of a 7 year old boy that presented with unconciousness and lethargy after a fall down the stairs of unknown cause. Due to loss of conciousness, lethargy, and the circumstances of the trauma, a brain CT was performed. This did not show intracranial hemorrhage, but diffuse white matter abnormalities. After further examinations, our patient was diagnosed with cerebral X-linked adrenoleukodystrophy (X-ALD), a devastating neurometabolic disease. His brothers were diagnosed at an early stage and underwent haematopoietic stem cell transplantation. In this article, we discuss X-ALD and the importance of critically questioning circumstances of the trauma.

## Case-report

A 7 year old Erithrean boy presented at the emergency department of a secondary care hospital after a fall down the stairs. There was immediate loss of conciousness during an uncertain amount of time. After the fall, he was drowsy, but did not vomit. The reason for the fall was unknown. His medical history was uneventful, except for a referral to the otorhinolaryngologist due to hearing problems. Afterwards, school reported short attention span and learning difficulties since the year before the fall. Family history was uneventful.

Initial examination revealed a frontal hematoma and a swollen clavicula on the right side. Quick neurological assessment showed a Glasgow Coma Scale (GCS) of 14 and mild lethargy. An X-ray showed a fracture of the right clavicula. Computed tomography (CT) of the brain, performed because of the unknown cause in addition to lethargy and unconciousness, showed no evidence for intracranial bleeding or skull fractures. However, there were diffuse low-density white matter abnormalities with calcium deposits in the parietal lobes (figure 1).

**Figure 1 :** CT shows white matter abnormalities with calcium deposites in the parietal lobes.

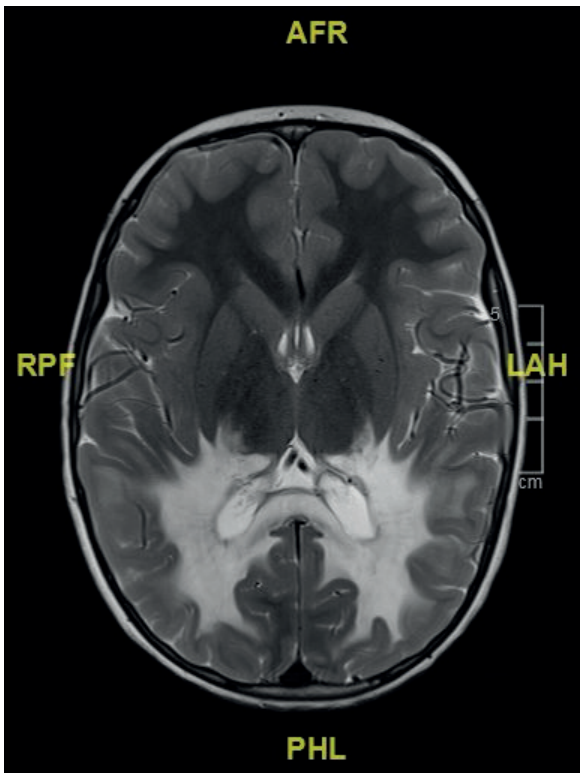


Parents reported regression shortly after the fall: he was unable to dress himself, to cycle, had frequent falls and urinary incontinence. He had developed visual impairment. Neurological assessment revealed ataxia. Magnetic resonance imaging (MRI) showed cerebral demyelinisation with white matter hypersignal on T2 sequences at the medulla oblongata, pons, splenium of the corpus callosum and parieto-occipital lobes (figure 2). The MRI severity score (Loes scale) was 16.5. After injection of gadolinium, there was peripheral lesion enhancement on T1 sequences. Blood analysis showed increased very long-chain fatty acids (VLCFA) and high adrenocorticotrope hormone (ACTH) with low to normal cortisol, suggesting adrenoleukodystrophy with adrenocortical insufficiency. Genetic analysis revealed a pathogenic variant in the ABCD1 gene on the X-chromosome (c.1628C>T) confirming the diagnosis of X-linked adrenoleukodystrophy (X-ALD). He was treated with steroids for his adrenocortical insufficiency and became more active. Unfortunately, his neurological condition was too advanced for haematopoietic stem cell transplantation (HSCT) to be effective. His disease progressed quickly and he died 2 years after diagnosis. The family was screened and his two brothers also had increased VLCFA levels and adrenocortical insufficiency, in the absence of neurological abnormalities. They had abnormalities on MRI and the same pathogenic variant on the ABCD1 gene, which confirmed the diagnosis of X-ALD. They were treated with steroids and HSCT was performed prior to symptom onset.

## Discussion

Our patient was diagnosed with X-ALD. X-ALD is a X-linked peroxisomal disease characterized by the deficient degradation and accumulation of VLCFAs. Patients are asymptomatic at birth, but virtually all male patients develop adrenocortical insufficiency during childhood and myelopathy during adulthood. About 40% of the boys develop cerebral demyelinisation. When cerebral ALD occurs in childhood, patients present with regression, declining school performance, and behavioural problems[1]. Initially, these symptoms progress slowly. MRI may show abnormal hypersignal of white matter on T2 and FLAIR sequences, and hyposignal on T1 sequences. The disease may suddenly become inflammatory, which is characterized by demyelinating lesion enhancement on MRI by gadolinium injection[2]an ATP-binding-cassette (ABC. This is followed by a quick onset of focal neurological deficits, such as visual or auditory agnosia, hemiparesis, dysarthria, and sometimes epilepsy[1], such as in our patient. About 10% of the boys may not develop the active inflammatory and devastating stage of the disease[2]an ATP-binding-cassette (ABC. Most females develop attenuated symptoms of myelopathy after the

**Figure 2 :** MRI revealed cerebral demyelinisation with white matter hypersignal on T2 sequences at the medulla oblongata, pons, splenium of the corpus callosum and parietooccipital lobes




age of 60 years old. The treatment of choice in patients with cerebral ALD is HSCT. The prognosis of patients with early stage disease that receive HSCT is excellent, with mortality rates less than 5%. After a period of approximately 6 months post transplantation, stabilisation of the disease occurs[1]. The brothers of our patient are an example of this disease course. Patients treated with HSCT at a later stage of the disease, however, are at risk for neurocognitive decline even after HSCT. Prognosis of these patients is usually poor[1,3]. A recent and promising therapeutic strategy is gene therapy. A phase 2-3 clinical trial showed halt of disease progression in large proportion of boys with cerebral X-ALD that received haematopoeietic stem cell gene therapy with a lentiviral vector[4]mutations in ABCD1 lead to loss of function of the ALD protein. Cerebral adrenoleukodystrophy is characterized by demyelination and neurodegeneration. Disease progression, which leads to loss of neurologic function and death, can be halted only with allogeneic hematopoietic stem-cell transplantation. METHODS: We enrolled boys with cerebral adrenoleukodystrophy in a single-group, open-label, phase 2-3 safety and efficacy study. Patients were required to have early-stage disease and gadolinium enhancement on magnetic resonance imaging (MRI. A following phase 3 trial has been initiated in 2019[5].

A fall of unknown cause preceded the diagnosis of our patient and his brothers. Developmental changes in children result in changes in exposure and interaction with hazards, and may increase the risk of falls. Age-related differences in causes of falls have been investigated by Agran *et al*[6]*E880 to E929, or E950 to E999, calendar year 1997, were analyzed. Annual rates of injury hospitalization/death by year of age were calculated using combined hospital discharges and deaths as the numerator for major causes and important subcategories. For comparison, rates of injury hospitalization/death were calculated for conventional vital statistics age groups: <1 year, 1 to 4 years; 5 to 9 years, 10 to 14 years, and 15 to 19 years. RESULTS: In 1997 in California, 35 277 children and adolescents 0 to 19 years were hospitalized and 1934 died as a result of injury, a ratio of 17 hospitalizations to 1 death. The distribution was bimodal with rates highest among 18-year-olds (732/100 000* in 2001. This study provides information on the age of onset of different risks of falls, peak age, and ages at which risks begin to decline. Falls that are not typical for the age group may suggest developmental deficits in motor skills, cognitive deficits or abnormal social interactions that increase risk of injury. As to our patient, the mean rate of falls in 7 year old children is estimated around 100 per 100.000 children per year. Falls from stairs at the age of 7 years old, however, are rare[6] E880 to E929, or E950 to E999, calendar year 1997, were analyzed. Annual rates of injury hospitalization/death by year of age were calculated using combined hospital discharges and deaths as the numerator for major causes and important subcategories. For comparison, rates of injury hospitalization/death were calculated for conventional vital statistics age groups: <1 year, 1 to 4 years; 5 to 9 years, 10 to 14 years, and 15 to 19 years. RESULTS: In 1997 in California, 35 277 children and adolescents 0 to 19 years were hospitalized and 1934 died as a result of injury, a ratio of 17 hospitalizations to 1 death. The distribution was bimodal with rates highest among 18-year-olds (732/100 000. Therefore, if the loss of conciousness and lethargy in our patient would be absent, the circumstances around the fall alone, e.g. a fall down the stairs in a 7 year old patient, should have also led us to further investigations towards underlying neurological disease.

Our case-report emphasizes the importance of questioning the circumstances in children that present with falls. The circumstances and the characteristics of the patient have to be weighted against the probability of the fall, and with that, the possibility of underlying disease, such as in our patient.

## Conclusion

We present a case of a 7 year old boy that presented with a fall down the stairs and was diagnosed with a severe neurometabolic disease. Our case-report emphasizes that circumstances around trauma and traumatic brain injury need to be questioned, so that underlying problems such as neurological disease, are not missed.

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# A iatrogenic cause of encephalopathy in a 9-year old boy – a rare side effect of a commonly used drug

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## Keywords

Valproic acid ; Valproate ; Valproate-induced ; Pediatric ; Encephalopathy ; Delirium

## Abstract

A 9-year old boy presented with convulsions and was treated with lorazepam and valproate. Within hours he developed an encephalopathy. Laboratory tests and magnetic resonance imaging (MRI) of the central nervous system imaging were normal. After cessation of valproate symptoms rapidly resolved, diagnosis of valproate-induced encephalopathy (VIE) was assumed.

VIE is a complication of valproate therapy, most commonly met in cases with polypharmacy or underlying disease. In our patient, due to timing and absence of risk factors, VIE initially was mistaken for a symptom of underlying disease. Cessation of valproate relieved encephalopathy and prevented permanent damage. In encephalopathy, it is important to consider iatrogenic causes.

## Introduction

Acute agitation, delirium or encephalopathy can have many different causes. In paediatric practice, central nervous system (CNS) infection, intoxication, status epilepticus, intracranial processes or metabolic disturbances are most common. So the initial work-up should always include blood and cerebrospinal fluid (CSF) culture, meningitis/encephalitis polymerase chain reaction panel (PCR-panel) of CSF, toxicology screening, blood gases (including lactate), glycaemia, plasma amino acids and acylcarnitine and organic acids on urine. Though less frequent, iatrogenic causes should not be overlooked, as is shown in our 9-year old patient.

## Case presentation

A 9-year old boy with previously blank medical history presented after a first tonic-clonic epileptic seizure while traveling with his parents on a trip through Belgium. Spontaneous resolution seemed to take place after ten minutes. Serum electrolytes, ammonia level and liver tests were normal. There was no fever nor other signs of infection in patient history, clinical examination and lab results. Toxicologic screening in urine was negative. A few hours after admission a second tonic-clonic seizure was observed with need for benzodiazepine administration (lorazepam intravenously (IV) 0.1 mg/kg). Since the recurrence risk was esteemed as high a treatment with valproate was started (loading dose 20mg/kg IV followed by continuous IV administration of 1mg/kg/hour).

Within the next hours the boy developed an encephalopathic state with agitation, aggressive behaviour and lack of adequate interaction. A computed tomography (CT) scan and MRI of the brain showed no abnormalities. An electroencephalogram (EEG) did not demonstrate epileptic activity, however a slower base-line rhythm compatible with encephalopathy was present. Lumbar puncture showed no evidence of CNS infection or other pathology (leukocytes 1/mm3 (normal 0-7), glucose 69 mg/dl (40_80), protein 17,7 mg/dl (5-40), lactate 1,7 mmol/L (1,1-2,1).

Acyclovir was added to the therapy and the child was transferred to a paediatric intensive care unit (PICU) (university centre). In the meantime, meningo-encephalitis PCR-panel testing proved negative.

After cessation of valproate and acyclovir (since Herpes was negative) in the PICU, there was a quick and complete resolution of encephalopathic symptoms in less than 24 hours. Levetiracetam was started and for the remaining time of hospitalisation no further events occurred.

## Discussion

Valproate-induced encephalopathy (VIE) is a complication of valproate therapy, most commonly described in patients with polypathology (especially neuropsychiatric) and polypharmacy.[1-4] It is most likely thought to be caused by interference in the urea cycle with resulting increase in serum ammonia levels, even without disturbance in liver function.[5,-7] This effect is only partially dose-dependent, the serum ammonia level does not always correlate with encephalopathic symptoms and hyperammonemia can occur with valproate serum levels within therapeutic range. [5,7]

Most reported cases developed symptoms within days to weeks after (re) starting valproate or elevating valproate dose. Our case has a different timing with development of encephalopathy within hours. This can be partially explained by the loading dose that was administered intravenously. Risk factors for development of valproate-induced encephalopathy are young age (under 3 years of age), polypharmacy and especially combination of valproate with phenobarbital or topiramate, underlying urea cycle defect, underlying psychomotor retardation or psychiatric disease. None of these predisposing factors applied to our patient.

In the university center no other cause of encephalopathy was identified. Further blood tests showed normal values for glycaemia, lactate, electrolytes, liver and thyroid function and copper metabolism. Ammonia level was not determined again.

The quick resolution of symptoms after discontinuation of valproate treatment seems to indicate that our patient suffered from VIE. Since valproate and ammonia levels were not checked at that moment, the exact mechanism will remain unknown.

The most likely mechanism causing VIE seems to be direct inhibition of hepatic mitochondrial carbamylphosphate synthetase (CPS 1) [8], the first enzyme of the urea cycle ,and/or indirect interference with the carnitine handling (valproate inhibits transport and increases renal excretion of carnitine). Increasing ammonia- and decreasing carnitine levels are the result and hyperammonemia has been suggested to be the main cause of encephalopathy. However, several cases of non-hyperammonemic valproate-induced encephalopathy are reported in literature. [9,10] An underlying mitochondropathy should be considered in those cases, especially if blood lactate is raised.

Remarkable in our patient is that there was no predisposing history, no abnormalities in any blood test, no co-administration of other drugs, and development of an encephalopathic state in no more than a few hours after the start of valproate therapy. As such it was very difficult to recognize the encephalopathy as an adverse effect of the treatment rather than as a symptom of the underlying disease. By presenting our case we want to raise special awareness of this possibility, as valproate is one of the most widely-used drugs in treatment of childhood epilepsy, even in encephalopathy. In Belgium, valproate is still the first-choice for epileptic seizures.

## Conclusion

The combination of seizures and acute encephalopathy in a previous healthy child is a challenging paediatric emergency. Status epilepticus, infection, intoxication, intracranial process and metabolic disease should all be ruled out. Though less common, iatrogenic causes should also be considered. In our patient valproate-induced encephalopathy occurred as a rare adverse event, caused by a widely-used drug.

Our case shows that this entity can be difficult to recognize and can easily be mistaken for a symptom of underlying disease rather than an adverse effect of treatment. Even in the absence of risk factors it is important to always consider the latter option, since early recognition is crucial to stop the responsible drug (In this case valproate), resolve symptoms and prevent permanent damage.

We are also convinced that, especially in young children, levetiracetam rather than valproate, should become the first choice for treatment of a first episode of seizures, certainly if the previous history of the child is not well known since underlying disease can increase the risk of serious adverse effects. [11]

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# Beta-lactam hypersensitivity: Epidemiology and optimized diagnosis

PhD thesis presented on 26th of October 2020 at Universiteit Antwerpen, Antwerpen, Belgium

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Promotors: Didier Ebo, Vito Sabato, Margo Hagendorens

β-lactam antibiotics are a group of antimicrobial agents including penicillins, cephalosporins, carbapenems and monobactams (an overview is shown in figure 1).

β-lactam antibiotics, especially penicillins, are one of the predominant causes of drug hypersensitivity reactions. The majority of β-lactam hypersensitivity reactions is categorised as immediate (< 1 hour) humoral likely IgE-mediated (type I) and nonimmediate (> 1 hour), mainly cellular (type IV), hypersensitivity reactions. Immediate reactions mostly present with urticaria and/or angioedema, bronchospasm but anaphylaxis and death can occur [1]. A maculopapular exanthema is the predominating presentation of nonimmediate type IV hypersensitivity reactions [2,3].

Alternatively, unverified and false "β-lactam allergies", mainly to the first-line preparations natural penicillin and aminopenicillins, have evolved into a worldwide plague with serious financial and medical consequences.

According to the literature, as much as 10-20% of the population reports a "penicillin allergy" that was never accurately documented [4-7]. However, over 90% of these individuals tolerate the alleged culprit(s) during controlled drug challenges and are at unnecessary risk for more expensive and suboptimal second-line antibiotic treatments [8-36]. Actually, "penicillin allergy" is associated with erroneous avoidance and unnecessary substitutions, prolonged hospitalizations, more readmissions, poorer outcomes, increased costs and increased rates of *Clostridium difficile* and antimicrobial resistance, *e.g.* vancomycin [37-44].

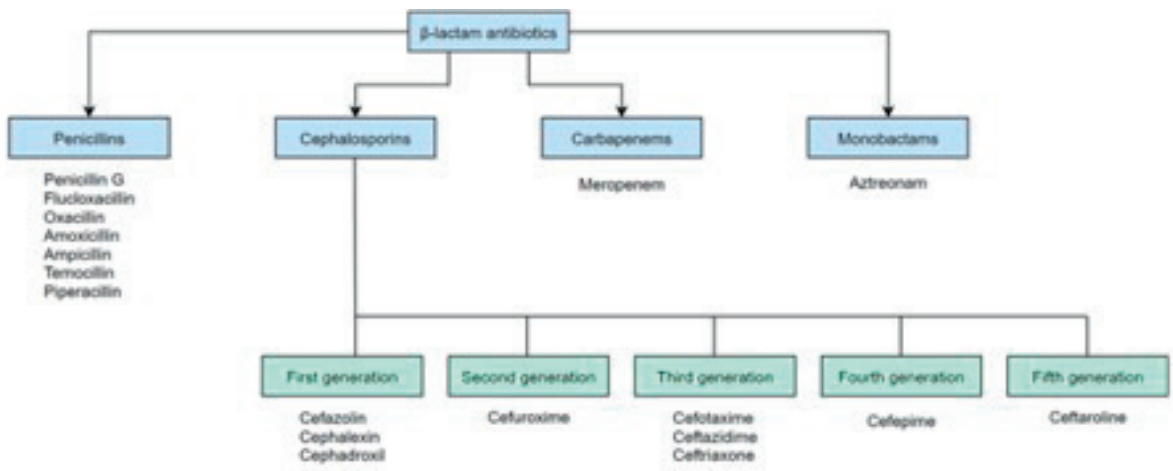
This dissertation aims at improving awareness of this scourge and motivating treating physicians for referral of their patients for correct diagnosis in order to confirm or discard clinical suspicion.

Hence, we present data on the prevalence of self-reported "penicillin allergy" in a Belgian outpatient population. To the best of our knowledge, such data have not been published yet. From our survey it appears that as much as 12% of the individuals attending the outpatients' clinic of Allergology and Paediatric Allergology of the Antwerp University Hospital claim to have a "penicillin allergy". However, in 91% of these individuals this claim appears to be false, as they tolerated these antibiotics during a controlled drug challenge. Importantly, as these cases could be safely delabelled, we were able to improve their antibiotic stewardship, mainly by safeguard them against the unnecessary risk for use of suboptimal and expensive second-line treatments. However, almost 10% of the participants who were successfully delabelled remained reluctant for any subsequent intake which was reinforced by other physicians. Efforts to improve general awareness of clinicians and strengthen their believe in the benefit of confirmatory testing to establish correct diagnosis in their patients are needed.

From the literature and our experience, it is clear that diagnosis of penicillin allergy cannot rest upon history alone but needs judicious diagnostic work-up by a trained physician and that correct diagnosis is necessary in every case of both witnessed or self-reported "penicillin allergy". We show that the label of "penicillin allergy" generally already originates in childhood and that in most cases information about the index reaction (culprit, clinics, timing,…), regrettably is lacking or simply limited to the description of an 'undefined rash'. Consequently, we argue firmly for a more detailed documentation of any potential drug hypersensitivity reaction. History and clinical presentation are critical to allow identification of the underlying pathophysiological mechanism and guidance of subsequent confirmatory testing.

However, diagnosis of β-lactam hypersensitivity reactions is not always straightforward and optimization of the diagnostic approach of β-lactam hypersensitivities is needed. Therefore, one of the main aims of this thesis was to study the performance of new or recently introduced diagnostics.

**Figure 1:** Overview of β-lactam antibiotics available for medical use in Belgium



First, we investigated the potential of CD154, a member of the TNF superfamily that is primarily, but not exclusively, expressed on activated $CD4^{+ve}$ T helper lymphocytes, as an alternative readout for drug-specific T-lymphocyte activation in the context of nonimmediate hypersensitivity reactions to amoxicillin and amoxicillin clavulanic acid. We showed that a CD154-based lymphocyte activation test (CD154-LAT) is a safe and quick in vitro diagnostic test, especially in cases with mild cutaneous nonimmediate drug hypersensitivity reactions to amoxicillin or amoxicillin clavulanic acid, who required drug challenges because of equivocal or negative skin tests. Although CD154 upregulation was also observed in some amoxicillin (clavulanic acid) tolerant individuals, the median upregulation was numerically lower than in patients with amoxicillin hypersensitivity responsive in the SD154-LAT. However, larger studies are required to confirm these promising data. Alternatively, it is obvious that the value of a CD154-based lymphocyte activation test should additionally be evaluated in severe cutaneous nonimmediate drug hypersensitivity reactions, where intradermal testing and drug challenges are contraindicated for safety reasons.

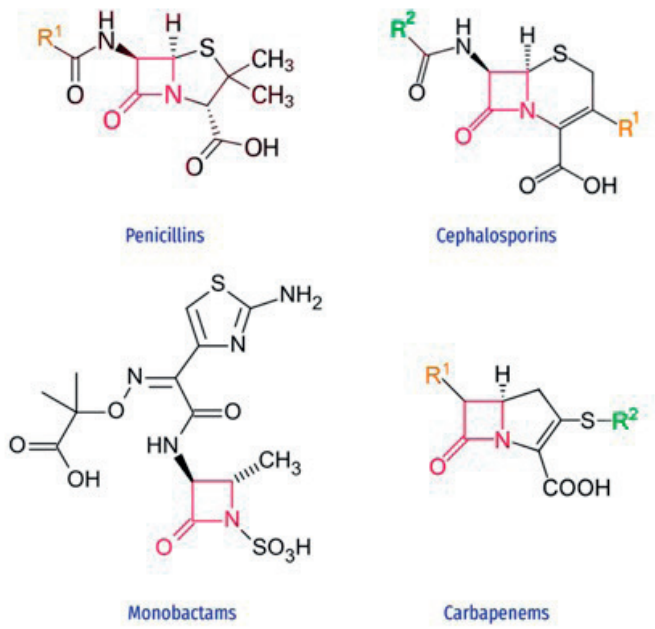
Further, we demonstrated that a prolonged drug challenge extending over several consecutive days is of limited use in the diagnosis of nonimmediate drug hypersensitivity reactions to amoxicillin and amoxicillin clavulanic acid, as 116 prolonged drug challenges have to be performed to identify one single patient demonstrating a mild maculopapular exanthema. Consequently, we currently dissuade to systematically impose prolonged drug challenges as a final diagnostic in nonimmediate drug hypersensitivity reactions to amoxicillin and amoxicillin clavulanic acid, especially as potential pharmacological adverse events (e.g. diarrhoea, mycoses, and the development of antimicrobial resistance) outweigh the benefits. Taking into account the accuracy, safety and cost of our diagnostics, the traditionally recommended diagnostic algorithm that offers a 1-day drug challenge as a final diagnostic in patients with negative work-up for amoxicillin (clavulanic acid) is still appropriate.

In our country cefazolin, a first-generation cephalosporin antibiotic mainly used in perioperative prophylaxis, has evolved to one of the major causes of perioperative anaphylaxis with serious consequences of misdiagnosis. Confirmatory diagnosis generally starts with skin tests and, if needed, potentially dangerous intravenous challenges. Therefore, and having access to sera of patients with a well-documented cefazoline allergy, we explored the performance of a recently developed specific (s)IgE assay to cefazolin. We observed that when the sIgE result for cefazolin was corrected for total (t)IgE by use of a sIgE/tIgE ratio, predictive values were comparable to sIgE assays for other β-lactam antibiotics. In contrast, sIgE to cefazolin was not able to discriminate between cefazolin allergic patients and control individuals. However, the sIgE/tIgE ratio does not substitute skin testing and sensitivity of the ratio drops over time.

Finally, it is known that cross-reactivity among β-lactam antibiotics is unpredictable but mostly related to the R1-side chain (see figure 2). Besides, physicians tend to overestimate cross-reactivity and too often other β-lactam antibiotics are unnecessarily forbidden. However, we demonstrated that fine structural differences in the R1-side chain can suffice to explain absence of cross-reactivity and clinical tolerance. Clearly, molecules with a similar, but not identical R1-side chain, should not be precluded or administered using a desensitization protocol, provided they test negative in skin testing.

In conclusion, self-reported "penicillin allergy" has grown into a vast epidemic with unacceptable consequences for the individual patient and the society. Moreover, cross-reactivity among β-lactam antibiotics is often overestimated. Therefore, confirmatory testing is absolutely needed in every patient with a history of signs/symptoms that are possibly caused by β-lactam antibiotics. In contrast to a prolonged drug challenge, a CD154-LAT seems to be an attractive instrument to document mild cutaneous nonimmediate drug hypersensitivity reactions to amoxicillin or amoxicillin clavulanic acid. A sIgE to cefazolin is of no added value to the diagnosis of immediate cefazolin hypersensitivity. Further efforts are required to optimize and harmonize a cost-conscious diagnostic approach of "penicillin allergy" and "β-lactam allergy" in general.

**Figure 2:** Chemical core structures of β-lactam antibiotics. The β-lactam ring (red) is common to all β-lactam antibiotics. Penicillins share a stable 5-membered thiazolidine ring, cephalosporines contain an unstable 6-membered dihydrothiazine ring. "R" denotes the side chains that vary among the antibiotics

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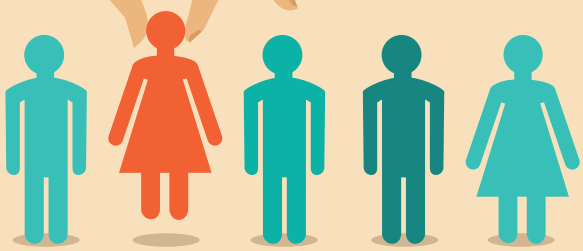
# Alone: unspecific, combined: a hint

THE PROJECT **find**

## THE IMPORTANCE OF EARLY DIAGNOSIS[1,2]

Early diagnosis and early treatment are essential to slow down the progression of the disease and enhance quality of life.[1,2]



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### IF YOU SUSPECT AN MPS, THINK OF FOLLOWING DIAGNOSTIC TESTS:[3,4]

- URINARY GAGs
- ENZYMATIC ACTIVITIES (ON DBS OR BLOOD)
- GENETIC CONFIRMATION


**1.** *Gabrielli O et al. 12 year follow up of enzyme-replacement therapy in two siblings with attenuated mucopolysaccharidosis I: the important role of early treatment. BMC Medical Genetics (2016) 17:19* **2.** *Lachman R et al. Mucopolysaccharidosis IVA (Morquio A syndrome) and VI (Maroteaux–Lamy syndrome): under-recognized and challenging to diagnose Skeletal Radiol (2014) 43:359–369* **3.** *Stapleton M et al. Clinical presentation and diagnosis of mucopolysaccharidoses. Molecular Genetics and Metabolism 125 (2018) 4–17* **4.** *Lehman T et al. Diagnosis of the mucopolysaccharidoses. Rheumatology 2011;50:v41v48 5. NORD. Mucopolysaccharides. https://rarediseases.org/rare-diseases/mucopolysaccharidoses/ accessed November 21st, 2019.*


***GAGs:*** *glycosaminoglycans / DBS: dry blood spot /* ***ENT:*** *ear nose throat /*

## The mucopolysaccharidoses (MPS) are progressive multisystemic storage diseases that frequently AFFECT:[3,4,5]

- **NERVOUS SYSTEM** (psychomotor delay, cognitive deterioration, behavioural disorders)
- **MUSCULOSKELETAL SYSTEM** (multiple dysostosis, contractures, carpal tunnel syndrome, kyphoscoliosis)
- **VISCEROMEGALIES**
- **ENT** (recurrent otitis and colds, hypoacusis, obstructive sleep apnoea syndrome)
- **EYE** (corneal opacity, retinopathy)
- **HEART** (heart valve disease, cardiomyopathy)
- **CONNECTIVE TISSUE** (inguinal and umbilical hernias)
- **FACE** (coarse features)

Not all signs/symptoms may be present in every patient


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JANUARY 2020

# Optimisation of long-term outcomes in paediatric inflammatory bowel disease patients: role of therapeutic drug monitoring and endoscopic remission

PhD thesis presented on 13th of May 2020 at KU Leuven, Leuven, Belgium

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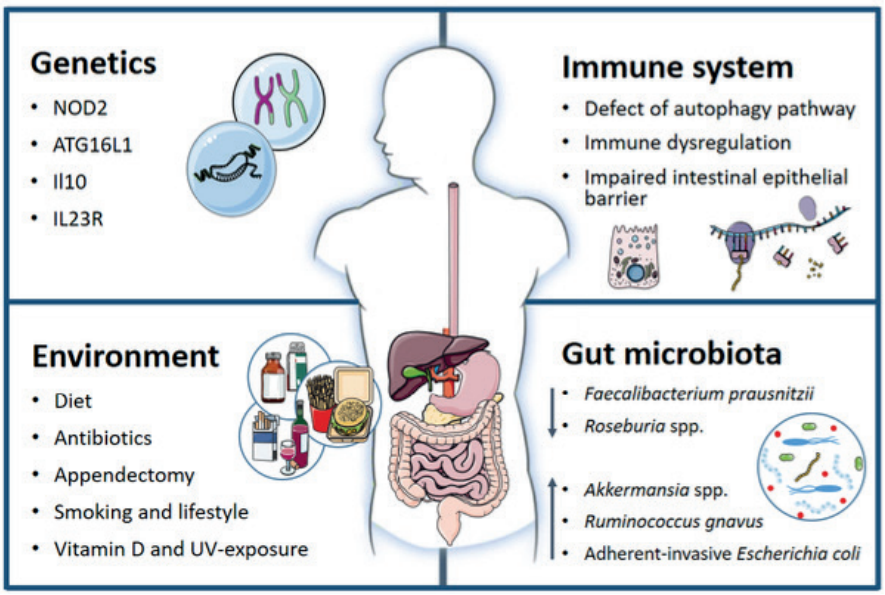
## Introduction

Inflammatory bowel diseases (IBDs) are chronic, relapsing-remitting disorders of the gastro-intestinal tract that are subclassified as Crohn's disease (CD) and ulcerative colitis (UC) [1-2]. Approximately 20-25% of newly diagnosed IBD patients present during childhood, with an incidence of 6.5-9.3 per 100.000 and 1.0-2.4 per 100.000 for CD and UC, respectively [3-4]. The clinical presentation depends highly on the disease location and behaviour, which fluctuates over time. The majority of patients will experience (bloody) diarrhea, abdominal pain, weight loss, growth impairment, fever and fatigue [1-2]. In addition, uncontrolled inflammation puts them at risk for disease-associated complications, such as fibrosis, fistulas, repeated surgical resections and cancer.

The exact aetiology of IBD has not been fully elucidated yet [5-7]. There is a general consensus that the disease arises from a complex interplay of environmental factors in combination with dysbiosis of the gut microbiota that leads to an excessive activation of the intestinal immune system and subsequent inflammation in a genetic predisposed host (see figure 1).

Since IBD is still a life-long and incurable disease, the medical management remains challenging, particularly in children [1-2]. The aggressive nature of paediatric IBD has been well established, with a more extensive anatomical involvement at diagnosis in comparison to adults [8]. Therefore, biological agents are more often necessary to obtain endoscopic remission, which has emerged as the new treatment goal [9]. In addition, a more holistic approach is applicable in children addressing in particularly growth, puberty, and bone health; which can be impacted directly by the disease but also indirectly by the effects of treatment, and this at a period where the psychosocial development is most vulnerable [1-2]. Finally, the therapeutic armamentarium of children with IBD is still limited in comparison to adults as both the required randomised trials and evidence lag behind. Thus, especially in children, the focus of management should be on optimising our available treatment options in the best possible way to overcome these challenges and to treat inflammation adequately.

**Figure 1:** Pathogenesis of inflammatory bowel disease. This figure was created with images adapted from Servier Medical Art.



Several strategies have been proposed to achieve these goals. The general aim of this doctoral thesis was to improve the long-term outcome by further exploring and unravelling these strategies, specifically in paediatric IBD patients.

## Predicting response to conventional therapy in children

The key goal in IBD management is to achieve deep remission, as early as possible in this lifelong disease, and this with minimal toxicity. The time to achieve this goal is thought to be as important as reaching this goal itself [10-14]. Especially in the early stages of the disease, there exists a window of opportunity to prevent disease progression and disability [14-15]. The introduction of an accelerated step-up therapy (based on patients' risk factors) or even top-down therapy in association with a tight control of inflammation has led to the expectations that we could change the natural course of the disease. A top-down approach will start immediately with biologics instead of initiating treatment with conventional therapy (with e.g. 5-aminosalicylates, steroids and immunomodulators) and defer biologics until patients flares or become refractory (i.e. step-up therapy). This top-down approach is based on the superiority of infliximab (IFX) over immunomodulators in achieving corticosteroid-free remission, especially when given early after diagnosis [11-14]. It is noteworthy that not all patients require the same intense treatments. Currently, there are insufficient data to predict the disease course at diagnosis, and therefore to decide which patients will benefit most from early biologics, and who will not need early or even any biologics. Indeed, a top-down approach will certainly not be the ideal approach for all patients. In addition to the risk of over-treating, the high cost of these biologics will also limit its early use (especially since most local governments reimbursement regimes will only support a step-up approach). Thus, validated prognostic markers are urgently wanted that can identify at diagnosis which patients will progress and require more potent treatment. We found that especially a high disease burden at diagnosis predicted the need for step-up therapy with either biologics or surgery [16]. Patients were more likely to fail conventional therapy in case of higher C-reactive protein (CRP), lower albumin and growth impairment for CD and higher Paediatric Ulcerative Colitis Activity Index (PUCAI) score and lower iron levels for UC. The need for step-up therapy significantly increased with the number of risk factors. Since, this effect was already seen early during follow-up under conventional therapy, we probably can expect to catch the window of opportunity to modify the natural disease course when providing these high-risk patients an accelerated step-up therapy together with a tight control of inflammation.

In addition, we have shown that only one-third of paediatric IBD patients treated with conventional therapy remained free of biologics or surgery 5-years after diagnosis and more than two-thirds of patients required step-up treatment [16]. Therefore, also the therapeutic potential of these intrinsically powerful biologics needs to be maximised.

## Therapeutic drug monitoring of anti- tumour necrosis factor agents

While we wait impatiently for new biologics to become available for paediatric indications, anti- tumour necrosis factor (TNF) agents are the only approved biologics in paediatric IBD until now. TNF alpha is a pro-inflammatory cytokine that plays a key role in the intestinal inflammatory cascade. Neutralising TNF alpha with these agents has been shown to diminish inflammation and induce apoptosis of TNF-producing immune cells [17]. Currently, two anti-TNF alpha agents are approved for the treatment of paediatric IBD: infliximab and adalimumab, respectively a chimeric and a fully human, recombinant monoclonal antibody directed against TNF alpha [1-2].

Prevention of anti-drug antibody formation and loss of response remain the two most important challenges in the management of IBD with respect to anti-TNF alpha agents [18]. Therefore, therapeutic drug monitoring (TDM) has been proposed as one of the ways to optimize both initial response and long-term continuation of anti-TNF therapy. TDM is a tool based on clinical and laboratory measurements, typically drug and anti-drug antibody serum concentrations, which enables clinical decision-making in order to achieve the highest possible response without side effects. Research in TDM is rapidly expanding but mainly in the adult literature and TDM studies in children are still under investigated [18]. The objective of the second part of this doctoral thesis was therefore to study that adequate drug exposure to IFX would lead to better long-term outcomes in paediatric IBD and to define the optimal drug exposure.

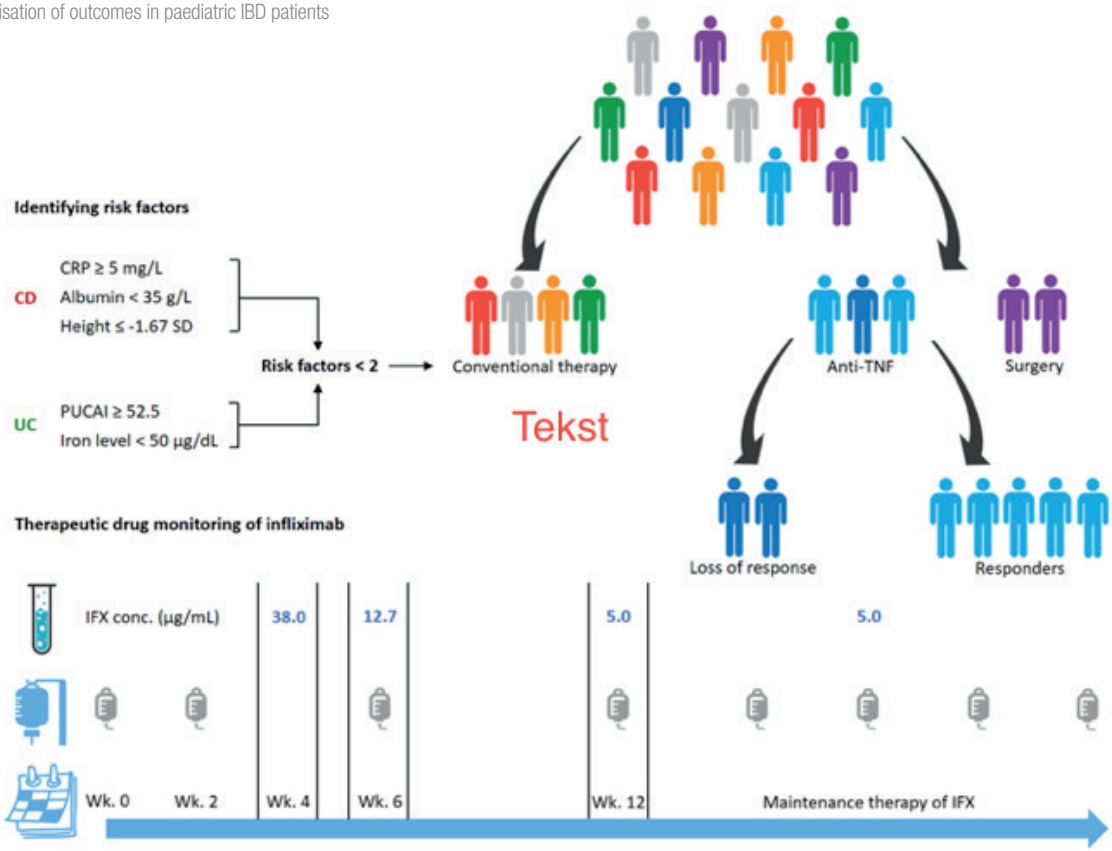
The optimal drug exposure (or therapeutic window) might however be patient-specific, vary over time throughout the treatment course (during induction phase, at the end of induction and during the maintenance phase) and might also depend on the treatment endpoint (such as clinical, biological or endoscopic remission). Therefore, our research has guided us through these three important phases of IFX therapy with respect to all different treatment endpoints. Specific attention went to endoscopic remission, since this has emerged as the Holy Grail instead of focusing on relieving symptoms alone [9]. However, data on this topic were lacking in paediatric IBD.

We demonstrated a strong exposure-response effect in children receiving maintenance IFX therapy, and for the first time a clear association between IFX trough levels and endoscopic remission in this population [19]. In the era where mucosal healing is the new gold standard, this is an important observation. Secondly, we showed that an adequate IFX exposure at the end of induction therapy was essential for a favourable long-term outcome. Patients achieving endoscopic remission at month six or clinical and/or biological remission at week 52 had already significantly higher post-induction IFX trough levels [20]. In fact, these trough levels were the only independent predictor for these different outcomes. A cut-off value of ≥ 5.0 µg/ml was deemed necessary to reach endoscopic remission both at the end of induction as during maintenance phase [19-20], which is in line with previously published adult literature. Furthermore, also the IFX exposure during the induction phase could predict endoscopic outcome at month six. Since, IFX concentrations could already discriminate remitters from non-remitters from week 4 after IFX initiation onwards. Threshold levels for different time points, including intermediate and trough levels during induction, were determined in order to achieve the highest possible response (see figure 2). Our results make it more feasible to translate the findings to routine clinical practice where patients usually present in the clinic at different time points and not only at trough.

Not only was an adequate drug exposure during induction but also during maintenance therapy essential for a long and durable response, including endoscopic remission [19]. Patients with mucosal healing at latest endoscopy (after a median follow-up of 1.4 years) had also a higher overall exposure to IFX during maintenance therapy in comparison to patients with lack of response with an excellent endoscopic outcome at latest follow-up of 72.5% [19]. Although, pro-active TDM-based treat-to-target strategies are currently not considered standard of care for IBD patients, our data support the use of pro-active TDM in children to improve long-term outcome. We therefore suggest applying pro-active TDM at least once after induction and then one time per year during stable maintenance therapy. Ideally, pro-active TDM is also implemented during induction therapy to prevent primary non-response driven by pharmacokinetic reasons, and to optimise IFX exposure to reach better long-term endoscopic outcome. During induction there is still a high inflammatory burden resulting in a higher drug clearance. In this respect, it has been shown that most paediatric patients will have subtherapeutic post-induction IFX trough levels when using the current standard regimen [20-22]. Therefore, determining an IFX concentration already at week 4 can help the physician to adjust dose and/or interval of the next infusion at week 6, and consequently improve further drug exposure. However, further prospective studies are now warranted to judge the cost-effectiveness of this approach in real-world practice (especially since it is safe to switch to cheaper biosimilars [23]).

Finally, the purpose of TDM is to dose the drug in such a way that the optimal drug exposure is achieved for each separate patient. Therefore, specific covariates needs to be determined that can explain the differences in drug exposure between patients. It has been known that IFX trough levels are greatly influenced by the degree of intestinal inflammation [24]. Our research confirmed this association, as especially patients with a lower haemoglobin at IFX initiation had lower IFX exposure during induction [19-20]. Thus, these patients could probably benefit from higher IFX doses already at the start and doses could be adjusted afterwards by TDM to achieve remission. In addition, lower serum IFX levels were found in patients with lower weight and stunted growth at IFX initiation [19-20]. Therefore, probably a more intensive treatment schedule than prescribed in the label is warranted to prevent under-exposure to IFX in younger patients. Nonetheless, development of pharmacokinetic models and prospective trials are crucial to further elucidate the ultimate treatment regimen prior to routine implementation into clinical practice.

**Figure 2:** Optimisation of outcomes in paediatric IBD patients




Legend: conc.: concentration; CD: Crohn's disease; CRP: C-reactive protein; IBD: inflammatory bowel disease; IFX: infliximab; PUCAI: Paediatric Ulcerative Colitis Activity Index; SD: standard deviation; TNF: tumour necrosis factor; UC: ulcerative colitis; wk.: week. iatric IBD patients

## Summary

To conclude, we discovered prognostic markers that could stratify at diagnosis, which patients were more likely to require surgery or biologics and thus, could benefit from accelerated step-up therapy. In addition, we demonstrated the importance of an adequate IFX exposure during induction and maintenance therapy in paediatric IBD patients. Since higher IFX trough levels throughout the different phases of the treatment course (induction, at the end of induction and maintenance phase) were significantly associated with better endoscopic outcome. IFX target concentrations were suggested for these different phases, specifically in children, what is necessary to implement TMD in clinical practice and to improve outcome. Our concluding findings are summarised in figure 2.

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In collaboration with Cebam, Cochrane Belgium
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# Use of reflective materials during phototherapy in neonates with unconjugated hyperbilirubinaemia: worth reflecting upon

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## Question

Does using reflective curtains improve the effectiveness of phototherapy of unconjugated hyperbilirubinaemia in newborn infants?

## Context

Neonatal jaundice occurs in about 60% of otherwise healthy new-borns and is usually due to an increased breakdown of haemoglobin while liver function is still immature, leading to unconjugated hyperbilirubinaemia. Although in most infants the jaundice does not lead to morbidity, the hyperbilirubinaemia can become so severe that bilirubin is deposited in the brain which could result in permanent brain damage.

Phototherapy has replaced exchange transfusion as the standard treatment since the late 1950's as the latter, although effective in removing bilirubin, was associated with many complications. In phototherapy, the energy provided by the specific wavelength light changes the structure of bilirubin allowing it to be excreted via the liver or the kidneys directly. It has already been shown that increasing the light intensity increases the rate of decline in bilirubin. A potentially inexpensive and easy way to increase the light intensity would be to hang reflective materials from the sides of the phototherapy unit which would reflect the dispersed phototherapy light back onto the baby. This systematic review addresses the question whether the use of reflective materials in combination with phototherapy is more effective in reducing unconjugated hyperbilirubinaemia as compared to phototherapy alone.

## Criteria for study selection

The Cochrane review included studies of term and preterm neonates up to 14 days (term) or 21 days (preterm) of age receiving phototherapy for unconjugated hyperbilirubinaemia. Studies had to compare the use of phototherapy in combination with curtains of reflective material of any type to the use of phototherapy alone or to other intensified phototherapy. The main outcome of interest was the decline in serum bilirubin levels per unit of time.

## Summary of the results

The review identified 12 trials with 1288 babies in total. Eleven studies compared phototherapy with reflective materials to phototherapy alone and one study compared a single phototherapy light bank with reflective materials to a double bank without reflective materials. The reflective materials used in the studies consisted of curtains on three or four sides of the cot made of white plastic (5 studies) , white linen (2 studies) or aluminium (3 studies) with two studies not specifying the material.

The use of reflective curtains probably results in a larger bilirubin decline at four to eight hours compared to not using curtains (MD: 14.61 µmol/L lower (95% CI*: 19.8 lower to 9.42 lower) (0.85 mg/dL lower (95%CI: 1.16 mg/dL lower to 0.55 mg/dL lower)); 3 studies, 281 infants, moderate-certainty evidence). Nine studies with a total of 893 participants reported a faster decline in bilirubin over 24 hours in the intervention group with curtains but the decline varied widely between studies from -5.00 µmol/L (-0.26 mg/dL) to -100 µmol/L (-5.57 mg/dL) and it was not meaningful to estimate an overall size of the effect. Due to this substantial inconsistency between studies as well as lack of blinding and possible selection bias, the evidence for this outcome was very uncertain (very low-certainty evidence). Subgroup analyses by type of reflective material used in the intervention group and by baseline serum bilirubin level did not explain the differences between the studies as heterogeneity remained very high within the subgroups. Duration of phototherapy was reduced in four studies, but once again results differed substantially between studies from -1.6 hours to -22.27 hours making a meta-analysis to calculate an overall effect size not meaningful. The evidence was also very uncertain for this outcome (very low-certainty evidence). The use of reflective curtains probably reduces the duration of hospital stay by almost 2 days (MD: -41.08 hours (95% CI: -45.92 to -36.25); 2 studies, 179 infants, moderate-certainty evidence). Exchange transfusion was reported by two studies, but both reported none in either group. None of the studies reported on costs, parental or medical staff satisfaction, breastfeeding outcomes or neurodevelopmental outcomes.

Only one study with 156 infants compared the combination of phototherapy and reflective curtains to double phototherapy. The evidence suggests that there is no difference in decline in bilirubin (MD: 0.17 µmol/L (95% CI -8.58 to 8.92); low-certainty evidence) nor in the duration of phototherapy (MD: 4.04 hours (95% CI -1.56 to 9.64); low-certainty evidence).

Adverse events were reported in nine trials and were similar between groups. Five of those nine trials reported that no adverse events occurred in either group. Due to the rarity of the adverse events, precise information regarding risks is lacking.

## Conclusion

The use of reflective curtains during phototherapy seems to result in a greater decline in serum bilirubin levels and a shorter duration of hospital stay. However, the effect varied greatly across studies and this heterogeneity could not be explained by type of material used nor by baseline bilirubin level. Unfortunately, the inconsistency in effect size limits the applicability of the results in clinical practice. The studies do not show an increase in adverse events when using curtains, but additional studies are needed as we are still uncertain about the possible harms.

## Implications for practice

Although the effect size is unpredictable, the evidence supports the use of reflective curtains to treat unconjugated hyperbilirubinaemia. Whether it also reduces the risk for an exchange transfusion remains unclear.

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# SPA® REINE
## l'eau et le microbiote du bébé

Dès les premiers mois de la vie, le microbiote intestinal joue un rôle important. **Entretien avec le conseiller en nutrition humaine Jean-Pierre Mans** qui explique le rôle du microbiote et la nécessité d'en maintenir la richesse pour prévenir, à terme, le développement d'infections ou de maladies comme le diabète, l'obésité et l'asthme[1].

### L'IMPORTANCE DU MICROBIOTE À LA NAISSANCE

JP MANS *Le microbiote du bébé se constitue dès la naissance au contact de la flore vaginale après un accouchement par voie basse. La colonisation bactérienne se déroule progressivement et dans un ordre précis. Les premières bactéries intestinales ont besoin d'oxygène pour se multiplier (entérocoques, staphylocoques,...). Viennent ensuite les bactéries qui se développent en l'absence de ce gaz (bactéroïdes, clostridium, bifidobactérium...)[2]. Sous l'influence de l'allaitement, de la diversification alimentaire, des traitements médicaux et de l'environnement, la composition du microbiote va évoluer pour se stabiliser vers l'âge de 3 ans.*

### UNE BONNE HYDRATATION POUR UN BON MICROBIOTE

JP MANS *Chez le petit enfant, l'hydratation est particulièrement importante puisque le corps du nourrisson est constitué à presque 80% d'eau contre 60% à l'âge adulte[3]. Dès lors, les besoins en eau du bébé sont très élevés: 150ml/kg/j[4]. L'eau faiblement minéralisée et surtout l'allaitement maternel vont jouer de nombreux rôles dont celui du transport des nutriments, des vitamines et des minéraux vers le microbiote pour faciliter leur assimilation.*

### RESTAURER UN MICROBIOTE ALTÉRÉ

JP MANS *En cas de diarrhée ou de gastro-entérite chez le bébé, un des risques est la déshydratation (jusque 15% du poids du bébé, en particulier avant 6 mois). Dans ce cas et si l'enfant est nourri au sein, l'allaitement doit être poursuivi. Par ailleurs, une solution de réhydratation reconstituée avec une eau faiblement minéralisée doit être administrée. De plus, si une antibiothérapie a été initiée, il faudra recoloniser le microbiote intestinal[5]. En effet, 80% des cellules immunitaires du corps humain se situent au niveau du tube digestif. Un microbiote intestinal altéré va augmenter le risque de développer par la suite des infections ou des maladies[1]. Dans ce contexte on pourra recourir aux probiotiques dont certaines souches ont démontré leur utilité.*


(1) Harstra et al: Insights into the role of the microbiome in obesity and type 2 diabates, Diabetes care 2015; 38 : 159-65.
(2) Rémy Burcelin, unité INSERM 1048 / Université P. Sabatier & Institut des maladies métaboliques et cardiovasculaires, Hôp. Rangueil, Toulouse.
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NUTRICIA

# UW PARTNER IN ALLERGIE

## VOOR IEDERE ZUIGELING MET (KANS OP) ALLERGIE
## HET JUISTE ADVIES


Nutrilon® Prosyneo HA


Nutrilon® Pepti Syneo™


Neocate® LCP

Neocate® Junior

**RISICO OP ALLERGIE**

PHF

**BEWEZEN ALLERGIE**

eHF

**AANHOUDENDE SYMPTOMEN OP eHF/ COMPLEXE ALLERGIE**

AAF

**VOOR MEER INFORMATIE OF ADVIES, NEEM CONTACT OP MET ONZE DIËTISTEN VAN NUTRICIA CARELINE: 0800 99 486 (VOOR NUTRILON) EN 0800 16 685 (VOOR NEOCATE)**

**Belangrijk:** Borstvoeding is de ideale voeding voor baby's. Nutrilon Prosyneo is een zuigelingenmelk en wordt gebruikt op advies van een arts. Nutrilon Pepti Syneo 1 en 2 zijn dieetvoedingen voor medisch gebruik bij koemelkeiwitallergie. Neocate LCP en Neocate Junior zijn dieetvoedingen voor medisch gebruik bij koemelkallergie, meervoudige voedselallergie en andere aandoeningen waarbij een elementaire voeding wordt aanbevolen. Uitsluitend onder medisch toezicht gebruiken. Deze informatie is uitsluitend bedoeld voor (para)medici. V.U.: N.V. Nutricia België, Werkhuizenkaai 160, 1000 Brussel - 09/2020