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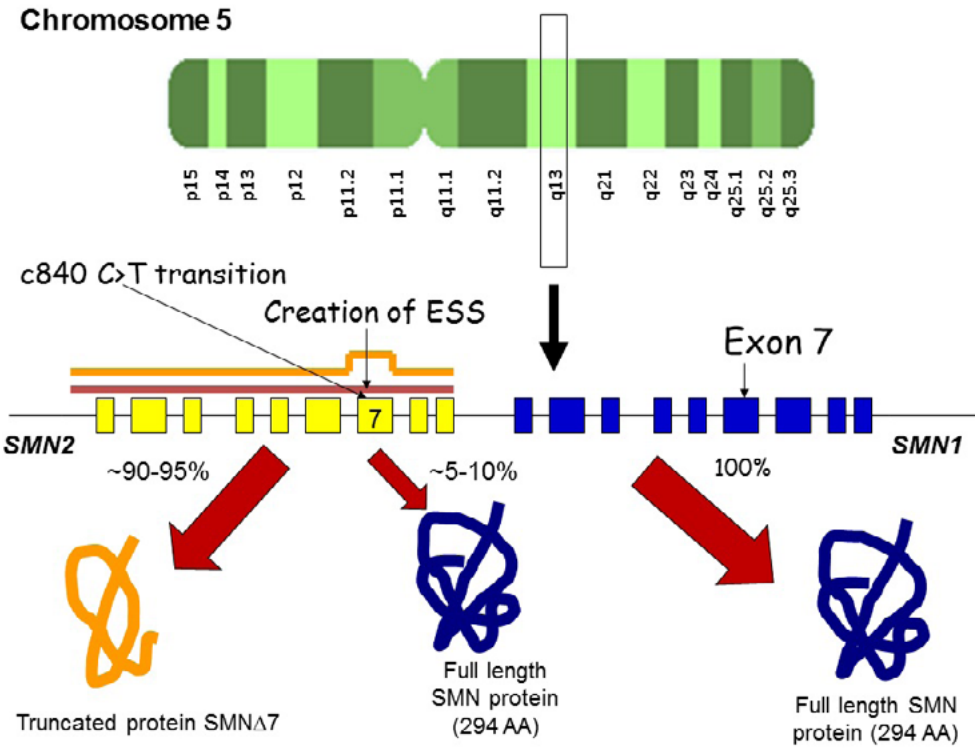

Theme: Pharmacology in Paediatrics

Articles

Paediatric Cochrane Corner

Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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A la vie

Editorial Board

NIEUW: PAMPERS® AQUA PURE BABYDOEKJES

De zuiverheid van water in het gemak van een doekje

De nieuwe Pampers® Aqua Pure babydoekjes zijn ontworpen om het meest water bevattende doekje te bieden, en daarbij nog steeds de best mogelijke huidbescherming te waarborgen.

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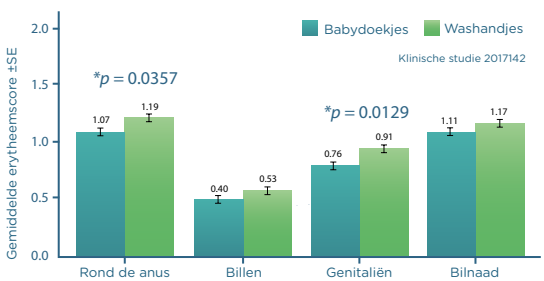
Een nieuwe klinische studie toont aan dat Pampers Aqua Pure-babydoekjes minstens even mild en zacht zijn als een washandje en water

In samenwerking met de ESPD heeft Pampers in een studie bij 130 baby's de invloed van babydoekjes op de luierzone vergeleken met die van een washandje en kraantjeswater.

Dit werd onderzocht in een willekeurig toegewezen, single blind parallel group design studie (dit wil zeggen dat onderzoekers niet weten welke de toegepaste verzorging is). Na een rustfase van één week waarbij enkel washandje en kraantjeswater werd gebruikt, werden de twee verzorgingen vergeleken gedurende een periode van twee weken. De aanwezigheid van erytheem werd daarbij gemeten op vier plaatsen.

Na twee weken gebruik bleken Pampers® Aqua Pure babydoekjes minstens even mild te zijn als washandjes en water. De huid die behandeld werd met babydoekjes, had ook een aanzienlijk lagere pH-waarde dan de huid die verzorgd werd met een washandje en kraantjeswater. Dat zou op lange termijn beter kunnen zijn voor de gezondheid van de huid.

Gemiddelde erytheemscore per meetplaats



Ingrediënten van plantaardige oorsprong die dermatologisch getest werden

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pH-buffer lotion

De lotion bevat een buffer op basis van citroenzuur die het natuurlijke pH-evenwicht van de huid helpt te behouden.[1] Wetenschappelijke studies hebben aangetoond dat de verstoring van het pH-evenwicht door een vuile luier één van de belangrijkste oorzaken van luieruitslag is. De combinatie van urine en stoelgang bevat verteringsenzymen die de huid irriteren. De babydoekjes van Pampers zijn voorzien van een speciaal ontwikkelde lotion die een pH-buffer functie vervult en de pH-waarde van de huid snel herstelt naar het normale niveau van ca. 4,5-6,0.

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[1] Interne gegevens van P&G

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PAMPERS STEUNT DE BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE

European Society for Pediatric Dermatology

Goedgekeurd door ESPD

Editorial

September concludes the holiday period and is synonymous of “back to work”, although the summer season is frequently a busy period where those who remain need to compensate the vacation (etymologically it means emptiness) of colleagues by extra days of duties. Consequently, the autumn issue of the journal is the result of a difficult compromise between the race to comply with the publication deadlines and the necessary check of the quality of the manuscripts. In order to respect the complex editorial process, manuscripts counting for the recognition in paediatrics should be submitted by the end of March as deadline. Many thanks to our co-editor Marek Wojciechowski for his great job in checking the editorial quality of the articles and to our secretary Natacha Meignen who is due to harass the authors in her efficient but friendly way.

In this issue of the BJP (2019 vol 21 nr 2) an interesting message derives from the article *“Congenital cytomegalovirus infection after reactivation in a seropositive mother: innocent infection or not?”* stressing the importance of prevention strategies in pregnant women because reactivation of cytomegalovirus in seropositive women, is responsible for the greatest portion of symptomatic congenital CMV infections in neonates.

A review article *“Inflammatory polyps of the tracheobronchial tree in children: case-series and review of literature”* deals with a rare disease in children originating from chronic inflammation of the airway that causes unexplained chronic cough and dyspnoea. In the presence of atelectasis and hyperinflation, especially in a child that has been intubated, early endoscopic removal allows confirmation by histopathology and possible recovering of lung function.

The authors of the article *“Deformational plagiocephaly as a marker for developmental delay”* have conducted an extensive study of the literature about the possibility of considering cranial asymmetry due to position in children younger than two years and stress the fact that what had been considered only as an aesthetic problem is probably a real risk factor of developmental delay.

Our very useful paediatric Cochrane corner concerns *“Current rotavirus vaccines: effective and safe”* whereas our regular sections “Made in Belgium”, ”Focus on symptoms” and “Metabolic diseases” are absent in this autumn issue but should not be considered as “fallen leaves” since we expect their comeback in next issues of your BJP.

The core contents of this issue of BJP is devoted to the theme *“Pharmacology in Paediatrics”* coordinated by our guest editors Koen Norga and Thierry Schurmans. This topic is becoming more and more important for the understanding of the correct and reliable management of therapeutic drugs. We should remember the surprising withdrawal, some years ago, of the very helpful prokinetic cisapride (Prepulsid), a spectacular illustration of the necessity to understand better the pharmacology of the drugs we use regularly: metabolism, timing, distribution, interferences, side effects and so on. Since randomized control trials are uneasy to conduct in children, relevant data are difficult to collect but, quite evidently, adaptation of doses solely to bodyweight is a rough and very insufficient method. The articles of this theme constitute an interesting approach of this prominent topic that will probably benefit from further advances not only from genetics but also from possible interactions of the microbiota.

Samy Cadranel and Marc Raes

Uw vragen of commentaar
Vos questions ou commentaires

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SOCIÉTÉ BELGE DE PÉDIATRIE

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Marc Raes
President BVK - SBP

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SOCIETE BELGE DE PEDIATRIE

Hernieuwing lidgeld 2020

Beste Collega,

De leden van de Raad van bestuur wensen u uit te nodigen voor het lidmaatschap van onze verenging. Door uw bijdrage als lid van onze vereniging kunnen we samen werk maken van de toekomst van de pediatrie. Wij, Belgische kinderartsen, hebben elkaar nodig. De BVK heeft in de eerste plaats een wetenschappelijke rol en steunt en handhaaft de wetenschappelijk gezondheidszorg voor kinderen en werkt daarvoor ook samen met **de Vlaamse Vereniging Kindergeneeskunde (VVK) en de Groupement Belge des Pédiatres de langue Française (GBPF)**. De BVK werkt ook samen et de Academie en het College pediatrie in de beleidsvisies en de organisatie van de pediatrie op maatschappelijk vlak.

Laat ons samen aan de Belgische Vereniging voor Kindergeneeskunde de naam en de uitstraling geven die ze verdient. Een lidmaatschap van alle gevestigde kinderartsen en elke assistent in opleiding kindergeneeskunde kan de uitbouw en uitstraling van onze vereniging verder optimaliseren en moderniseren. We blijven via meerdere initiatieven de belangrijkste wetenschappelijke spreekbuis op nationaal niveau, niet enkel naar de eigen discipline toe, maar evenzeer naar andere professionelen en zorgverleners, de overheid, naar onze patiënten en hun families alsook naar het bredere publiek.

De voordelen van een BVK lidmaatschap zijn talrijk: via de site van de BVK, krijgen 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. Verder krijgen de leden ook gratis het tijdschrift “Belgian Journal of Paediatrics”, met interessante artikels van eigen bodem.

Door uw bijdrage als lid van onze vereniging kan u zich ook **aan een voordelig tarief inschrijven voor het komende Jaarlijks Congres van de BVK op 19 en 20 maart 2020**. Mede door uw lidmaatschap kunnen wij **een beurs voor onderzoek uitreiken aan het beste werk** dat ons wordt toegestuurd. Help ons onze onderzoekers aan te moedigen en ze in België te houden!

Het hernieuwde lidmaatschap loopt tot 30 september 2020.

De jaarlijkse bijdragen blijven ongewijzigd:

- **-120€ voor de kinderartsen**
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Wij rekenen graag op jullie bijdrage om samen te werken aan de realisatie van onze toekomst.

Van harte,

Dr Marc RAES
Voorzitter BVK/SBP

Renouvellement cotisation 2020

Cher collègue,

Les membres du Conseil d'administration vous remercient pour la confiance que vous placez dans la SBP. Grâce à votre contribution en tant que membre de notre association, nous pouvons travailler ensemble à l’avenir de la pédiatrie. Nous, pédiatres belges, avons besoin les uns des autres. La SBP est avant tout une association de scientifiques sensibilisés aux aspects médicaux auxquels l’enfant est confronté et travaille ensemble avec de **Vlaamse Vereniging Kindergeneeskunde (VVK) et le Groupement belge des Pédiatres de langue française (GBPF)**. La SBP coopère avec également avec l'Académie et le Collège de pédiatrie au niveau des visions politiques et dans l'organisation de la pédiatrie au niveau social.

Donnons ensemble à la Société Belge de Pédiatrie le nom et la visibilité qu’elle mérite. L’adhésion de tout pédiatre avéré et de tout assistant en formation de pédiatrie contribue à optimaliser et moderniser le rayonnement et l’extension de notre association, en tant que porte-parole scientifique reconnu au plan national non seulement au sein de notre propre discipline, mais aussi vis-à-vis d’autres professionnels de la santé, des autorités, de nos patients, de leur famille et d’un public plus large.

Les avantages d'une adhésion à la Société sont nombreux : notamment, les membres bénéficient, via le site de la SBP, **d’un accès à la bibliothèque virtuelle CEBAM** (Belgian Center for Evidence Based Medecine). Je vous rappelle que l’accès au volet pédiatrique du site de la CEBAM permet la lecture et le téléchargement d’articles des principaux journaux pédiatriques (entre autres Pediatrics, Journal of Pediatrics, Pediatric Infectious Disease, 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 d’Evidence Based Medecine (Cochrane Library, etc) ainsi qu’à des livres électroniques. Les membres reçoivent aussi gratuitement le BJP (Belgian Journal of Paediatrics).

Votre adhésion en tant que membre de notre association vous permettra de vous inscrire **à un tarif réduit au futur Congrès Annuel de la SBP qui aura lieu le 19 et 20 Mars 2020**. Grâce à votre adhésion, nous pouvons, en autres, donner un prix pour la recherche à la meilleure contribution. Aidez-nous à encourager nos chercheurs et à les garder en Belgique!

L’adhésion renouvelée est valable du 1ier octobre 2019 jusqu'au 30 septembre 2020.

Les cotisations annuelles restent inchangées :

- **120 € pour les pédiatres**
- **60 € pour les assistants en pédiatrie**
- **60€ pour les pédiatres pensionnés**

Vous pourrez renouveler votre cotisation par le site web : www.bvk-sbp.be

Nous comptons à nouveau sur votre contribution et travaillons ensemble à la réalisation de notre avenir.

Cordialement,

Dr Marc Raes
Président SBP/BVK

SAVE THE DATE

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Introduction

All of us prescribing medicines for neonates, infants, children and adolescents expect that these drugs are effective and safe for our patient. It implies that these products should have previously proven their efficacy in clinical trials, their effectiveness in clinical practice, their safety from clinical trials and pharmacovigilance, their utility in terms of quality of life and their efficiency (cost/benefit) in the neonatal and paediatric age. Even with medicines authorized further data is still required on therapy optimization and many childhood diseases a pressing unmet need remains, including for numerous orphan diseases.

Since legislation to address these challenges came into force globally more than a decade ago, much progress has been made. Nevertheless we have to be aware that for many medicines commonly prescribed for this young population the evidence base is still weaker compared to the adult indications, with frequent off-label use, i.e. for an unapproved indication or in an unapproved age group, dosage, or route of administration, despite substantial efforts of all stakeholders, not least the children and families participating in rising numbers of paediatric clinical trials. Challenges remain, particularly for neonates and infants, and in paediatric intensive care medicine. Even for labelled uses, further improvements are required. Surely all of us engaged in this area, have learned that neonatal and paediatric clinical research remains complex and resource consuming.

In this issue of the Belgian Journal of Paediatrics 2019/3, we have the privilege to present original contributions by several Belgian key opinion leaders and their teams in the fascinating field of developmental pharmacology. Johan Vande Walle has been active in this area for a long time and he is now coordinating the Belgian branch of the Collaborative Network for European Clinical Trials for Children (C4C) of the European Innovative Medicine Initiative (IMI). Pauline De Bruyne, his former student, is rapidly developing a remarkable expertise in regulatory aspects of paediatric medicines. Karel Allegaert has energetically spearheaded the field of neonatal pharmacology in Belgium for many years. An Van Damme, newly elected BSPHO president and longtime coordinator of its national clinical trial coordination unit, reports on a unique model of collaboration in the Belgian paediatric oncology community enhancing clinical trial preparedness in this rapidly evolving field. Pieter De Cock et al present original insights from the lab in the difficult field on intensive care pharmacology research. Last but not least, as esteemed clinical investigators, Nicolas Deconinck et al report on recent breakthroughs with innovative medicines development for spinal muscular atrophy.

The neonatal and paediatric pharmacology's revolution is underway. We sincerely hope that the present series may instill even greater enthusiasm into the Belgian paediatric community. Many medicines are now under development and numerous paediatric clinical studies are awaiting to be performed. Belgium has historically a strong track-record in clinical trials research. The challenge for all of us in the coming years is to extend this know-how to paediatrics. Only by doing so will we be able to effectively tackle, in the end, the challenges we still face daily as prescribing clinicians.

On behalf of the editorial board, we wish you a fruitful reading.

Koen Norga, MD, PhD, Chair of the Paediatric Committee (PDCO) at the European Medicines Agency (EMA), Universitair Ziekenhuis Antwerpen.

Thierry Schurmans, MD, member of the Belgian Paediatric Clinical Research Network (BPCRN), Hôpital Universitaire des Enfants Reine Fabiola and Centre Hospitalier Universitaire de Charleroi

Clinical trial preparedness for paediatric medicines development: the Belgian model of clinical trial organisation in paediatric haematology and oncology

An Van Damme [1,2], An Michiels [1,3], Gaëlle Dufour [1,2], Marlies Bekaert [1,4], Bénédicte Brichard [2], Alina Ferster [5], Geneviève Laureys [4], Koen Norga [6], Caroline Piette [7], Jutte van der Werff ten Bosch [8], Anne Uyttebroeck [3]

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Key words

academic clinical trial, early phase clinical trial, trial networks

Abstract

Childhood cancers are inherently rare diseases and diagnostic and therapeutic progress relies heavily on participation of patients in clinical trials. Frontline treatment of many paediatric cancer patients involves enrolment in a late-phase or therapy optimisation trial. The Belgian Coordination Cell for Clinical Trials coordinates these efforts and supports the treatment centres for the logistical, financial and organisational burden of trial participation.

To enhance prognosis further, and thanks to increased biological understanding of cancer, new treatment options are needed. New compounds such as targeted therapies need to be studied in early phase clinical trials in children. Children who are eligible for these trials are often confronted with relapsing or refractory disease. In order to improve access to these trials, to decide which trials to prioritise and to use resources judiciously, Belgian centres have established an early phase clinical trial board.

Clinical trial organisational burden and efficiency has significantly improved with the creation of the Coordination Cell for Clinical trials and the development of a network of centres who perform early phase clinical trials in paediatric haematology and oncology in Belgium. However, significant hurdles remain for early as well as late phase clinical trials in paediatric oncology. We describe current organisation and perspectives for further improvement of clinical trial support for the centres and for enhancement of trial accessibility for patients.

Importance of clinical trials for the treatment of children with cancer

In Belgium, approximately 320 children aged 0-14 years and 175 adolescents (15-19 years) are diagnosed with cancer every year and 70 patients younger than 20 years die from cancer[1]. Childhood cancers thus account for approximately 1% of all oncological diseases with current five-year survival rates currently approaching 85% for all paediatric cancers combined[1].

The field of paediatric oncology is small in terms of patient numbers, but it covers at least 60 different types of cancer. Current molecular analysis of tumours and improved biological understanding has revealed a greater variety among diseases that were formerly believed to be one diagnostic entity. Consequently, any type of paediatric oncologic diagnosis can likely be catalogued as a 'rare disease', defined as affecting 1 person or less per 2000[2].

Since the nineteen sixties, survival rates have increased steadily and significantly for most childhood cancer types. This improvement has largely been due to a more accurate use of chemotherapeutic drugs and combinations of treatment modalities. Clinical trials aiming to improve prognosis and survival require sufficient numbers of patients to gain meaningful results. These trials are typically conducted in the framework of (inter)national academic collaborative groups and require first-line treatment of as many patients as possible within clinical trials. The 'routine' practice of including newly diagnosed patients in these trials has been adopted by many centres worldwide since several decades and has contributed to the current good overall survival rates. These trials typically are investigator-driven and funded by academic or charity resources, rather than by pharmaceutical companies. Participation and inclusion of patients require a high level of involvement and motivation of the physicians proposing the trials to their patients. The Belgian centres treating children with cancer have made considerable efforts to facilitate access to these academic clinical trials and to implement them conform the current national and European regulations.

The Belgian Society for Paediatric Haematology and Oncology (BSPHO) has founded the National Coordination Cell for Clinical trials in 2011. The task of the Coordination Cell is the advancement of clinical research in paediatric oncology in Belgium by providing support for the administrative and logistic burden of academic clinical trials and by coordinating the clinical research efforts between centres. Clinical trial awareness in paediatric oncology in Europe and across the globe and organisation of these trials has improved over the last fifteen years.

Despite these efforts, improvement of survival rates has stagnated, underscoring the need for innovative treatment approaches that are currently not routinely available to children and adolescents with cancer[3]. Meanwhile, the field of oncology, including paediatric oncology, has experienced an explosive increase in the amount of biological knowledge over the last decade. Genomic, epigenomic and transcriptional alterations have been shown to be implicated in and/or drive cancer development and are linked to natural evolution, prognosis, response to therapy etc… The clinical application of these molecular datasets is termed 'precision medicine' and includes the multi-layered diagnosis of diseases and their targeted therapies[3].

The concept of targeted therapies is based on the notion that directing treatment towards somatic genomic alterations that are unique to cancer cells, will improve therapeutic efficacy and decrease adverse events[4]. For adult cancers, the use of these oncogenic mutations and their therapeutic counterpart is already implemented in a number of upfront, standard of care therapies. It has been shown that adult patients with advanced disease have a higher response rate, longer time to progression and better overall survival if they receive a phase 1

therapy matched to a molecular alteration in their tumour[4].

As childhood malignancies are mostly biologically distinct from adult cancers, it is currently not clear to which extent this therapeutic validation can be extrapolated to paediatrics. Additionally, the role of inherited cancer susceptibility plays a larger role in the development of cancer in children. It is currently not known how this will influence the response (or lack thereof) of new molecules in clinical practice[4]. Moreover, the long-term effects of current paediatric cancer treatments can be more devastating than in adults, since it occurs early in life and the late effects from disease and treatment continue to develop over several decades[5]. Increasing scientific knowledge of the use and benefits of innovative treatment modalities for children with cancer is therefore urgently needed. Currently, access to innovative drugs is mostly limited to paediatric cancer patients included in early-phase clinical trials, where eligibility is reserved for exceptional cases of therapy resistance or relapse. They are rarely life-saving, since this is not the primary objective of these pharmacokinetic and safety trials. Access to innovative drugs within clinical trials or in routine practice represents an unmet need for children with cancer.

In this paper, we describe the current organisation of clinical trials in paediatric oncology in Belgium. More in particular, we explain how the collaboration between centres aims to maximize efficiency and use of resources, while striving for improved availability of clinical trials and innovative treatment options for patients.

The National Coordination Cell for Clinical trials of the BSPHO – late phase academic trials

The BSPHO was founded in 1996 by Belgian paediatric oncologists aiming to promote education and scientific knowledge in the field of paediatric haematology and oncology in Belgium. It is led by a board, consisting of members from all recognized treatment centres and includes several scientific committees, each covering a specific subdomain of paediatric haematology and oncology (e.g. leukaemia & lymphoma, brain tumours, bone and mesenchymal tumours, neuroblastoma, kidney and liver tumours, benign haematology).

As stated above, optimal therapeutic management in first line treatment (i.e. 'standard-of-care') for children with cancer often involves participation in a late phase clinical trial, a so-called 'therapy optimisation trial'. Since 2010, Action 12 of the Cancer Plan provides funding for 'the stimulation of research in paediatric haematology and oncology (PHO) and for networking between centres'. This funding is centralised by the BSPHO, who combined it with a grant from Kom op tegen Kanker for the support of clinical research in all Flemish paediatric oncology centres. The acquisition of these two funding sources was the incentive for the foundation of the National Coordination Cell Clinical Trials in 2011.

The Clinical Trial Coordination Cell coordinates clinical research efforts between centres and supports them for the administrative and logistic workload related to the implementation of clinical trials. It currently consists of a coordinating physician and collaborators based in three different paediatric haematology/oncology (PHO) centres (UZ Gent, UZ Leuven and St Luc University Hospital Brussels). Additionally, the coordination cell funds a collaborator at the Belgian Cancer Registry who specifically works on paediatric cancer registration as stated in the financing requirements of the Cancer Plan. Together they form a virtual cell that supports trials led by any principal investigator based in a Belgian PHO centre. This support is mostly limited to academic trials with no or minimal central funding, executed in the frame of international collaborations. It includes trial applications to the competent authorities, ethical committee submissions and preparation of submission packages for the centres, the organisation of data monitoring, grant applications, contract negotiations etc… The trials involved are typically so-called 'late-phase' and 'therapy-optimisation' trials, mostly academic trials, and accessible to patients in first-line treatment or, less frequently, in first relapse situations.

The first studies prepared and supported by the coordination cell opened in 2012. Almost 30 trials have been supported since, with almost 20 additional trials currently in the pipeline. The opening of an academic late phase trial has been rendered more feasible for the PHO centres. Currently, the time needed to open such a trial in Belgium is among the shortest compared to other European countries.

However, significant hurdles continue to exist. There is no structural budget to cover the cost of academic clinical research, even in the context of standard of care therapies and on the other hand costs of no-fault insurance, pharmacy fees, data collection, pathology/imaging review, biobanking, monitoring etc.[5], needed to conduct a trial according to legal and scientific standards

All Belgian PHO centres employ at least one study coordinator, usually funded by charity sources. These local study coordinators are responsible for support of the local investigators, the local trial implementation (local ethical committee submissions, budget, local contract negotiations and logistics, etc.) data management, safety reporting, etc. These trial teams are thus an integral part of the care team of paediatric oncology patients and their management is part of the day-to-day organisation of a PHO centre.

Early phase clinical trials in paediatric oncology

Classical treatment practices and well established participation in late phase clinical trials are currently still not able to provide cure for all paediatric cancer patients and result in a significant cost in terms of long-term toxicities. For some rare tumour entities and refractory or relapsing tumours, classical multimodal treatment approaches have failed to improve prognosis, despite intensification of already toxic therapies[3]. New treatment modalities are urgently needed to improve survival in these patients.

New biological and pathogenetic insights based on the analysis of the genomic features of cancers are increasingly being described, including the identification of genes that cause and drive malignancy[3]. As is the case in adult oncology, new cancer treatment strategies are increasingly based on the genomic profile of the tumour.

The picture of genomic alterations that characterize paediatric cancers is also becoming clearer[6-8]. For some paediatric cancers, genomic alterations have been described that are rarely seen in adult cancers. Molecularly targeted therapies are therefore usually not available to treat these children. For another subset of cancers, genomic alterations that are well known for adult cancers of different histology are found, and targeted therapies exist for the treatment of some of these adult cancers (e.g. BRAF, ALK). Finally, breakthroughs in cancer immunotherapy have been achieved in the last decade[6-8].

These discoveries provide new therapeutic opportunities that could improve outcome for children with cancer. However, specific paediatric clinical trials are needed due to the relative rarity of paediatric cancer, differences in aetiology and natural history of childhood cancer and fundamental differences in pharmacokinetics. These trials are faced with substantial logistical difficulties[9].

A large number of clinical trials testing new compounds have been offered to adult patients for almost two decades. Children with cancer have had fewer opportunities to enter those clinical trials, even though more clinical trial options for children have become available more recently. According to the EU Paediatric Regulation, pharmaceutical companies are compelled to develop Paediatric Investigation Plans (PIPs), leading to industry-sponsored early phase clinical trials (ECTs), dedicated to testing specific molecularly targeted drugs (in monotherapy or combinations) in children[10-11].

To face the problem of reaching meaningful results in small study populations, newer trial designs are being developed. For example, a master protocol is a clinical trial model that includes multiple treatment cohorts based on a molecular screening approach that assigns patients to a matched targeted therapy, regardless of histology[9]. Master protocols can employ umbrella, basket or platform designs to study a single targeted therapy in multiple diseases, multiple targeted therapies in a single disease, or multiple targeted therapies in diseases spanning multiple histologic subtypes harbouring one or more molecular features.

Several European initiatives have aimed at increasing access to innovative treatments for children with cancer. The Innovative Therapies for Children with Cancer consortium (ITCC) was created in 2003 as a non- profit organisation under the French Law. It gathers 56 European PHO departments with expertise in conducting ECTs for children and 22 European research laboratories. The aim is to coordinate the development of novel therapies for children with cancer, in cooperation with regulatory bodies, pharmaceutical companies, parents and patients. Other ECTs are being conducted in sites with early-phase trial expertise outside the ITCC network through direct interaction between the pharmaceutical industry and the sites. The ACCELERATE international platform provides a transparent forum to address and discuss overarching issues in the development of innovative anticancer agents for children and adolescents.

The wealth of new biological information and new therapeutic compounds, combined with the rarity of paediatric cancers leads to the need for prioritisation in early phase clinical trials, which should be based on the mechanism of action of the agent, the rationale for target and agent selection, availability of paediatric formulations, safety

profile, ongoing trials that compete for patient enrolment. This can for example be done by a Paediatric Strategy Forum as implemented in the EU by the ACCELERATE platform and the EMA. A Paediatric Strategy Forum is a scientific meeting where information is shared with all stakeholders in a precompetitive setting, in order to inform a paediatric drug development strategy[9].

Only a small fraction of available early-phase industry-sponsored trials are currently recruiting in Belgium. The Paediatric Oncology Department of the Ghent University Hospital, as ITCC institution, conducts ECTs, mainly in the area of paediatric malignant haematology, while other Belgian paediatric/haematology departments are also conducting early-phase trials in the framework of early-phase facilities in their hospitals, aiming to increase the capacity for ECT access for Belgian patients within the country. Nevertheless, children with advanced cancer who may be eligible to these trials may have to travel abroad to enrol or to explore enrolment in these trials.

In order to expand ECT capacity in Belgium and to allocate resources in the most judicial way by prioritising trials, Belgian PHO centres have agreed to discuss all ECT (phase I and II) proposals from industry or academia, including stem cell transplantation and supportive care trials, before accepting proposals. These ECT board discussions are held by teleconference on a weekly basis and were started in November 2017.

Discussion points for each proposed trial include: feasibility in Belgium, utility for our patients, competitive trials open or in preparation, number of sites required in Belgium, etc. Up until July 1st 2019, 17 meetings have taken place and 25 trial proposals have been discussed. Two trials have been declined and 8 trials are open. Seven ECTs are currently recruiting patients in one or more Belgian centres, while one trial is completed and closed.

When the ECT board concludes that a trial is interesting and that one Belgian site is sufficient, the other centres commit to referring patients to the centre opening the trial and sign a written commitment letter to the company. In other cases, the board feels that it would be useful to open more than one centre (for example one Dutch- and one French- speaking centre), which is then communicated to the company. All decisions are taken unanimously by all participating centres and the ECT board decides which site(s) will be proposed for the trial.

The publicly available part of the BSPHO website (www.bspho.be) provides an overview of ECTs that are available in Belgium, including useful information such as the pathology, type of trial and a link to another publicly available website https://clinicaltrials.gov/, which gives a general overview of each trial. A closed part of the BSPHO website accessible to the treating physicians and trial teams of the PHO centres, includes more detailed and up to date information regarding indications, compounds, eligibility criteria and the open centres. Further improvements to this system are being developed, such as the establishment of one contact point for pharmaceutical companies or Clinical Research Associates (CRAs) that are exploring the possibility of opening a commercial trial in Belgium.

Conclusion and perspectives

The field of PHO has a long-standing tradition of treating patients in multi-institutional, multinational academic clinical trials. This practice has contributed to the current very acceptable cure rates for most paediatric cancers in these inherently rare diseases and is now considered 'standard-of-care' in first line treatment of many paediatric cancer types.

The BSPHO has created a coordination cell for clinical trials that supports centres for the administrative and organisational burden of conducting a large number of clinical trials, each recruiting a small number of patients. This has significantly enhanced clinical trial preparedness in Belgian centres, while improving quality of care and generating of scientific data. Remaining challenges include the securing of funding of academic clinical research, the financing of standard-of-care drugs that are not reimbursed by Belgian health care security and the workload of the local clinical trial teams.

More recently, BPSHO centres have established an ECT board to discuss all proposed ECTs in order to prioritise trials, to optimise the use of available resources and to improve availability for Belgian patients. This recent initiative is still under development and will require continued collaboration in other areas, such as the creation of reference labs, centralisation of expertise, and improvement of work flows for accelerated trial availability. Further enhancement of collaboration and support to centres will lead to optimized access to cutting edge treatments in first- line treatment and in relapse/refractory disease for Belgian paediatric cancer patients.

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Neonatal clinical pharmacology: current evolutions and future perspectives

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Key words

neonatal pharmacology; physiology-based modeling; PK data driven software tools; prediction; therapeutic drug monitoring; adverse event severity assessment

Abstract

Pharmacotherapy is a very powerful tool to improve outcome in neonates. Clinical pharmacology supports this by predicting drug-related (side)-effects, driven by pharmacokinetics (PK) and pharmacodynamics (PD). The dynamic changes related to maturation and growth in newborns, combined with population-specific disease characteristics result in a unique setting with extensive variability in both PK (drug concentration-time profiles) and PD (drug concentration-effect profiles). Only in part because of these dynamic alterations, neonatal pharmacotherapy is still lagging behind when compared to the available level of knowledge and research tools in other populations. However, relevant progress has been made.

We therefore wanted to highlight some ongoing efforts to 'translate' this recently emerged knowledge on neonatal pharmacology by facilitating access for prescribers as an obvious need to improve our current clinical practice. The Neodose project and data driven PK software tools hereby serve as illustrations of such clinical 'translation' efforts. This will be followed by some perspectives to further improve neonatal drug development and research tools. Adaptations of research tools to the characteristics of neonates are hereby crucial. The relevance of such adaptations will be highlighted, using physiology-based (PB)-PK modeling and the development of an adverse event severity grading research tool tailored to neonates as examples.

In conclusion, neonatal pharmacology is still lagging behind and full catch-up on knowledge driven pharmacotherapy has not yet been attained. However, this subdiscipline is for sure on the move to further improve neonatal outcome, driven by multidisciplinary collaboration.

Introduction

Drug therapy is a very powerful tool to improve outcome. This obviously also applies to neonates [1,2]. Prescription of a specific drug should be made with the intention to be effective and safe. Clinical pharmacology supports these aims in predicting drug-related (side)-effects driven by pharmacokinetics (PK) and pharmacodynamics (PD). PK (***a***bsorption, ***d***istribution and elimination, through either ***m***etabolism or primary renal ***e***limination, ***ADME***) hereby aims to describe the relationship between a drug concentration at a specific site (e.g. plasma, cerebrospinal fluid) and time ('*what the organism does to the drug*'). PD estimates the relationship between a drug concentration and (side)-effects ('*what the drug does to the organism*'). Unfortunately, the potential impact of drugs to improve outcome is still underexplored in neonates [1-5].

Age related subcategories within pediatrics are defined by authorities like the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) (***Figure 1***). Neonates are hereby a particular subcategory, covering the time interval from birth up to 28 days of postnatal life, although this definition has been adapted to the maturational age of 44 weeks postmenstrual age (term equivalent age + 4 weeks) to incorporate the subpopulation of (former) extreme preterm neonates [6]. ***Figure 1*** hereby further stresses the impressive changes (like growth, weight gain, caloric needs,) that occur throughout young infancy. These dynamic changes related to maturation and growth in newborns result in a unique setting for pharmacotherapy [6]. Since clinical pharmacology mirrors (patho) physiology, it is obvious that this will result in extensive variability in PK and PD in early infancy, while non-maturational changes (like disease characteristics, drug-drug interactions, pharmacogenetics) further add to this intra- and interpatient variability [3]. The impact and extent of maturational ADME aspects on neonatal pharmacotherapy is illustrated in ***Table 1***. Unfortunately and only in part because of these dynamic alterations, the knowledge on neonatal pharmacology and the scope of available research tools is still lagging behind when compared to other populations. A recent meta-analysis (2015) confirmed that off-label drug prescription in neonates is still common practice (90%) [7], despite legal initiatives to stimulate pediatric studies, and additional initiatives like the Food and Drug Administration Safety and Innovation Act (FDASIA) to boost neonatal drug research [6].

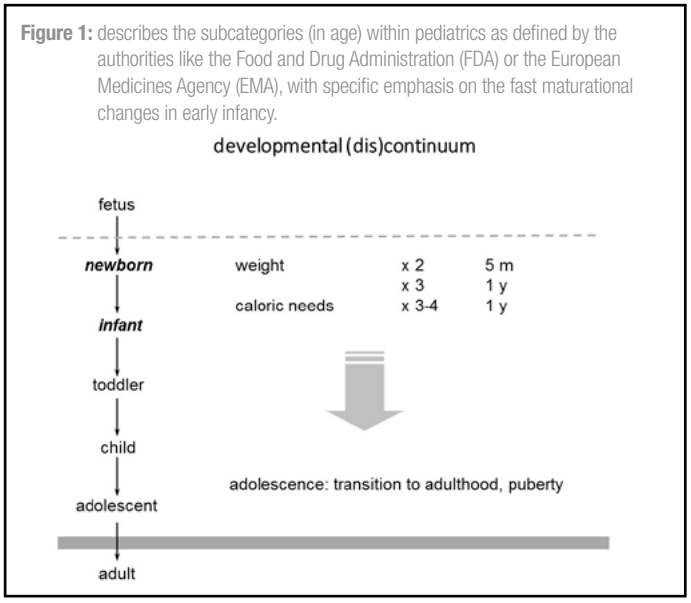

Figure 1: describes the subcategories (in age) within pediatrics as defined by the authorities like the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), with specific emphasis on the fast maturational changes in early infancy.

Within the scope of this paper, we decided not to discuss again *in extenso* aspects of maturational PK. We refer the interested reader to recently published reviews on different aspects of neonatal pharmacokinetics, and can be contacted to share specific pdfs upon request, corresponding author [1-6,8,9]. Instead, we decided to highlight the current evolutions and efforts made to 'translate' the emerged knowledge on neonatal pharmacology to ensure access for prescribers as an obvious need to improve current clinical practice. This will be followed by some reflections on future perspectives to further improve and tailor the current setting of drug development tools to neonatal needs and characteristics.

Current evolutions: integrate the available knowledge, and make this knowledge accessible

As many drugs in children - including neonates - are commonly used off-label, prescribers routinely face a lack of evidence-based dosing guidelines and remain in need of access to integrated, best available knowledge databases on drug prescription practices. In the Netherlands, a framework has been developed

Table 1: Examples of developmental changes in neonatal pharmacokinetics and how these changes affect drug dosing in this population. (Tmax: peak time (time at which peak concentration occurs); Cmax: peak concentration)

PHYSIOLOGICAL SYSTEM	NEONATAL PHYSIOLOGY	PHARMACOKINETIC IMPLICATIONS	CLINICAL IMPLICATIONS
Gastrointestinal	Reduced and irregular peristalsis followed by slow gastric emptying, (breastmilk faster compared to formula)	Slower absorption of the drug (e.g. delayed Tmax and lower Cmax)	Possible sustained action after oral administration of the drug
	Increased gastric pH (> 4) in relation to infants	Faster absorption of acid-labile, and reduced absorption of weak-acid drugs	The possibility of altered bioavailability
Muscle tissue	Reduction in muscle perfusion, decreased muscle contractility	Poor perfusion limits the absorption, unpredictable pharmacokinetics	Avoid intramuscular administration of drugs if short term effects are aimed for (e.g. antibiotics, resuscitation)
Skin	Thinner stratum corneum, increased skin perfusion, increased water content and higher body surface area-to-weight ratio	Increased rate and extent of absorption of the drug through the skin	Increased bioavailability and potential toxicity of drugs applied topically The need for a reduced amount of the drug applied to the skin
Body composition	Lower proportion of adipose tissue (10%), decreased muscle mass, increased amount of total body water related to the body weight (80%), an increased proportion of the extracellular (45%) compared to the intracellular fluid compartment	Increased volume of distribution for water-soluble drugs and a reduced volume for drugs which accumulate in muscles and adipose tissue	Consider to adjust the loading/maintenance dosing (mg/kg) to achieve therapeutic plasma concentrations of the drug
Plasma protein binding	Reduced concentrations of albumin and α-1 acid glycoprotein, with a decreased drug protein-binding affinity	Increased plasma concentration of unbound drug, with an increased volume of distribution and the possibility of occurrence of toxic effects	For drugs with high protein affinity (e.g.> 70%), please consider an alternative, or maintain the plasma drug concentrations to the lower limit of the recommended therapeutic range, interaction with e.g. indirect bilirubin
Drug metabolism	Immature isoforms of cytochrome P450 and phase II enzymes with iso-enzyme specific maturation	Iso-enzyme specific, reduced hepatic drug metabolism, with increase in half-life	To increase dosing interval of the drug and/or reduce the maintenance dose
Renal drug excretion	Decreased glomerular filtration rate and active tubular secretion or absorption	Drug accumulation and/or the active metabolite that are secreted by renal route	increase dosing interval drug or reduce the maintenance dose

to provide both prescribers and pharmacists with dosing guidelines based on best available evidence. This best available evidence is a 'provisional final' integrated dosing guideline based on - currently available - registration data, an increasing volume of investigator-initiated research papers or otherwise, professional guidelines, clinical experience and consensus [10]. As important, these integrated dosing guidelines routinely (annual to biannual) undergo systematic re-assessment to keep this database up to date. Even more relevant for the topic of this paper, the ***Neodose initiative*** aims to further develop the current database to the specific needs of preterm neonates [11]. In a first step, 21 drugs have been assessed using an expert opinion approach in combination with a systematic literature search. Because of the still limited available data, it is anticipated that these dosing guidelines also will need re-assessment.

As part of their regular updates, the 'kinderformularium website' also incorporated an amikacin dosing regimen after this underwent prospective validation at the University Hospitals, Leuven [12]. However and because we aimed to respect the extensive variability in renal drug clearance for aminoglycosides, like amikacin, we ended up with a more accurate, but also more complex dosing regimen. The dose regimen described in ***Table 2*** subdivides the maturational renal elimination clearance into 10 different subgroups [5 different weight categories, postnatal age dichotomous at 14 days], with an additional prolongation of the dose interval (+10 h) when ibuprofen is co-administered or when asphyxia is diagnosed [13] For the different aminoglycosides, dosing charts for neonates with varying gestational or postnatal age, or weight (maturational covariates) have been developed with additional adaptations when ibuprofen or indomethacin are co-administered, or in the setting of perinatal asphyxia (non-maturational covariates). However, these subgroups remain somewhat arbitrary to mirror a continuous maturational process, further affected by disease characteristics, making dosing adaptations following therapeutic drug monitoring (TDM) at present still arbitrary and opinion driven, instead of data-driven despite the fact that these data to guide decision are available [13,14,15].

Integration of online available ***pK model software tools*** (drug exposure estimates using the initial raw datasets [14,15]) may hereby be very supportive to guide clinical decisions based on such data-driven concepts, including the maturational changes with increasing postnatal age. In a *first step*, validated dosing regimens (e.g. ***Table 2***) can be used to initiate treatment. In a *second step*, software tools like NeoGent (for gentamicin, freely available) subsequently hold the promise to guide individualized dosing based on the demographics of the newborn and TDM observations as collected [14,15]. An example as extracted from the NeoGent website is provided in ***Figure 2***. An additional benefit of such a software, data driven approach, is that decisions on dosing regimens can also be made based on 'at random' opportunistic TDM observations, so that a trough level is no longer compulsory: data driven PK models allow TDM to be performed opportunistically, like at the time of scheduled routine blood tests. In contrast, traditional trough TDM is time-consuming, disruptive to neonatal clinical care, and has patient safety issues related to the need of 24/7 availability of bio-analysis and PK skills. Similar efforts have been reported for e.g. vancomycin (DosOpt) [16] and can be considered for other drugs (e.g. amikacin, phenobarbital) for which TDM is performed.

Table 2: Proposed amikacin dosing regimen for neonates (with postnatal age ≤ 30 days) after prospective validation [13].

Current bodyweight (grams)	PNA <14 days	PNA ≥14 days
<800	16 mg/kg/48h	20 mg/kg/42h
800-1200	16 mg/kg/42h	20 mg/kg/36h
1200-2000	15 mg/kg/36h	18 mg/kg/30h
2000-2800	15 mg/kg/36h	18 mg/kg/24h
≥2800	15 mg/kg/30h	18 mg/kg/20h
The dosing interval is prolonged 10 hours, when ibuprofen is co-administered or when asphyxia is diagnosed/considered by the treating physician. Duration of the intravenous infusion is 20 minutes. PNA= postnatal age.		

Future perspectives: the need for drug development programs tailored to neonates

The earlier mentioned legal initiatives to stimulate neonatal drug discovery and development should be accompanied by the development of a tool box of valid research tools to boost a newborn-driven research agenda. The International Neonatal Consortium (INC) group has suggested on how such a tool box should evolve [6]. In their opinion, this should include (*i*) tailor product development to neonatal physiology (*drug discovery*) and pharmacology (*drug development*), while making the most of already available knowledge in other settings (juvenile animal model, other populations, other drugs), (*ii*) the central role of families in clinical research, and (*iii*) the value of the neonatal team in study design, implementation and interpretation [6].

At present, the overwhelming majority of drugs are developed with adult pathophysiology in mind, driven by adult indications and markets, subsequently potentially considered for neonatal diseases as part of a given pediatric investigation plan (PIP). Surfactant is the latest (dating from 1980ies !) example of drug discovery specific to neonates, and illustrates how knowledge on neonatal pathophysiology ('hyaline membrane disease') may result in drug discovery and development (exogenous surfactant), and subsequent improved neonatal outcome [17]. Unfortunately, the available knowledge on neonatal pathophysiology is still poor (e.g. protein expression, receptor expression, mechanisms) when compared to other patient populations. Again, access to research tools adapted to the characteristics of neonates are crucial to facilitate future research. Besides knowledge integration on juvenile animal models applicable to neonatal diseases [18], ***physiologically-based PK (PB-PK) modeling*** is a potent systematic approach to attain the first INC aim, i.e. to make the most of already acquired knowledge (neonatal physiology, system knowledge) as facilitator to develop the tools to support neonatal drug development [5,19]. PB-PK integrates different types of information, such as *in vitro*, *in vivo* and/or *in silico* (from computer simulation/use) and clinical data (population related) to result in simulations, including a range of certainty [5,19]. PB-PK hereby explicitly discriminates between physiological properties of the population (system) and the compound specific properties [5,19]. PB-PK has applications in drug development for first-in-human, first-in-child or first-in-newborn dose selection, simulations for study design, or drug-drug interaction. The currently available PB-PK models overall still have poor predictive performance in neonates. We are aware that clinicians and clinical researchers may perceive that this as out of scope for their activities and interests, but progress necessitates contributions of clinicians by generating PK datasets and observations on maturational physiology (e.g. trends in body weight, body composition or biochemical reference values) to refine PB-PK model predictions.

When conducting studies, research tools - commonly developed for adults or children - should be further tailored to neonates. This should also consider aspects of pharmacovigilance (adverse event monitoring), since drug assessment considers both efficacy as well as safety. Identifying core datasets for neonatal clinical trials hereby advice researchers on which outcome measures to include and report on as a minimum outcome set to facilitate later comparability and meta-analysis of study data. A general core outcome set for neonatal medicine has recently been reported [20].

When adverse events are considered, several aspects need to be considered. As provided in ***Figure 3***, this covers assessment of *seriousness* (this is a regulatory obligation, but when is a hospitalization prolonged, or when is there impact on the long term outcome in a preterm ?), *causality* (attempts to discriminate drug related exposure from common co-morbidity characteristics in a newborn) and *severity grading* (is a central apnea mild, moderate, severe, life-threatening or just 'normal' behavior in a preterm?). Standardization of adverse event severity criteria could make safety information more reliable and comparable across trials. Severity assessed the intensity of an event in a more nuanced and layered way, and can enhance safety data quality, since assessment should not only consider the number (frequency), but also the impact to result in more reliable and comparable safety information.

All these aspects of adverse event assessment should be tailored to neonates. Recently, a population specific tool to assess *causality* in neonates has been published, but standardization on adverse severity criteria in neonates was not yet done [21]. Along this line and within the INC consortium, our research group has recently coordinated a project to develop an ***adverse event severity grading*** tool, tailored to neonates. In 3 consecutive phases, generic severity criteria for adverse events were developed, followed by severity criteria for specific neonatal adverse events, to end by linking these results to the Medical Dictionary for Regulatory Activities (MedDRA) and the National Institute of Child (NCI) Thesaurus to ensure sustainability and access. At present, the generic neonatal adverse event severity grading score has been reported as abstract [22]. Furthermore, the severity scale is publicly available on the NCI Thesaurus website [23].

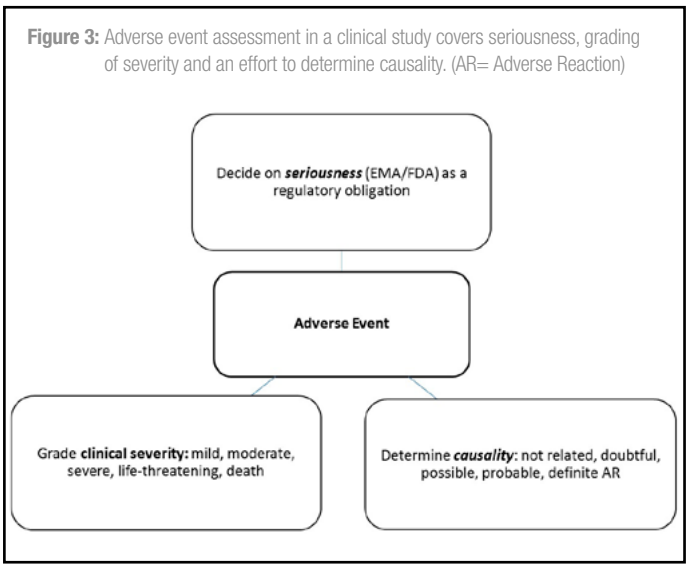

Figure 3: Adverse event assessment in a clinical study covers seriousness, grading of severity and an effort to determine causality. (AR= Adverse Reaction)

Discussion and conclusions

Despite the fact that neonatal pharmacotherapy is still lagging behind compared to the available level of knowledge in other populations, progress has been made. It therefore is of relevance to take the next steps, i.e. make the available knowledge available and accessible for prescribers to improve current practices and create impact. The *Neodose project* and *data driven PK software tools* hereby serve as illustrations of such 'translation' efforts [11,14,15].

Such datasets also contain additional information that can serve to further develop neonatal research tools to stimulate neonatal drug development. Combined with *in vitro*, *in vivo* or *in silico*, clinical data (population related) can be integrated in *PB-PK models* to result in simulations [5,19]. Such simulations can subsequent be used in new drug development projects to predict drug exposure. Furthermore, neonatal drug development also need tailored tools to facilitate clinical studies and to create as much as possible knowledge out of individual clinical studies. This should also cover aspects related to adverse event assessment, including *adverse event severity grading* tailored to neonates [21-23].

In conclusion, facilitation of access to integrated knowledge is crucial to improve current practice and to generate clinical relevant impact (neodose project, software tools), while a newborn-tailored drug research approach (PB-PK, adverse event severity grading) is crucial to facilitate further progress. Neonatal pharmacology is still lagging behind and full catch-up on knowledge driven pharmacotherapy has not yet been attained. However, this subdiscipline is for sure on the move to further improve neonatal outcome, driven by multidisciplinary collaboration.

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Figure 2: 2 illustrates the add on value of TDMx NeoGent as PK data driven model driven prediction tool 14,15. Applied to a single newborn (35 weeks, 3.5 kg, creatinine 60 µmol/l at birth, 13.3 mg gentamicin shortly after birth) with therapeutic drug monitoring (TDM) at 24 h, the suggested adaptations (dose, time interval) are hereby based on the raw dataset of the initial study 14,15. (AUC: Area Under the Curve; MIC: Minimal Inhibitory Concentration)

In figure 2a, the TDM trough gentamicin level (indicated in the figure as °) at 24 h is 8 (high, toxic), so that the software package suggest the subsequent doses of 4.2 mg at 24 h, to 6.2 and 6.4 mg at 60 and 96 h

In figure 2b, the TDM trough gentamicin level at 24 h is 1, subsequent doses as suggested were 13 mg at 24 h, followed by 13.2 mg at 48 and 60 h.

Figure 2A

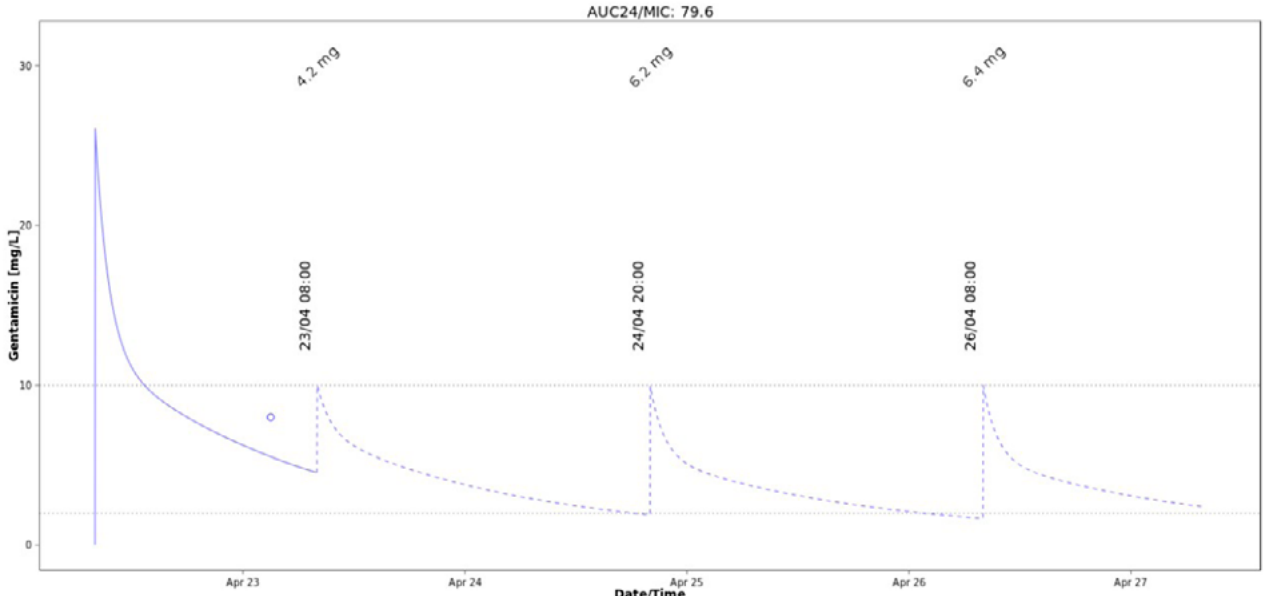
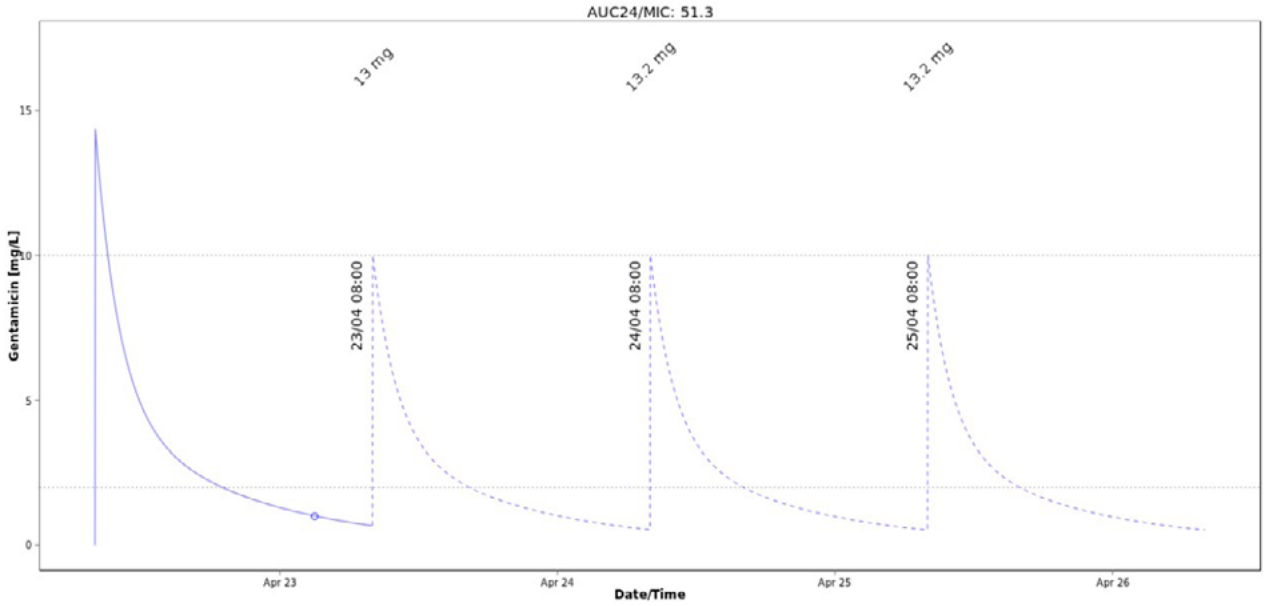


Figure 2B



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Drug research in the critically ill child: beyond the beaten track

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Key words

drug research, critically ill, pediatrics, pharmacokinetics/pharmacodynamics

Abstract

In addition to maturational changes, both major pathophysiological alterations and therapeutic interventions related to critical illness affect drug disposition and effects in children. However, appropriate drug dosing to result in appropriate drug exposure in critically ill children is rarely studied. Given the ethical issues and practical constraints, clinical trials in critically ill children are more difficult to perform. The introduction of new consent procedures, establishment of international trial consortia, minimal risk trial designs and quantitative modelling tools opens new horizons for pediatric drug research in this most vulnerable patient population.

Introduction

Pharmacokinetics (PK) describes the relationship between administered dose and drug concentration over time ('what the body does to the drug') at a specific site (e.g. blood, cerebrospinal fluid) and is described by its absorption, distribution and elimination through metabolism and excretion (ADME). Maturational changes in body composition, drug metabolising enzymes, cardiac output, blood flow, function of eliminating organs and functionality/expression of drug receptors occur, leading to major changes in pharmacokinetics (PK) and pharmacodynamics (PD) from birth up to adulthood (1). Additionally, critical illness and treatment may hugely impact drug PK and PD in children, both between patients, as well as during the course of a disease in a given patient **(Figure 1)** (2).

Patients admitted to the neonatal intensive care unit (NICU) or the pediatric intensive care unit (PICU) are exposed to a large number of drugs and total numbers increase with duration of ICU therapy and length of ICU stay (3-5). Despite the importance of evidence-based drug treatment in this vulnerable population, PK/PD knowledge and efficacy or safety data are scarce and dosing regimens remain often empirically derived from adults, relatively 'healthy' and/or older children. Consequently, most drugs used in the ICU are prescribed outside the terms of product license (off-label) or even without market authorization (unlicensed use). Frequencies of off-label and unlicensed use in the NICU/PICU between 50-85% have been reported (3, 5, 6).Risk factors for receiving an off-label drug included young age (<5 years), chronic health conditions, acute organ failures, mechanical

Figure 1: Major pathophysiological and treatment factors related to PK changes in critically ill children

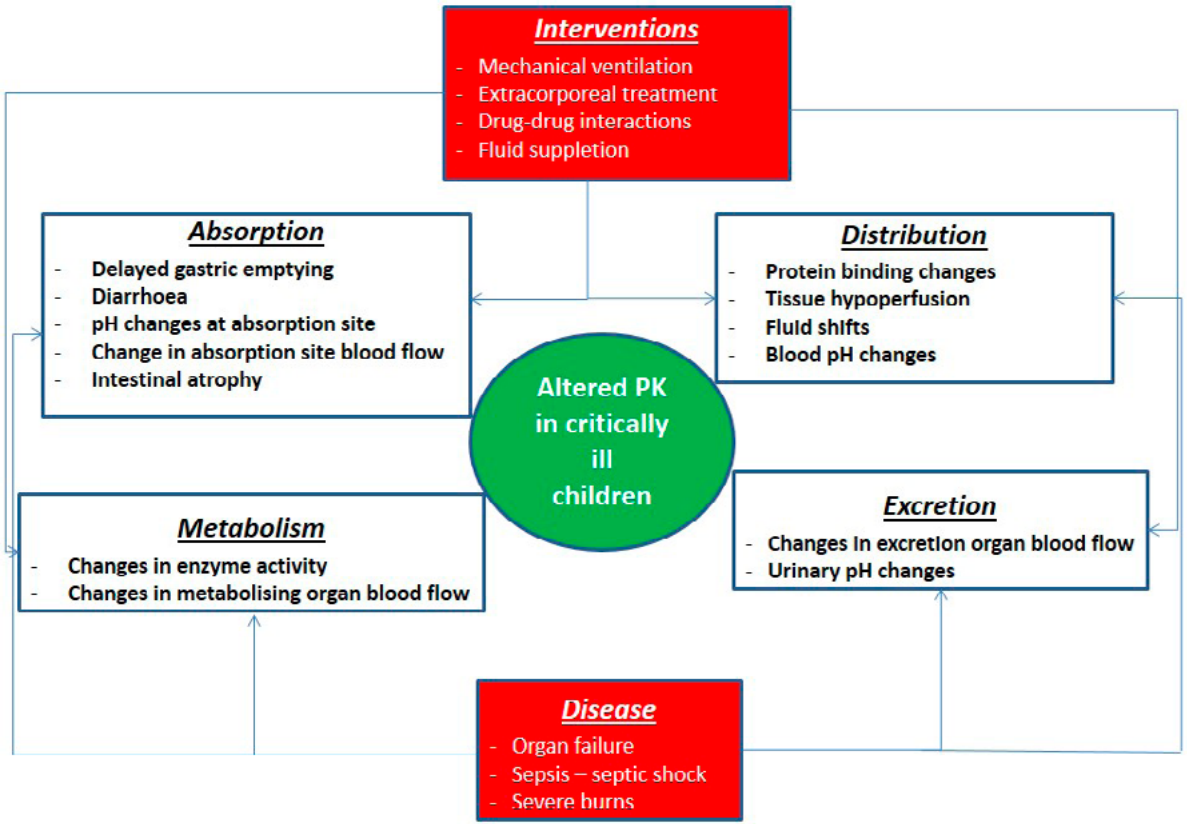

Table 1: Barriers and opportunities to increase pediatric drug research in the ICU

Barriers	Potential solutions/ opportunities	Examples
Low number of patients per unit	Networking – research consortia	Innovative Medicines Initiative – Conect4Children consortium
Low consent rates	Alternative consent and assent procedures	Deferred consent Dynamic consent
Patient burden	Minimal risk trial designs	Microsampling Opportunistic sampling Alternative non-invasive sampling matrices Microdosing Optimal (sparse) sampling design Model-based extrapolation for first-dose estimation
Regular protocol deviations	Advanced data-analysis methods	PK/PD modelling and simulation

ventilation, having arterial or venous catheters, dialysis treatment and receiving blood products (5, 6). Most commonly reported types of off-label use were the prescription of drugs in another dose or frequency, in a different formulation, or in an another age group (7).

Previous research has also shown that these practices undoubtedly contribute to an extensive variability in dosing regimens (8). Moreover, unlicensed/off-label drug prescribing has been associated with medication errors and unpredictable responses, related to either toxicity or therapeutic failure (9, 10).

In this review paper, we aim to discuss barriers to perform drug research in the ICU, and elaborate on some recent developments/initiatives, with a potential to increase drug research in this most vulnerable patient population.

Ethics and barriers in drug research in the intensive care unit

As it is our collective responsibility to obtain sufficient information to develop medicines for children, the conduct of clinical research in neonatal and pediatric intensive care, although necessary, poses some unique ethical and practical challenges.

After the Second World War, the Nuremberg code stated that the voluntary consent of the human subject in clinical research is absolutely essential (11). Later, this statement was amended by the Declaration of Helsinki and allowed the parents of minor children (or their legal representatives) to consent, as they were thought to act according to the presumed will of their child (12). Several steps are distinguishable in the informed consent process of which objective transmission of the information by a competent physician, a good understanding by the parents of this information and sufficient time to come to a decision (without coercion) are the most important. However, the emotionally strained circumstances of intensive care carry an enormous potential to compromise this process (13). Especially in emergency and life-threatening conditions, parents are overwhelmed by the disease severity of their beloved child in an extraordinary environment, leading to an impaired ability to understand the proposed research and take a decision within a short timeframe (14). Previous studies reported that parents regularly experienced recall-bias on the consent procedure, had difficulties understanding the proposed research and identified the timing and ways in which they received the information needed to be improved (15).

In randomised controlled trials (RCT) on the ICU, the concept of 'therapeutic misconception' may also occur, with parents believing that giving consent for conducting a study is an *a priori* for getting better, while underestimating potential risks (16). Also under these circumstances, one cannot speak of a rationally given consent.

The EU clinical trial regulation requires that in addition to the informed consent by the parents, a capable minor, should assent himself or herself to participate in a clinical trial . This capability is not solely depending on the child's age but also on their individual experience (e.g. chronically ill children). Of course, in most circumstances on the ICU, the child is often too sick to participate in the assenting process prior to inclusion (17).

In Western Europe and Canada, the treating physician and the person asking for informed consent are in most recruitment centres the same (18). Herein lies another ethical challenge with the physician balancing between the moral duty to treat his individual seriously ill patient according to evidence-based guidelines and his or her intention to generate new insights and hope on a better care for future patients. This ethical conflict was nicely illustrated in a study in which 1050 pediatric intensivists were asked about their opinion on conducting randomized, controlled trials in critically ill children (19). In this study, 96% of respondents indicated that they believed that RCTs of potentially life-sustaining therapies must be performed, although only 10% indicated that they did not experience ethical conflict with this type of study. Eighty-four per cent indicated that an earlier published data would have the potential to bias them towards the investigational product.

Enrolment of children in clinical trials should not only be considered if scientifically needed but also the potential benefit of an optimised drug treatment should outweigh the risks and burden for the individual child (20). Both benefit, risks and burden should be considered in relation to the severity of the disease e.g. when testing life-saving therapies, a higher risk level and/or burden could be accepted. In vulnerable ICU children, however, it is known that side-effects can be more frequent and severe and are not always easily predictable from other (pediatric) populations (21). Trial related burden should also be minimised as most ICU patients already undergo many invasive and painful procedures (20).

Recruitment problems were reported as the major difficulty for conducting and completing PIP studies in the 10-year report on the pediatric regulation (22). In the NICU/PICU environment, patient recruitment is even more challenging due to a high population heterogeneity and a relatively low number of admissions per single centre. Duffett *et al.* previously reported that one third of initiated PICU RCTs was prematurely stopped, mainly due to recruitment problems (23). Interestingly, main barriers for recruitment were reported as the lack of availability of parents, language barriers between physician and parents, and parents being overwhelmed when asked for consent as discussed above (24). Nevertheless, more than 80% of RCTs are reported as single-centre studies, hence compromising the likelihood of producing study results that can be subsequently generalised to the ICU population (23).

Since intensive care also requires frequent blood sampling for routine monitoring, very limited blood volume is available for PK/PD related purposes.especially newborns, create many ethical challenges that can be analyzed in terms of respect for persons, justice, and beneficence/maleficence as outlined in the Belmont Report. This report describes some of the ethical challenges in conducting drug studies in pediatric patients that must be considered when planning studies and offers some solutions to meet those challenges. Methods of optimal study design should be utilized to limit the number of patients and the number of blood samples. Parental permission should be obtained with equipoise, although the parents of a sick newborn may feel an internal pressure for their child to participate in a study of a new and potentially superior therapy. If appropriate to the study, consent before labor and delivery when parents are less stressed is optimal. It may be difficult or impossible to know all the risks and benefits accompanying studies in newborns due to the limited number of randomized controlled studies in this population. Many more carefully designed, randomized controlled studies of drugs are needed to address the therapeutic needs of the developing pediatric population. For sick newborns cared for in the neonatal intensive care unit (NICU Available guidelines suggest a 1-5% safe limit of the total blood volume, with the lower ranges applicable to preterm neonates (22, 25-27).

Venous and arterial cannulation of the small blood vessels in young children is challenging and the use of multilumen catheters is not always an option. In particular for PK studies, having a separate access for drug infusion and blood sampling is therefore often difficult.

Finally, protocol deviations in this setting are common as reported in a survey by Morris *et al.* In this observational study, 65% of pediatric intensivists indicated that they did not adhere to the research protocol when the patient deteriorated or parents asked for the study drug (19). Evidently, this practice may compromise the validity of study results.

Recent initiatives, developments and future perspectives

performing clinical research in an ICU environment is challenging. Below, we identify priorities and discuss promising developments to improve and accelerate pharmacological research within the NICU/PICU environment **(Table 1)**.

Networking and collaboration

In the 10-year European Medicines Agency report on the Pediatric Regulation, the lack of sustained funded research infrastructure, coordination of research activities at a network level, and awareness of existing networks to the industry were identified as some of the main hurdles to tackle (22) . As we encountered in clinical trials our research groups performed, this is especially the case for the ICU setting, due to the high population heterogeneity and the relatively low number of admissions per single centre.

To date, few (inter)national research networks, addressing the specific pharmacological needs of critically ill children, exist. The Foundation Pediatric Intensive Care (Stichting Kinder Intensive Care) is an example of a national academic research network in the Netherlands between 8 pediatric intensive care units in which, currently, 2 medication trials were initiated (28).Within Europe, only the European Society on Neonatal and Pediatric Intensive care medicine Research Network (ESPNIC) is a dedicated research network recognized by the European network of pediatric research and specialist networks at the EMA (Enpr-EMA) (29). Currently, no collaborative medication trials were initiated yet within this ESPNIC network. A promising pan-European research network for pediatric drug research (Conect4Children) is currently being enrolled. Objective of this private-public collaboration is to develop a high-quality, sustainable network for clinical research, by supporting innovative trial design and trial implementation using resources between studies across Europe. Although the network is focussing on pediatric clinical research in general, a clinical expert group has been installed within this network to advise on trial design in ICU trials in the pediatric or the neonatal ICU setting respectively (30).

In the future, such sustainable collaborative research efforts should be more actively encouraged as they undoubtedly increase patient recruitment and study performance. Furthermore, they may raise more awareness amongst regulatory agencies for this vulnerable subpopulation and challenge the pharmaceutical industry to the setup of more clinically relevant research in critically ill children.

Essential for the prosperity of such multicentric collaborations, will be a more streamlined ethics board review and harmonised informed consent and assent procedure to guarantee a similar level of information, protection from risks and potential benefit of the drug between trial participants (31, 32). In this context it is worth to mention that a new European clinical trial regulation is scheduled to come into application during the year 2020. In this regulation, harmonisation of submission requirements and ethics board assessment are planned. The ultimate aim of this piece of legislation is to conduct clinical trials with the highest standards of safety for participants and increased transparency (33).

Ethical conduct – trial participation

Ethically performing research is of utmost importance, including the requirement of a high standard of informed consent. NICU/PICU researchers, however, may face several practical barriers to implement a valuable informed consent, as described above.

All these hurdles illustrate the limitations of the standard consent and assent procedure in this setting and highlight the importance of alternative strategies to be studied. Essential to improve this process in terms of voluntariness and patient recruitment, is the input of parents and children on both procedures and trial design (15). To date, the insight in encouraging and discouraging factors for participating in drug research in the NICU/PICU is, however, rather small and sometimes conflicting. Characteristics of the consent encounter, individual parent, child and study have been reported to be related to the decision making process (34).

Regarding the timing and modalities of consent and assent, some alternative options to the standard method have been proposed. Allmark *et al.* demonstrated that a stepwise designed parental consent procedure improved the quality of the consent in a randomised, controlled trial in critically ill neonates (35). In this approach, a selection of crucial information is given before asking for consent to enrol the patient, due to the time constraints and potential impaired ability of parental decision making. As time goes on, more detailed information and explicit choice to opt out is given, both on a continuous basis. Deferred consent is another method to deal with the emergency of decisions to be taken in an acute care setting like NICU/PICU and implies that the consent is requested after the patient is recruited. This approach is currently only allowed when, owing to the urgency of the treatment and the trial, it is impossible to obtain prior consent from the patient or legal representative, provided that an ethics committee has given its approval (17) . Preliminary research suggests that parents can appreciate this way of consenting, if appropriately timed and explained (36-38). A waiver of consent is another method and implies that consent is not required. To date, this method has only been used in pediatric resuscitation research. Many of these studies used community consultation and public disclosure on the unit to inform parents and caregivers that children could be enrolled in a clinical trial (39). Overall, there is a reluctance of caregivers, parents and ethic boards towards this practice. Innovations in communication technology may also contribute to solving some issues with the informed consent process. The newest method is the so-called 'dynamic consent' in which online communication platforms (e.g. video calls, webinars, websites) are used for personalised consenting (40). Usually, it is designed to facilitate the dialogue between researchers and parents (or children) before, during and after the study through online communication. It also enables the parents or children to refine their consent to specific parts of the study (e.g. data sharing with drug companies) or change it at any time. Finally, such platforms may offer the possibility to provide updates on study results and outcomes. Regarding alternative methods to ask for assent of minors, video game technology support is currently under development (41). To date, studies on the use of new communication technology in a pediatric intensive care setting are lacking.

In most hospitals, consent is usually asked by the treating physician. However, during the patient recruitment in studies from our research groups, some physicians reported that they had some moral objections against this common practice. Current ethical guidelines are also cautious with regard to dependent relationships between patients or parents and the study team professional. Especially, the voluntary informed consent may be compromised, due to a potential conflict of interest (42). Interestingly, however, it was previously reported that parents preferred their treating physician to advise on their decision, rather than to take it independently (43). Menon *et al.* also reported that introducing the researcher to the patient's family by any member of the patient's intensive care team resulted in higher consent rates (42). This suggests that the existing relationship with and trust in the treating care team, may increase the parents' decision rate to participate. To the best of our knowledge, no studies on ICU are available investigating the influence of the above mentioned factors on the decision process.

In order to guide regulatory agencies, ethics committees and NICU/PICU researchers on the most valuable approach to ask for consent and assent, more knowledge is needed on the wishes and preferences on trial design, decision making process of both parents and children (including capabilities) and the roles of the treating physician and research team (43-45).

Minimal risk designs

Blood sampling volume limits PK/PD research in young and critically ill children. Potentially beneficial blood sampling techniques for facilitating PK studies in this protected population are currently under investigation (46).

Microsampling, which is the collection of smaller-than-normal plasma samples for bio-analysis, may provide a solution and includes mainly dried blood spots (DBS), dry plasma spots (DPS), volumetric absorptive microsampling (VAMS) and capillary microsampling techniques. In DBS or DPS, a small volume of blood or plasma is applied on an absorbent paper which is dried after saturation has occurred. In the laboratory, the blood or plasma is eluted out of the paper and subsequently analysed. Cohen-Wolkowiez *et al.* recently reported on the feasibility of using DBS concentrations in combination with plasma samples for PK model building of piperacillin and tazobactam in infants (47). A quite similar, optimized technique is VAMS, in which a fixed volume of blood is absorbed by the porous, hydrophilic tip of the device. After the tip is dried, it is sent to the lab for drug extraction and bio-analysis. In capillary microsampling blood is collected in a capillary tube and subsequently centrifuged in this tube before bio-analysis of the sample. Overall, microsampling in critically ill children seems promising as it would allow a significant reduction in the blood volume required, thereby reducing the risk of further upsetting fluid balance which may already be compromised.

Another non-invasive technique for measuring drug exposure is using saliva as matrix. The advantages of saliva monitoring in pediatric PK trials are acknowledged by the FDA and mainly relate to the fact that saliva sampling potentially reduces blood sampling, is easy to collect and causes minimal patient discomfort (48). The

usefulness of saliva for TDM has been studied for several drugs including mainly anti-epileptics, antiretrovirals, antipsychotics, antibiotics and antifungals (49-53).

Opportunistic sampling, also known as scavenged sampling or left-over sampling, uses remaining blood, plasma or other body fluids from routine biochemical tests for measurement of drug concentrations. Several studies in children have successfully used opportunistic sampling alone or in combination with timed blood sampling to characterize drug PK (54-58). Interestingly, this process can also be useful in the opposite direction: Germovsek *et al.* presented a PK model that allows healthcare providers to take a gentamicin TDM sample at a time that is convenient (i.e. during a routine blood test) rather than needing to take a specific "trough" sample to determine whether drug levels are low enough (59). Finally, routinely collected TDM data can also provide useful data to build PK/PD models for the monitored drug, as illustrated for gentamicin by Medellín-Garibay *et al* (60).

Microdosing is another promising method to minimize patient burden while efficiently studying the pharmacokinetic behaviour of a drug under development. Commonly, the given dose is 1/100th of the No Observed Adverse Effect Level and is labelled with a microtracer [^{14}C] for quantification using the most sensitive HPLC techniques. A prerequisite is the dose linearity from the magnitude of the microdose up to therapeutic ranges. In ICU children, three proof-of-concept PK microdosing studies, characterising paracetamol and midazolam PK were published (61-63).

Modelling and simulation

Biological models are defined as simplified representations of a biological system to provide knowledge and understanding of this system. In the field of medicines, mathematical models are developed to describe and predict the drug PK and PD.

Over the last few years, advanced modelling and simulation is rapidly evolving in the design and data analysis of PK/PD experiments in ICU children, as it may assist to overcome a lot of challenges encountered in pediatric drug development (64). One increasingly important method to optimize a clinical trial is the use of mathematical algorithms to design the study in such a way that the collected information is maximally informative (65). In these algorithms, prior knowledge on the structure of the model and parameter distributions are mandatory as input (e.g. published PK/PD model from older children). Typically, in PK/PD trials, the total number of patients, sampling times and/or number of samples are optimised for, taking into account the ethical (e.g. blood sampling volume limits) and practical constraints (e.g. minimum timeframe between two blood sampling times).

Quantitative extrapolation of PK and/or PD for first-dose estimation is recognized by International Conference on Harmonisation, Food and Drug Administration and EMA as another valuable study design aid to explore dosing scenarios increasing the benefit-risk ratio, before even enrolling children into the clinical trial (66-68). Through the use of extrapolation, also unnecessary studies can be avoided and the number of children minimised (e.g. fewer data needed in adolescents when reasonably similar to adults). Still, bridging PK, efficacy and safety data from older age categories to the youngest age categories (neonates and infants) has shown variable success, mainly depending on the modelling approach and individual compound (69, 70). Also, the usefulness of extrapolation to children with serious pathophysiological changes and/or comorbidity needs further study.

Overall, a strong trend of moving from pure "empirical" models towards more mechanistic physiologically-based models is noticeable in the field, with the ultimate goal to create generalisable PK/PD models that distinguish between drug and system parameters (71). More knowledge on the time course of physiological processes (e.g. maturation in renal transporter activity) and disease specific changes (e.g. sepsis) is first needed to be applicable to the pediatric intensive care setting (72).

Conclusion

Critical illness can largely impact drug PK and PD. To date, ICU children remain deprived from evidence-based drug dosing, mainly due to ethical and practical barriers to perform clinical trials in this most vulnerable patient population. Promising developments in trial design and data-analysis References will hopefully increase the number of drug trials in the near future.

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Paediatric Medicines Initiatives: how far have we come?

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Abstract

In addition to maturational changes, both major pathophysiological alterations and therapeutic interventions related to critical illness affect drug disposition and effects in children. However, appropriate drug dosing to result in appropriate drug exposure in critically ill children is rarely studied. Given the ethical issues and practical constraints, clinical trials in critically ill children are more difficult to perform. The introduction of new consent procedures, establishment of international trial consortia, minimal risk trial designs and quantitative modelling tools opens new horizons for pediatric drug research in this most vulnerable patient population.

'THERAPEUTIC ORPHANS'

Before any new medicine can be manufactured and marketed, it must receive a marketing authorisation (MA, or license). This authorisation was introduced in most European countries in the Sixties (e.g. the law on medicinal products of March 25, 1964 in Belgium[1]). The aim of the licensing system is to ensure that medicines are examined for efficacy, safety, and quality. Pharmaceutical companies apply for a product licence for a particular drug, and in their submission they include the indication, dose, route of administration, and age group of patient for which this applies[2]. These data should result from extensive trials looking at different dosage regimes, pharmacokinetics, and drug toxicity and are mentioned in the 'Summary of Product Characteristics' (SmPC; in Europe) or 'Product label' (in The United States) of the drug. It is worth considering that many drugs used in children have not had the advantage of these formal clinical trials.

The phrase 'therapeutic orphans' was used to describe children in 1963 by dr. Harry Shirkey[3]. This phrase refers to the lack of medicines available for use in children. Studies - executed between 1995 and 2012 - showed that over 50% of the medicines used for children have not been tested in this specified age group[4]. Consequently, many drugs used to treat children are used off-label or unlicensed. The term 'off-label' use refers to *use of a drug that is not included in the package insert (approved labelling) for that drug. This may involve using the medicine in a different age group, for a different indication, for a contraindication, at a different dose, or by a different route to that recommended.* Unlicensed medicines are *where the medicine has been modified from that specified in its product license* or *the use of imported drugs*[5, 6]. Roughly half of drugs used in children are off-label or unlicensed, and the number is much higher in the advanced care settings and the neonatal population. Magalhães et al report in their most recent systematic review of papers published from 1994 to 2012 that prescriptions ranged from 12,2% to 70,6% for off-label and from 0,2 to 47,6% for unlicensed drugs, depending on definition and setting[7].

In several studies, off-label use of drugs was shown to be associated with a lack of efficacy due to subtherapeutic dosing and a greater risk of drug toxicity[8-10]. Studies examining the aspect of adverse drug reactions (ADRs) linked to off-label and unlicensed use have found differing results. However, many suggest a greater adverse drug reaction risk associated with off-label and unlicensed drug use in children[5-7, 11]. This may result from a failure to understand the impact of developmental, physiological, or metabolic influences on a drug's pharmacokinetics[8, 12]: children of different weight or age groups can behave very differently in terms of response to treatment, dose–response relationship, pharmacokinetics and toxicity[13].

It should be noted that the practice of off-label prescribing does not necessarily mean 'off-knowledge' prescribing. Often, dosage regimens are based on paediatric clinical trials and published experience in children, not integrated in the labelling of the product. Additionally, these off-label dosage regimens may be recommended in clinical practice guidelines or pharmacotherapeutic handbooks but these may show remarkably variable dosing regimens for the same drug[14]. A recent policy statement of the 'American Academy of Pediatrics' states that *off-label prescribing does not necessarily imply an improper, illegal, contraindicated or investigational use*[15] and *that it is in the best interests of the child if no other treatment with at least a comparable benefit-risk ratio is available*[12]. However, when assessment of the risks and benefits has not been done at the population level by the regulatory authorities, i.e. there is no paediatric labelling, higher requirements are asked from the prescriber when making the individual risk-benefit assessment for the patient[9, 12]. Obviously, such an assessment can only be performed if the data on efficacy and safety of the medicinal product have been generated are available to the prescriber, preferably directly on the product leaflet[5, 9, 12].

Paediatric medicines initiatives

During the past three decades, awareness has been growing that it is more ethical to evaluate medicines in children than to treat children off-label with drugs that have not been tested in this population[16]. The United States (US) and the European Union (EU) have introduced strong paediatric initiatives to improve the paediatric situation, mostly through legislative measures aimed at increasing the number and quality of studies in children.

Worldwide initiatives to stimulate paediatric clinical trials

The US legislation

The US Federal Government was the first to take initiative and issued in 1997 the Food and Drug Administration Modernization Act (FDAMA)[8, 16]. The FDAMA encouraged studies of certain therapies being used in paediatrics by providing an exclusivity incentive provision. It provided an additional 6 months of marketing exclusivity (i.e., no generics can be approved), if the sponsor voluntarily conducted the studies requested by FDA in the written request, submitted them in the specified time frame, and the studies fairly responded to the written request[8]. This provision was reauthorized in 2002 as the Best Pharmaceuticals for Children Act (BPCA) and was reauthorized again in 2007 as part of the Food and Drug Administration Amendment Act (FDAAA). Meanwhile, the FDA issued a regulation in 1998 that mandated paediatric assessment of new drugs (or already marketed drugs under certain circumstances), which was later codified as the Pediatric Research Equity Act (PREA) of 2003 and was also reauthorized in 2007 under the FDAAA. The US legislation has been reauthorized every five years, emerging each time with a new name and modifications[17]. In 2012, the FDA Safety and Innovation Act (FDASIA) came into force, reauthorizing and strengthening the two complementary federal laws (BPCA and PREA) (table 1). The paediatric labelling process in the US progressed from the FDAMA encouraging the pharmaceutical industry to conduct

paediatric studies in the 1990s, to a combined 'carrot-and-stick' approach of voluntary incentives and mandatory regulation[8].

The European Paediatric Regulation

Based on the experience of the US, the Paediatric Regulation (N°1901/2006[18] and amendment N°1902/2006[19]) entered into force on January 26, 2007. This is a regulation which means that it should be directly implemented throughout Europe without the need for transposition into national laws (as opposed to a European directive). Due to this Paediatric Regulation, drug development in Europe is no longer possible without considering the effects of the future use of the drug in children. For any application for medicines approval, pharmaceutical companies must include either the results of all studies performed in compliance with a paediatric investigation plan (PIP) or a decision on a waiver or a deferral that has been reviewed and agreed by an expert committee at the European Medicines Agency (EMA), the Paediatric Committee (PDCO)[18]. This is the case for all new medicines, and for new indications, new pharmaceutical forms and new routes of administration of authorised medicines[20]. Generic products, homeopathic and herbal products are exempted from this obligation. The submitted PIP includes information concerning the timing and measures proposed to obtain a paediatric indication, in all paediatric subsets affected by the condition. In practice, a PIP defines the required clinical trials, the necessary age-appropriate formulations and forms and the need for juvenile animal studies[20]. A PIP should be submitted early in development, upon completion of the PK studies in adults, and is reviewed by the PDCO. The PDCO, established in July 2007, is an expert body including members appointed by the EU member states, two members from Norway and Iceland (of the European Economic Area) and six members representing health professionals and patients associations[18, 21]. The PDCO can grant a waiver if: 1) the disease or condition only occurs in adults; 2) the medicine is likely to be unsafe or ineffective in children, or 3) the medicine does not offer a significant therapeutic benefit in children. Waivers can be granted for the whole paediatric population (full waiver) or some subsets only (partial waiver)[18, 20].

When an agreed PIP is completed and all the information has been submitted to the regulatory authorities, the medicinal product will be granted an extra 6 months patent protection (extension of the duration of its Supplementary Protection Certificate [SPC]), which represents the financial reward to pharmaceutical companies. This extension is granted whether or not the data support a paediatric indication[20]. There is much debate among stakeholders on whether this financial incentive is sufficient. In the US, the 6-month patent extension awarded to companies completing agreed paediatric research has proven powerful and sufficient[9]; though this was mostly the case for blockbusters such as medicines used in the treatment of gastroesophageal reflux or type 2 diabetes[22]. The economic value of the reward depends on the turnover of the product concerned. In the case of blockbuster products the amount may be considerable, while for niche products the effect is small[4, 22]. Professor J. Ramet stated in his reflection paper that this situation for Europe might be different, as the European medicines market is different from the American market and Europe has almost a decade of paediatric research to catch up[9].

It is estimated that 20-35% of all recognised diseases are rare, the prevalence of which is defined to be equal to or lower than 5 in 10000 persons in Europe. Several issues (such as the scarcity and geographical dispersal of eligible research subjects and the small market for excessively expensive, newly developed treatments) render the development and provision of drugs for the diagnosis, prevention and treatment of rare diseases a difficult enterprise. In the EU, a specific regulatory framework was created in 2000 to encourage the development of 'orphan drugs': The Orphan Regulation[23]. Contrary to the situation in the US, orphan drugs are not exempt from the EU Paediatric Regulation.. Products that have been designated as orphan medicinal products benefit from a 10-year period of market exclusivity by the Orphan Regulation but are not commonly protected by patent[24]. As a result, the reward of an extension of the related SPC is not available. The financial incentive chosen for these products in the Paediatric Regulation consists of an additional two year added to the ten years of market exclusivity granted in the EU to orphan medicines[20]. This reward for designated orphan medicines (2 additional years of market exclusivity) has been given to seven medicines so far[13].

The EU Paediatric Regulation also created a new type of MA to give an incentive to medicinal products that have been on the market in the EU states for some time and therefore are no longer covered by a patent[17, 20]. This *Paediatric Use Marketing Authorisation* (PUMA) procedure permits application for authorisation of a paediatric indication for an existing medicinal product that is no longer covered by intellectual property rights[18]. Up until now, only three drugs received a PUMA[13]: 1/buccal midazolam for the treatment of prolonged, acute, convulsive seizures in paediatric patients, 2/oral propranolol for the treatment of proliferating infantile haemangioma and 3/glycopyrronium for the treatment of sialorrhoea in children with neurological disorders[25].

The Paediatric Regulation has now been in force for more than ten years. At the end of 2016 (ten years after the implementation of the Regulation) the European Commission undertook a public consultation. Most agree that The Regulation has created a new landscape for paediatric research in Europe[13], though there are some difficulties:

- There is an important back log of studies that need to be carried out. Between August 2007 and December 2016, the EMA agreed 950 PIPs. This resulted in 267 new medicines for use in children and new paediatric indications, together with 43 new pharmaceutical forms appropriate for children[13]. This discrepancy may be due to the high attrition rate during the drug development process[26], but also due to the fact that paediatric trials requested by EMA can be deferred for years until after the adult development. Paediatric medicines development is generally performed once safety and efficacy data have been obtained in adults, and only when the development in adults has been successful. Therefore, deferrals can be granted by the PDCO (either of the initiation of studies and/or their completion) because the PDCO wants to prevent that delaying MA until all paediatric studies are completed would delay approval in the adult population by several years. Tomasi et al state that In practice, approximately 90% of the PIPs for new medicines agreed in 2016 (January–December) included a deferral of one or more measures[13]. This leads to considerable delays in making medicines available to children[20]. However, this situation is better than the time before the Paediatric Regulation in which most drugs were not evaluated in children.
- The PIPs received by the EMA mainly concern medicines targeting adult diseases, which is in line with economic profit expected by companies[17, 27].
- The number of products being developed for the adult market, coupled with the relative scarcity of paediatric patients with the same condition, can create significant feasibility issues for the conduct of the paediatric trials. Examples of this are drugs for treatment of type 2 diabetes[28].
- Clinical trials before market authorisation tend to be small and provide a very limited safety database. The unique risk for long-term adverse developmental effects cannot adequately be addressed before MA of the product [12].

Although much still needs to be done, developments to date indicate that with joint efforts and appropriate resources, change is possible[17].

'Better Medicines for Children' Resolution of the World Health Assembly

Also the World Health Assembly (WHA) – the highest governing body of the World Health Organization (WHO, with all of the 194 member states having a seat) - took initiative to stimulate research on medicines for children. In May 2007, the WHA adopted the 'Better Medicines for Children' resolution 60.20[29]. Importantly, this resolution was endorsed by almost all governments of the world[17]. This resolution raises the concern on the lack of access to essential medicines of assured quality for children, as well as of the insufficient investment in clinical trials of drugs for children.

Paediatric medicines initiatives in other countries across the globe

The problem of off-label prescribing is global: it concerns all children of the world, those in the developing world and those in the developed world. Next to the above-mentioned EMA, FDA, and WHO initiatives, only a few individual countries have taken paediatric medicines initiatives. These have been less extensive and weaker, with modest results[16, 17], although most of the countries have endorsed the WHA Better Medicines for Children Resolution[17]. Japan and Canada grant incentives for paediatric drug development but currently do not include any requirement or obligation for paediatric drug evaluation in their legislation. In the other countries, the initiatives are even weaker. Unfortunately, the pharmaceutical industry does not appear to be interested in transferring the benefits of approved paediatric appropriate medicines in the US and EU to other countries[16, 17]. This may be due to lack of economic incentives and the high costs associated with amending the labels of existing medicines with new paediatric data or registering new medicines[16].

Conclusion

The paediatric medicine initiatives have had a positive impact on paediatric drug development. Paediatric development has become an integral part of the early development of medicinal medicines across the world: While further efforts are needed to increase positive outcomes and to address challenges described above, the 'cultural shift' induced by these initiatives is leading to more information on the paediatric use of medicines.

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Setting up a Belgian paediatric clinical research network

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The creation of a national paediatric clinical research network has been a dream for long time, which has finally come true. The process of creation until now included 3 major phases, spread over more than a decade:
1) A top-down approach from the Belgian Society of Paediatrics (BVK/SBP);
2) A bottom-up approach from the SAFE-PEDRUG project, an IWT SBO 130033 project involving multiple Flemish universities;
3) An ultimate opportunity and push from a pan-European Innovative Medicine Initiative 2 (IMI2) project, conect4children (c4c, https://conect4children.org/).

Phase I: the beginning

The Belgian Pediatric Clinical Research Network (=BPCRN, http://www.bpcrn.be/), was created in 2009 in response to an emerging need for a harmonised approach for executing high quality paediatric clinical trials, a key element to support **drug research for children in our country**. In fact, following the European Medicine Agency (EMA)-regulations from 2007 on, all new drugs developed for adults (with some exceptions) must also be tested for children. To this extent, the drug manufacturers are obliged to have a paediatric investigation plan (PIP). The BPCRN aimed to promote paediatric clinical trials in Belgium in order to expedite the marketing of appropriate drugs for children in line with the EMA regulations and initiatives. In the initial concept, the consortium aimed to create a national multicentre network to support clinical research not only focusing on industry- and academia-driven drug studies, but also to study other paediatric issues, including nutrition for children.

The BPCRN was launched on February 2nd 2009. This initiative was co-founded by Prof José Ramet† and Prof Allegaert, former and acting chairman of the BVK/SBP, respectively. The BPCRN core group consisted of following doctors/specialists and scientific researchers: Allegaert Karel (acting chairman), Christiaens Daphné (secretary), De Bruyne Pauline, Langhendries Jean-Paul, Matthys Dirk, **Ramet José†,** Schurmans Thierry, Sokal Etienne, Vande Walle Johan, Van Overmeire Bart, van der Werf ten Bosch Jutte.

The BPCRN aimed to make an inventory of the institutions, investigators and specialties involved in former and current clinical trials, and to provide an outline of every expertise and recruitment potential of each centre. There was a true believe that this initiative would facilitate networking between all interested parties involved in paediatric clinical research in Belgium.

The two main objectives of this network were:

1) To use the BPCRN website as an **interface** for **stakeholders,** including academicians and pharmaceutical industry actively engaged in paediatric clinical studies of drugs and nutrition. The BPCRN aimed to use this interface to provide details of the centres who have the appropriate expertise to carry out paediatric clinical trials.
2) To facilitate **communication** between research teams who are active in the same speciality. In this way, the BPCRN hoped, among other things, to support recruiting of patients.

In order to achieve these two objectives, the BPCRN encouraged **study centres** and **pharmaceutical industry** to register themselves on the website. In this way, interested stakeholders were able to provide and exchange specific **information**. This information could cover:

a. both public and private centres which play a role in paediatric research;
b. specific expertise of each centre;
c. paediatricians and doctors participating in paediatric research;
d. any recruitment offers from centres and industry
e. clinical trials being carried out in Belgium;
f. practical details of a specific study (design, reference numbers, client, etc.).

Furthermore, the BPCRN aimed to provide **information on drug research** to parents and patients so that they can better understand what paediatric drug research exactly means and what it means to be involved in clinical trials.

The vision was definitely correct, the ambition was huge, and the future looked bright, but was too far ahead of its time. The realisation of these objectives was only partly succeeded, whereby the lack of a well-organized paediatric national network still remained. This has also been proven in the conect4children (c4c) application for the IMI2-call10 (*see phase III below*), where many of the above stated objectives have been included in the project proposal as urgent gaps that still needed to be filled.

Parallel to this BPCRN initiatives, other countries initiated similar network activities, i.e. the Dutch Medicines for Children Research Network (MCRN-NL, and the British Medicines for Children Clinical Trials Unit (MCRN-BR, https://www.mcrnctu.org.uk). The Dutch MCRN-NL network, was initially supported by the government, but once the seeding money was ceased, the network went in a hibernation-like state. However, the network is currently being transformed to PEDMED-NL within the c4c project. The MCRN-BR became a dedicated guidance structure and an exemplary success story, certainly facilitated by significant financial support from the National Health Service. The observation that the Dutch and the Belgian clinical trial networks were not very successful in succeeding their objectives, stresses the weaknesses from these structures once the seeding money is ceased. There is a clear need of harmonisation of these networks, whereby an overall paediatric specific business model supported by academics, government and industry should be implemented. Although the concept was at first glance well supported, sustainability of such a national network is only realistic if there is a continuous inflow of clinical trials/seeding money (cfr. MCRN-BR) coming to the network.

Investing in national networks could offer the promise that all patients across that country have the opportunity to participate in a clinical study, whereby high quality will be guaranteed. Moreover, for the industry, national networks could potentially provide detailed information on the centres, better recruitment strategies, harmonization of procedures and timely delivery of study data. In the past, national network creation attempts underestimated the cost of maintaining such a structure especially since at that time the industry did not consider to prioritize national networks as preferential partners. Industry and contract research organizations preferred to use their own local contacts (principal research investigators, PI) to perform their studies, rather than contacting the national networks. The rationale for these choices were complex, but obvious: (1) politics between sites; (2) scientific competition between sites and (3) budgets. Although this rationale was beneficial for the industry, this strategy was not in line with the overall aims of the EMA-regulation. The majority of PIP-driven studies failed at the end to get paediatric labelling and paediatric formulations on the market. Therefore, the creation of a pan-European paediatric clinical research network, involving different stakeholders (academician, industry and government) was urging, whereby development of a sustainable business model should be carefully considered (*see phase III, below*).

Phase II: SAFE-PEDRUG: (http://safepedrug.eu/)

Subsequent to the BPCRN initiative, a Flemish group of paediatric researchers identified the need for more paediatric specific data on pharmacokinetics and pharmacodynamics (PK/PD), to support paediatric adapted clinical trial design.

Evaluation of the implementation of 5-year EMA-regulation demonstrated that too little had changed for the patients. PIPs were mainly drafted in a **top-down approach** derived from adult data, mainly targeting the adult indication using adult study-design in children rather than focusing on paediatric specific indications. In the PIP's, neonates, critical ill children, children with comorbidities, or abnormalities in absorption, distribution, metabolism and excretion (ADME) characteristics were almost always an exclusion criterion. While these are the populations where appropriate drug testing is needed the most. Moreover, for ethical and safety reasons, paediatric studies were postponed until the end of patent rather than performing them simultaneously with adult early-phase studies. Postponing these studies was largely defended by arguments that phase I studies in children are not allowed, that there had to be enough adult (safety) data before switching to children, and that it was difficult to calculate appropriate dosing for children. It was obvious that in the last five years the problem of off-label use had hardly changed.

There is an urging need for correctly labelled, safe and effective drugs for children, in the age ranges and subpopulations of patients for whom the drug is prescribed, with special emphasis on growth, development and maturation. Drug research in children is traditionally performed using a top-down approach in which data of adult drug studies are extrapolated to children. However, literature has shown that PK and PD characteristics in children can differ when compared to adults, whereby extrapolation from adults to children should be carefully considered. Consequently, the idea was drafted to submit a research project whereby a **bottom-up approach** is applied, namely starting from specific paediatric needs, by which paediatric ADME characteristics were studied, in order to improve the quality of paediatric clinical trials, leading to better designed PIPs. A multidisciplinary (scientists, pharmacists, veterinarian, ethicists, paediatricians), interuniversity consortium, including different paediatric disciplines was developed between different universities, namely **SAFE-PEDRUG**.

The key objective of the SAFE-PEDRUG project was to evaluate an alternative drug development strategy for the paediatric population (bottom-up approach). The latter approach included:

- introducing the concept of an appropriate juvenile animal model as potential surrogate for paediatric phase preclinical studies, during all maturation phases;
- collecting datasets for use in advanced PK and PD modelling & simulation analyses to help optimize trial designs, identify relevant covariates and allow the prediction of appropriate dosing regimens;
- performing adapted paediatric clinical trials in the diseased paediatric population and using a size dependent dosing approach to allow identification of maturation and/or disease specific covariates (including biomarkers and surrogate endpoints).

A special emphasis on drug research orphaned subpopulations, like critically ill patients and neonates, was also placed in this project. The ultimate objective of this project was to develop a SAFE-PEDRUG clinical trial unit to perform and monitor clinical trials within the consortium, eventually evolving in a centre of excellence. The experience gained during the SAFE-PEDRUG project, together with the previous launch of the BPCRN allowed to apply for the c4c consortium.

Phase III: the European conect4children consortium.

c4c is a European consortium supported by the Innovative Medicine initiative (IMI), a public-private partnership in life sciences between the European Union and the EFPIA (European Federation of Pharmaceutical Industries Association). The project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU), Europe's biggest Public-Private Partnership, under grant agreement No 777389. The JU receives support from the European Union's Horizon 2020 research and innovation program and EFPIA (the European Federation of Pharmaceutical Industries and Association).

The overall goal of the c4c network is to result in better medicines for neonates, children and adolescents through the creation of a pan-European clinical trial network. Four academic- and four industry-sponsored paediatric high-quality regulatory grade clinical trials will be performed to evaluate the viability of this pan-European clinical trial network, whereby the development of a solid business model beyond IMI funding is one of the prerequisites to create this sustainable network. The key objectives of this project are:

1) efficient trial implementation by creating national hubs (NH) and qualified sites;
2) implementation of harmonized, streamlined procedures
3) expert advice about clinical trial design by setting up pilot expert advisory groups and other fora;
4) patient and parent involvement by providing awareness rising campaigns for the general public;
5) training of health care professionals by providing educational programs;
6) identification of data standards and metrics.

The c4c network is built up around 18 paediatric national networks, 8 EU multinational specialty networks, 2 large patient advocacy groups, 3 global research networks, 200 large children's hospitals, and 10 major partners of the EFPIA.

The project is divided in 9 work packages: 1) management of the project, 2) governance of the network, 3) sustainability of the network, 4) scientific expert advice, 5) data management, 6) education and training, 7) clinical trials execution, 8) dissemination of results, 9) ethics.

The kick-off of the project was in May 2018. One year later, the consortium has already achieved important milestones: 1) 19 national hubs are operational; 2) expert groups have been set up; 3) the educational platform is live; 4) academic clinical trials are being initiated; 5) secured, shared clinical trial databases are being created; 6) business models to guarantee sustainability of the network beyond IMI funding are being drafted. Discussing the full current status of the c4c project is beyond the scope of this article, but we will further elaborate on objective 1: *" Efficient trial implementation by creating national hubs and qualified sites in Belgium."*

The role of the NH is to set-up a national network by bringing together potential sites with their respective specialities, interested in performing high quality paediatric clinical trials. The NH acts as the liaison between the c4c consortium and the sites on the one hand and the sponsor and the sites on the other hand, whereby the identification of single points of contacts (SPOC) per site/subdiscipline is one of the first objectives. In Belgium, Ghent University has applied to become the NH for Belgium within the c4c project. After approval of the project, the main goal of the Belgian NH was to reactivate the former BPCRN network, whereby endorsement by the BVK/SBP was key. Different steps were taken to create the BPCRN network. First, potential sites were identified who could become part of this network. All pediatric university hospitals (UZ Gent, UZ Leuven, UZ Antwerp, Vrije Universiteit Brussel, HUDERF, CHU Liège, CHU Charleroi, UCL) as well as one speciality hospital (Zeepreventorium) were included in the network. Second, within these sites local SPOC's (single point of contact) and their respective back-ups were identified (endorsed by their hospital), who are *inter alia* responsible for: 1) communication between NH and site; 2) communication within their site; 3) identification of SPOCs per speciality within their site; 4) follow-up of the general performance of their sites by providing metrics. Third, to stimulate communication between the sites within a specific speciality, a SPOC for each subspecialty was identified who is responsible for informing their speciality network when studies are announced. Different SPOCs for the specialities have been appointed (cardiology, gastroenterology and nutrition, hepatology, pneumology, endocrinology, obesity, infectious diseases, neonatology, intensive care, neurology, immunology, nephrology, rheumatology, vaccinology, oncology and haematology). The list is not limitative, whereby new specialities can be added according to the needs of the sponsors. At the moment three specialities yet have to be determined, namely dermatology, metabolic diseases and ophthalmology. Once the sites and the SPOCs were identified, a road-show across the sites was organized to introduce the c4c project within the different sites. The key of success of the network is to provide transparent communication, therefore, monthly teleconferences were implemented, whereby the current status of the project and network (national and European), including the academic- and industry-driven proof of viability studies, were discussed. Moreover, a face-to-face meeting is organised yearly, a three-monthly newsletter was drafted and individual meetings were performed on request. To facilitate communication with the NH, a single mail address (C4C-NHBelgium@uzgent.be) was activated. Within the scope of the project, the NH and sites have performed several tasks:

1) Identify SPOCs within the sites
2) Providing detailed information about the site's capabilities
3) Being involved in academic-driven trial applications
4) Feasibility assessments academic- and industry-driven trials
5) Harmonizing and streamlining standard operating procedures across the trial lifecycle

Setting-up paediatric clinical trial networks: what have we learned so far and what will we need to do in the future?

1) Selection of sites should be carefully considered, whereby quality but also willingness should be considered. In the current selection, it was opted to work with rather a limited number of hospitals, who all have a large track-record on performing clinical trials. In addition, in Belgium most university hospitals work closely together with local hospitals whereby exchange of patients often occurs. In the future, it might be advisable to add other, often more peripheral hospitals, especially when studies targeting this population will be presented.
2) Setting-up a paediatric clinical trial network is a team effort. Taking the time to identify highly motivated team members within the NH as well as the sites is therefore crucial for the success of the network. Within the Belgian network, the structure based on a SPOC and his/her respective back-up works. As the identified SPOCs are often clinicians with limited time, providing sufficient back-up is important. During the set-up and feasibility assessments, it has been noted that appointing the right person is crucial to fulfil the often stringent deadlines.
3) Transparent and open communication should always be maintained. This is the reason why we implemented teleconferences, meetings and newsletters. Informing the network is very important so that the sites are aware of the current status and know how to handle when something is asked. In the future, integration of some processes, i.e. feasibility assessment; PI identification; etc., on the BPCRN website will be necessary so that these can be automated and be less time-consuming.
4) The minimal and the maximal distance between the included Belgian sites is 30.3 and 208 km, respectively. This offers the advantage that organizing meetings and follow-ups of the sites is easier than in larger countries. Moreover, this stimulates regular face-2-face meetings between the sites on the one hand and within the specialities on the other hand. Also, for patients there are advantages, whereby the burden to reach the nearest speciality hospital is smaller than in larger countries.
5) It is important not to underestimate the cost (both FTE as working budget) of developing a paediatric clinical trial network. Although the BPCRN was already founded in 2009, it was only because of the IMI funding that this network could further develop. Moreover, in the future it will be important to create a self-sustaining network beyond IMI funding, whereby the network on its own should also be able to raise funding whether or not through governmental funding.

Emerging new therapies in Spinal Muscular Atrophy: a review

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Key words

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Abstract

Spinal muscular atrophy (SMA) is a group of autosomal recessive disorders associated with degeneration of motor neurons in the spinal cord and brainstem that lead to progressive muscle weakness and atrophy along a phenotypic continuum, SMA is caused by a homozygous deletion or mutation in the survival motor neuron 1 (SMN1) gene, which results in decreased expression of the survival motor neuron (SMN) protein and degeneration of motor neurons. A paralogous gene, survival motor neuron 2 (SMN2), also encodes the SMN protein; however, 90 to 95% of the translated protein is truncated and nonfunctional as a result of aberrant splicing. Understanding of the genetic basis of SMA and ongoing advances in drug development led to the first definitive treatments, with now two Food and Drug Administration (FDA) approved treatments, one of them for all subtypes of SMA. One of them uses antisense oligonucleotides (ASOs), synthetic ribonucleic acid (RNA) molecules, that interfere with the physiological splicing of exons, thus increasing the production of full length SMN2 messenger RNA (mRNA). The second uses recombinant adeno-associated viral vectors (rAAV) to deliver the full SMN1 gene copy to motor neurons. Ongoing research is being carried out to identify new therapeutic agents. Since it appears that pre-symptomatic treatment is much more efficient than early treatment, which is also by far more efficient than late treatment, whatever is the approach, newborn screenings programs are being launched in several US states and European Regions. Combination of different therapeutic strategies could optimize benefits of the treatments.

Introduction

Spinal muscular atrophy (SMA) is a group of autosomal recessive disorders characterized by progressive muscle weakness and atrophy. SMA is associated with degeneration of motor neurons in the spinal cord and, in the most severely affected patients, of the lower brain stem motor neurons. SMA is the most common monogenic cause of infant mortality.

The incidence of SMA ranges from 7 to10 per 100,000 live births, with 4 per 100,000 live births being SMA Type I, the most severe subtype[1].

A phenotypic continuum

Patients with SMA can be divided into 4 broad clinical subtypes (I, II, III, IV), The subtypes represent a phenotypic continuum. Most clinicians and guidelines classify these patients using maximum motor function or gross motor developmental milestone achieved.

Classically, patients with Type I, also known as Werdnig-Hoffman disease, are described as "non-sitters" and usually present from birth to 6 months of age with diffuse hypotonia and poor head control. On examination, patients with Type I SMA have a characteristic alert expression, tongue fasciculations, generalized weakness affecting the lower limbs more than the upper limbs, and areflexia. Weakness of the inspiratory respiratory muscles produces a bell-shaped chest and paradoxical breathing, In the past, most children with Type I SMA did not live past 2 years of age due to respiratory failure and recurrent respiratory infections; however, with the use of mechanical ventilator devices, lifespans of these children can be prolonged[2].

Patients with Type II are described as children who have achieved independent sitting ("sitters")

Onset of symptoms is classically between 6-18 months of age. Similar to patients with Type I SMA, they have diffuse hypotonia, tongue fasciculations, generalized weakness affecting the lower limbs more than the upper limbs, and areflexia. Frequency of respiratory symptoms is less in this subtype of patients. However, as weakness progresses, they are faced with orthopedic issues such as scoliosis, with resulting restrictive lung disease if the scoliosis is not corrected.

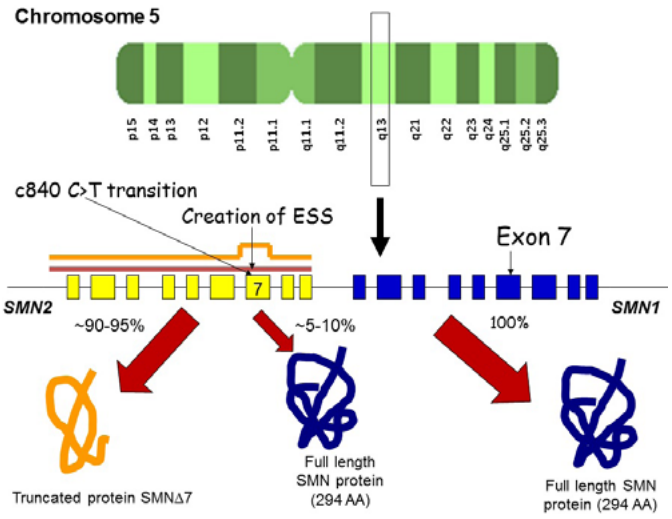
Cognition is normal with above average verbal intelligence[3]. Prognosis for patients with Type II is better; however, depending on the degree of respiratory compromise, life expectancy can be shortened[2].

Patients with Type III SMA, also known as Kugelberg-Welander disease, mild SMA or "walkers," are children who are able to stand unsupported and walk independently[4]. These children usually present later than 18 months of age. The onset of symptoms further subdivides these patients into 2 groups: patients with Type IIIA have onset of symptoms between 18 months and 3 years, and patients with Type IIIB usually present after the age of 3 years. The distribution of weakness is similar to that seen in patients with Types I and II SMA, but the progression of weakness is a more gradual process; some patients may eventually become wheelchair dependent at a later stage (this is seen more frequently in patients with Type IIIA). Respiratory and orthopedic complications are less frequent in this subset of patients, with life expectancy almost similar to the normal population[2].

SMN1 and SMN2 genes

Most common forms of SMA are caused by biallelic deletions or mutations in the SMN1 gene on choromosome 5q13.2.[5]. The SMN1 gene lies telomeric of the SMN2 gene which is the result of a duplication of SMN1 that differs from it by only 5 nucleotides. The critical difference between SMN1 and SMN2 genes is a C-to-T transition in an exonic splicing enhancer located in exon 7 of SMN2 gene (Figure 1)[6]. While this C-to-T transition does not create an amino acid sequence change (translationally silent), it affects the splicing of the gene so that exon 7 is excluded from most, but not all, SMN2 mRNA transcripts. Thus, as exon 7 is frequently spliced out of the SMN2 mRNA, the SMN2 gene produces about 5–10% full-length functional protein and 90–95% truncated protein6. In healthy carriers who have one SMN1 copy and zero SMN2 copy, having 50% functional full-length SMN protein is sufficient for normal functioning. In patients with SMA, the most common SMN2 copy numbers are 1–2 copies in Type I, 2-3 copies in Type II and 3-4 copies in Type III. About 50% of patients with Type III have 3 copies of SMN2[7]. At a maximum range of 10% functional protein production per SMN2 gene, these patients are predicted to have 20–30% full-length SMN protein production. Patients with milder Type III, with 4 copies of SMN2, would have about 40% SMN protein, still below the 50% level seen in healthy carriers with no SMN2 copies. Furthermore, asymptomatic individuals with 5 copies of SMN2 and zero copy of SMN1 have been described, and these individuals are predicted to have 50% SMN protein level[7]. The clinical severity of the disease in SMA patients depends partly on the copy number as well as on the quality of SMN2 genes

Figure 1: Diagram of survival motor neuron (SMN) SMN1 and SMN2 genes on chromosome 5 demonstrating that a C-to-T transition at position 6 of SMN2 creates an exonic splicing suppressor (ESS), which then leads to skipping of exon 7 during transcription, resulting in the production of truncated nonfunctional SMN protein. AA: amino acids.



that the copies carry. Although there is a rough correlation between SMN2 copy number, level and quality of SMN protein, and clinical severity, physicians often see a clinical overlap in the phenotypes of these patients.

SMN protein in conjunction with several Gemin proteins forms an SMN complex, whose chaperone function facilitates the assembly of spliceosomal small nuclear ribonucleoprotein (snRNP) particles, essential components of the spliceosome complex, and hence plays a critical role in pre-mRNA splicing. The SMN protein may also be essential, transporting axonal mRNAs in motor neurons, and perhaps in other processes in muscle and neuromuscular junction. The role of SMN protein in axonal mRNA trafficking and mRNA splicing may explain the selective vulnerability of spinal cord motor neurons to decreased SMN protein8. There is a clear relationship between the severity of the disease and the amount of SMN produced by motor neurones[5].

Prenatal and Newborn screening

The American College of Obstetricians and Gynecologists Committee on Genetics published their opinion that routine preconception and prenatal screening for SMA should be offered to all women who are considering pregnancy or are currently pregnant and have had appropriate counseling about the possible range of severity, carrier rate, and detection rate[9]. Two pilot experiences of newborn screening in Taiwan and New York have been conducted. A pilot program in southern Belgium was initiated in Liege area (17.000 newborns/year) on marsh 05th 2018 and expended to whole southern Belgium on December 31st 2018 (55.000 newborns/years)[10]. On June 01st 2019, 35.000 newborn had been screened and 5 patients had been identified. Similar programs are conducted in Bavaria, North Westfalia, Toscany and Lazio and are in preparation in several other European regions.

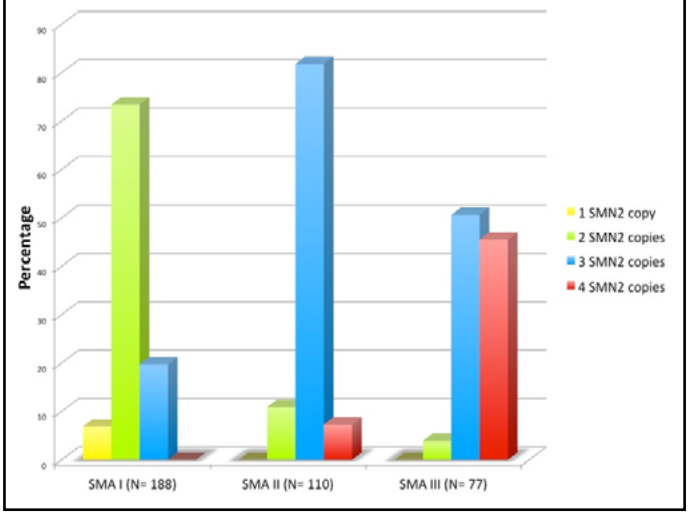
Drug Development in SMA

Up to a few years ago there were no approved drugs to treat SMA. Management consisted essentially in taking care of nutrition, growth, pulmonary and orthopedic care, physical therapy and rehabilitation, this under the umbrella of a multidisciplinary team that has a deep experience in the natural history of the disease[11]. The understanding of the genetic basis of SMA has resulted in numerous clinical trials exploring the efficacy and safety of various drug treatments. Up until December 2016, no definitive treatment for SMA was identified despite major efforts exploring pharmacological methods that could upregulate the expression of SMN2 or produce more functional SMN protein[12]. Now, several potential therapeutic developments are in the pipeline and showing potential, giving the SMA community around the world great hope that, one day, at least one therapeutic option may allow every SMA child to reach his or her best potential in terms of motor function.

SMN2 splicing modulation

Antisense oligonucleotides (ASOs) are synthetic RNA molecules that promote exon 7 inclusion by interfering with the physiological splicing of exons, thus increasing the production of full length SMN2 mRNAs[13]. In in-vitro and SMA mouse models, these effects appear to compensate for the lack of SMN1. ASOs can affect the splicing of SMN2 exon 7 by blocking the binding of trans-acting protein factors by steric hindrance[14], rearranging the structure of target RNA molecule[15,16] (Figure 2). Multiple challenges arise when translating this approach into clinical practice: (1) finding an efficient and safe route of administration of ASOs into the central nervous system; and (2) timing the introduction of this therapy to affected patients. Animal models suggest that intra-cerebroventricular injections of ASOs produce a higher level of SMN2 expression in motor neurons compared to systemic administration[17,14]. A preclinical study suggesting that timing of therapy is also important showed a median survival of 100 days or longer compared to 41 days in SMA mice that received the treatment immediately after birth compared to 4 days after birth.

Figure 2: Frequency of patients with spinal muscular atrophy (SMA) Types I, II and III and survival motor neuron (SMN) SMN2 gene copy numbers. In SMA Type I, 80% of patients had 1 or 2 copies of SMN2; in SMA Type II, 82% of patients had 3 copies of SMN2; and in SMA Type III, 96% of patients carried 3 or 4 SMN2 copies. Modified with permission from Feldkotter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time LightCycler® polymerase chain reaction (PCR): fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet 2002;70:358-68.



In December 2016, the Food and Drug Administration (FDA) and in June 01st 2017 the European Medicines Agency (EMA) announced the approval of Spinraza® (nusinersen) for patients with SMA, making it the first approved therapy for these patients. Nusinersen is a 2'-O-methoxyethyl phosphorothioate-modified ASO therapy developed by Ionis Pharmaceuticals in conjunction with Biogen, Inc. It increases the amount of functional full-length SMN protein, deficient in SMA patients, by changing the splicing of SMN2 pre-mRNA. In 2004, the Singh Laboratory at University of Massachusetts Medical School discovered intronic splicing silencer N1 (ISS-N1). In vivo studies showed that blocking ISS-N1 with an ASO enhanced SMN2 exon 7 inclusion during splicing events, and this finding was subsequently confirmed in studies involving both SMA patient cells and mouse models. In 2010, Ionis Pharmaceuticals (previously known as ISIS Pharmaceuticals) obtained the license for exclusive use, and in 2011 Phase 1 clinical trials began with encouraging results, demonstrating the drug's safety and effectiveness in reducing the disease severity and improving the phenotype in SMA patients[18]. These trials were followed by Phase 2 and later Phase 3 trials.

The phase 3 CHERISH study, a multi-center, randomized, double-blinded sham procedure-controlled study, assessed the efficacy and safety of nusinersen in children with later onset SMA (Types II or III)[19]. Symptomatic children between the ages of 2 and 12 years, diagnosed with 5q SMA, and with onset of symptoms at or older than 6 months of age, were eligible. They were randomized to receive 4 doses of 12mg of intrathecal nusinersen administered over a 15-month period versus sham procedure control. The primary endpoint of this study was the change in Hammersmith Functional Motor Scale Expanded (HFMSE) score at 15 months. Secondary endpoints included a greater or equal than 3.0 increase in

baseline HFMSE score, a new World Health Organization (WHO) motor milestone, the number of new WHO motor milestones achieved, any change in the Revised Upper Limb Module (RULM) score, and the proportion of children who achieved standing alone or walking with assistance. Significant statistical differences in the change of HFMSE score was observed between children who received nusinersen versus those in the sham procedure control group. There were no significant adverse side effects from nusinersen and the therapy was generally well tolerated by the children, although there were more complaints of back pain, headache and vomiting in the nusinersen group (>5% frequency) 72 hours after the administration of the drug. These complaints were attributed to the lumbar puncture procedures rather than a direct side effect from the drug.

The phase 3 ENDEAR study, a randomized, double-blind, sham-procedure controlled study, assessed the clinical efficacy and safety of intrathecal nusinersen in infants with SMA Type 1[20]. Patients between 3 weeks and 7 months of age, with genetically confirmed 5q SMA, and with symptom onset between 3 weeks and 6 months, were eligible. Outcome measures were event-free survival (time to death or permanent ventilation, defined as tracheostomy or greater than or equal than 16 hours of ventilatory support per day for more than 21 days in the absence of an acute reversible event), and changes in motor function and electrophysiologic assessments: the motor milestones portion of the Hammersmith Infant Neurological Exam and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scores, and compound motor action potential amplitudes. Age at death or permanent ventilation was compared with natural history. The study results were encouraging. Rate of survival without ventilation assistance was higher in infants who were treated with nusinersen compared to the control group (hazard ratio: 0.53; p value: 0.005). Fifty-one percent of nusinersen-treated infants showed improvements in their motor function assessments versus 0% of control infants[20]. The treatments were generally well tolerated. All reported side effects were felt to be expected in infants with SMA, with some related to the lumbar puncture itself; no safety concerns were identified.

Real-World data collection confirmed these findings and demonstrated the efficacy of nusinersen in a broader and older patients population[21, 22, 23, 24].

The approval of nusinersen by FDA and EMA as a therapy for SMA patients has been a major step for patients worldwide. Nevertheless, much work remains to be done as researchers transition to the next phase, in which the long-term efficacy of nusinersen is monitored. Follow-up trials to assess the long-term efficacy of nusinersen are in progress. Many other studies are underway, targeting other approaches or studying a less invasive route of administration for an effective delivery of drug into brain and spinal cord. In addition to studies of patients who are already symptomatic, an ongoing study (NURTURE) looks at the efficacy in preventing or delaying complications/symptoms in 25 pre-symptomatic, genetically-confirmed SMA patients (15 with 3 SMN2 copies and 10 with 2 SMN2 copies)[25], and so far the results seem promising. Indeed, patients with 3 copies of SMN2 have all acquired autonomous ambulation before 18 months, and patients with 2 copies present with a motor evolution much better than patients treated after the symptoms, about 50% of them present with a normal motor evolution.

The recommended dosage for nusinersen in SMA patients is 3 loading doses to be given 14 days apart (days 1, 15, 30) at 12mg (5ml)/dose and administered as an intrathecal bolus. The fourth loading dose is given 30 days after the last dose, around day 60. For maintenance, a dose every 4 months is recommended. Before each dose and as clinically indicated, recommendations include monitoring the platelet count, coagulation profile (prothrombin time and activated partial thromboplastin time), and baseline quantitative spot urine protein testing.

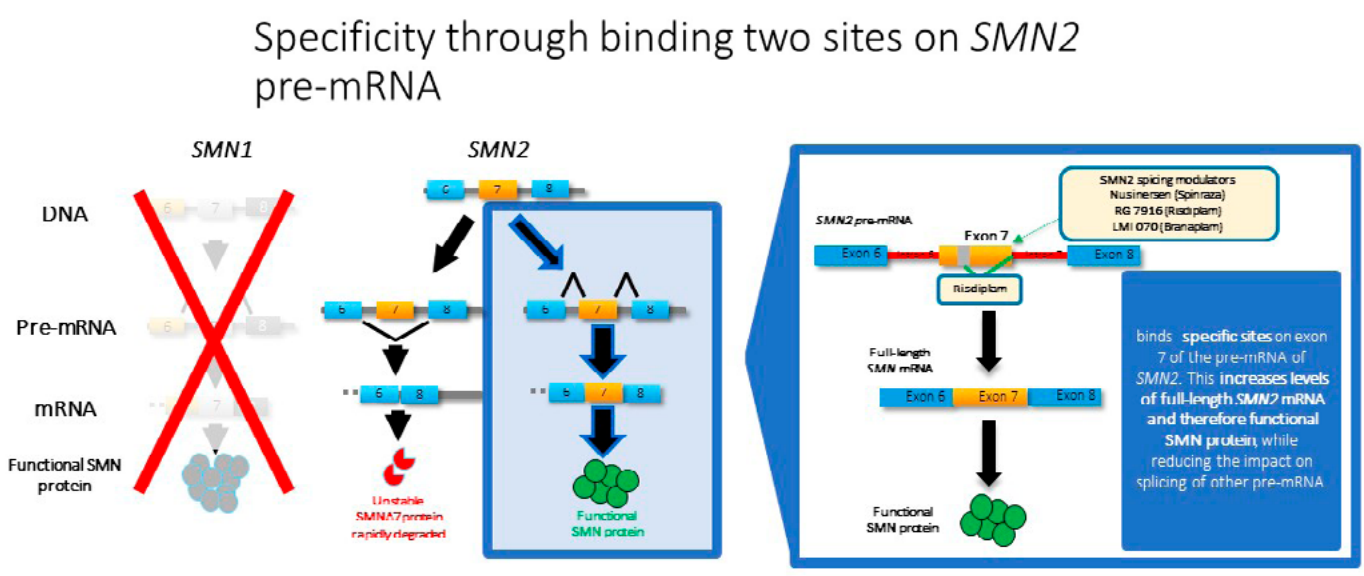
Small molecule or low-molecular-weight drugs have been found to increase SMN protein in the following ways: by activation of the SMN2 promoter and increasing its expression, or by alteration of the splicing pattern of SMN2 resulting in the inclusion of exon 7 (Figure 3).

Branaplam (LM1070) is a small molecule (developed by Novartis) designed to alter the SMN2 alternative splicing of exon 7, hence increasing full-length SMN. The Phase 1 trial is an open-label, first-in-human study of oral LM1070 in patients with Type 1 SMA[26]. SMA patients up to 8 months of age are eligible. This study examines the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy after 13 weeks, as well as the maximum tolerated dose and optimal dosing regimen in this group of patients.

Risdiplam (RG7916) is an oral SMN2 splicing modifier (developed by Hoffman-La Roche in collaboration with PTC Therapeutics and the SMA Foundation) designed to produce more functional SMN protein. Clinical trials are being planned in Europe and the United States to involve patients with Type I SMA aged 1-7 months old (FIREFISH) and patients with Types II and III aged 2-25 years (SUNFISH)[27,28] with very promising results. Another study, JEWELFISH, enrolls patients with Types II and III who have already been exposed to a SMN2 targeting therapy (such as RG7800 or nusinersen)[29].

In a pilot study of 13 patients with Types II and III SMA, treatment with albuterol, a β- adrenergic agonist, was associated with increased SMN2 full-length transcript levels and improvements in muscle strength and Hammersmith Functional Motor Scale score with no major adverse effects. Another pilot study of 23 patients with Type II SMA using salbutamol, a form of albuterol, also demonstrated improved Hammersmith Functional Motor Scale Scores[30]. However, these studies were not placebo controlled and the intervention not been subsequently evaluated in randomized, double-blinded placebo-controlled clinical trials.

Figure 3: Mechanism of action for survival motor neuron (SMN) SMN2 gene splicing modifiers. Antisense oligonucleotide (ASOs) or small molecules like RG7916 and LMI070 enter the cytoplasm of the cells and finally the nucleus where they bind to the SMN2 pre-messenger ribonucleic acid (pre-mRNA), displacing small nuclear ribonucleoprotein (snRNP) which normally suppresses splicing of exon 7. This action enhances exon 7 inclusion and results in the production of full-length SMN protein.



*Please note that risdiplam has not yet received regulatory approval in any country.
SMN, survival of motor neuron.
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SMN1 Gene therapy

In the early days of gene therapy research, adenoviruses were used as gene delivery vectors. However, immunogenicity was found to be a major issue. Subsequently, recombinant adeno-associated viral vectors (rAAV) proved to be promising as a gene transfer vehicle due to their lower immunogenicity. An open-label Phase 1 trial studying a gene therapy product AVXS-101 (onasemnogene abeparvovec) given intravenously in patients with SMA Type 1 has recently been completed; the results seem promising and similar to nusinersen in terms of event-free survival (100% of enrolled patients alive and not requiring permanent ventilation at 20 months compared with historical cohort rate of event-free survival of 8%), motor milestone acquisition (patients in the high-dose cohort achieved milestones such as sitting unassisted, rolling over, oral feeding and speaking, and 2 walked independently), and scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (increase of 9.8 points and 15.4 points at 1 and 3 months respectively, compared with decline in scores in historical cohort)[31]. AVXS-101 is derived from a non-replicating adeno-associated virus serotype 9 vector that is used to deliver a functional copy of SMN gene via an intravenous or intrathecal injection. In preclinical studies, it demonstrated its efficacy in targeting motor neuron cells when administered either intravenously or via an intrathecal route. Two phases three studies are ongoing in the US and in EU in symptomatic patient, and one phase 3 study in pre-symtomatic patient is also ongoing. A Phase 1 trial to evaluate safety and efficacy of AVXS 101 intrathecally administered in type 2 patients is currently recruiting. Onasemnogene abeparvovec has been approved by the FDA in December 2018 for the treatment of patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.

Other compounds not targeting SMN

Olesoxime is a molecule with cholesterol-like structure and neuroprotective properties. Preclinical studies suggest that it improves the function and survival of neurons. For the first time in the field of SMA, a Phase 2 randomized, double-blind placebo-controlled clinical trial in patients with Types II and III SMA between the ages of 3 and 25 was organized. Results were promising, with results suggesting that olesoxime maintained motor function and prevented the deterioration of muscle function[32]. However the long term exposure did not suggest a significant clinical benefit and the development of this safe drug was stopped.

A novel compound (CK-2127107) designed to improve the function of skeletal muscle via a skeletal muscle troponin activator is currently in a Phase 2 clinical trial to examine its efficacy in both ambulatory and non-ambulatory SMA patients[33]. This compound is unlike others in that it is not intended to increase the levels of SMN protein. Instead, this drug slows down the rate of calcium release from the troponin complex of fast skeletal muscle fibers.

Conclusion

Spinal muscular atrophy is a chronic, progressive, inherited motor neuron disease. Over the years, increasing knowledge and advances in research have given families with children affected by SMA great hope and optimism. Although there are now two FDA-approved treatments – one of them for all subtypes of SMA - ongoing research is being carried out to identify new therapeutic agents through the development of novel compounds. Standards of care are also developed to guide clinicians and caregivers to optimize the holistic, multidisciplinary management of these patients. Since it appears that pre-symptomatic treatment is much more efficient than early treatment, which is also by far more effective than late treatment, whatever is the approach, newborn screenings programs are being launched in several US states and European Regions. Combination of different therapeutic strategies could optimize benefits of the treatments. As more therapeutic agents are being developed, standards of care and treatment guidelines will continue to evolve and may encompass more pro-active respiratory intervention and support in an acute hospital setting. While the availability of new drugs has given many SMA families hope, the cost of the drugs together with the vast differences in health care policies in countries worldwide have meant that many children still may not have access to these drugs.

Lastly, support groups such as SMA Foundation, CureSMA and Fight SMA have provided a vital role in research efforts as well as a community for families affected by SMA.

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Inflammatory polyps of the tracheobronchial tree in children: case-series and review of literature

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Abstract

Objective:

Inflammatory bronchial polyps (IBP) are nonneoplastic endobronchial lesions rarely seen in children. The aim of this study is to compare our cases with published data and to propose a clinical approach.

Study design:

Literature review of all cases of IBP diagnosed in children and description of two cases from our clinic.

Results:

Information on 20 children was identified: 18 from literature and 2 own cases. A history of intubation was present in 12/20, chronic inflammatory lung disease in 2/20 and inhalation of a foreign body in 1/20. The etiology remained unclear in 4/20, including ours. Predominant symptoms were cough, dyspnea and fever. Chest X-ray typically showed atelectasis and hyperinflation. In our cases additional bronchiectasis or bullous lesions were seen. The polyp was endoscopically removed in 15/20 patients, while 5/20 had surgical intervention. No recurrence or malignant transformation was reported. Complete resolution of the bronchiectatic changes was observed in our patient, the bullous lesion regressed slightly.

Conclusion:

IBP are extremely rarely reported in children and originate from chronic inflammation of the airway. Unexplained chronic cough and dyspnea, in the presence of atelectasis and hyperinflation, should alert the health care professional to consider IBP, especially in a child that has been intubated. Endoscopic removal is the recommended therapeutic option, enabling diagnostic confirmation with histopathology. Lung damage can still recover if early diagnosis and removal of the IBP is performed. Only clinical follow-up is advised as the risk of recurrence or malignancy is negligible.

Introduction

Inflammatory bronchial polyps (IBP) are rare nonneoplastic lesions consisting of a fibrovascular core, interspersed with abundant inflammatory cells (mainly lymphocytes and plasma cells) and covered by a layer of normal bronchial epithelium[1-3]. They are predominantly encountered in the adult population and rarely reported in pediatric patients[4,5]. The underlying pathophysiology has been postulated from their histological findings. When a break in the mucosa occurs, granulation tissue may develop with subsequent replacement by fibrous tissue and epithelialization to form a polyp[6]. In the adult population, IBP may be seen in multiple chronic inflammatory conditions such as inhalation injury (thermal, chronic smoke and chemical injury), trauma (foreign body aspiration or after transbronchial needle aspiration), or chronic inflammatory respiratory diseases like asthma, chronic bronchitis, and mycobacterial infections[4,7-24]. Occasionally, the etiology in adults remains unclear[24,25]. These polyps can lead to nonspecific respiratory symptoms due to bronchial obstruction mimicking obstructive lung diseases like asthma or COPD.

We report two cases of IBP and reviewed the pediatric literature.

Study Design

Based on two cases in our pediatric clinic, we conducted a literature review. Publications on PubMed, Medline and Embase were reviewed until April 2019, using “inflammatory polyp”, “endobronchial polyp”, “bronchial polyp” and “inflammatory endobronchial polyp” as keywords. Only English papers were selected. Reports were only included if the histopathological features corresponded to the definition of IBP, as described previously.

Results

Case 1

A 2-year old boy was admitted for a first episode of febrile convulsions associated with a lower respiratory tract infection. His medical history reveals a premature birth at 36 1/7 weeks accompanied by a respiratory distress syndrome requiring non-invasive respiratory support the first days of life. He presented no further symptoms later on. Clinical examination showed diminished breath sounds on the left hemithorax, a transcutaneous oxygen saturation of 94% and a temperature of 38,7°C. He had white blood cell count (WBC) of 17440/µL with 13850/µL neutrophils and C-reactive protein (CRP) of 14,9 mg/L. Chest X-ray (CXR) showed beginning infiltrates on the right lung and hyperinflation of the left lung with a bullous lesion in the left lower lobe (LLL) (Fig.1A), being considered as a pneumonia for which he received intravenous antibiotics and oxygen therapy. A nasopharyngeal aspirate demonstrated the presence of bocavirus. EEG and neurological follow-up were normal. His clinical condition improved after 24 hours of treatment. Because of the suspicion of a bullous lesion, a chest computed tomography scan (CT-scan) was performed, confirming a unilocular cyst (19 mm) posterior in the right lower lobe and a multilocular cystic lesion (diameter 64 mm) medio-basal in the LLL (Fig.1B). Differential diagnostic considerations were a lung sequestration or a congenital cystic adenomatoid malformation (CCAM).

Consecutively, a flexible bronchoscopy (Olympus 3.6) was performed, showing a round and pinkish, cystic mass in the left main bronchus (Fig.1C). This peduncular mass obstructed the bronchus partially, moving during inhalation and blocking the airway almost completely during expiration. The surrounding mucosa was normal, with white secretions coming from the deeper airways at broncho-alveolar lavage (BAL). BAL-culture remained negative (aerobic, anaerobic, viral and mycobacterial culture). Tuberculin skin test was negative.

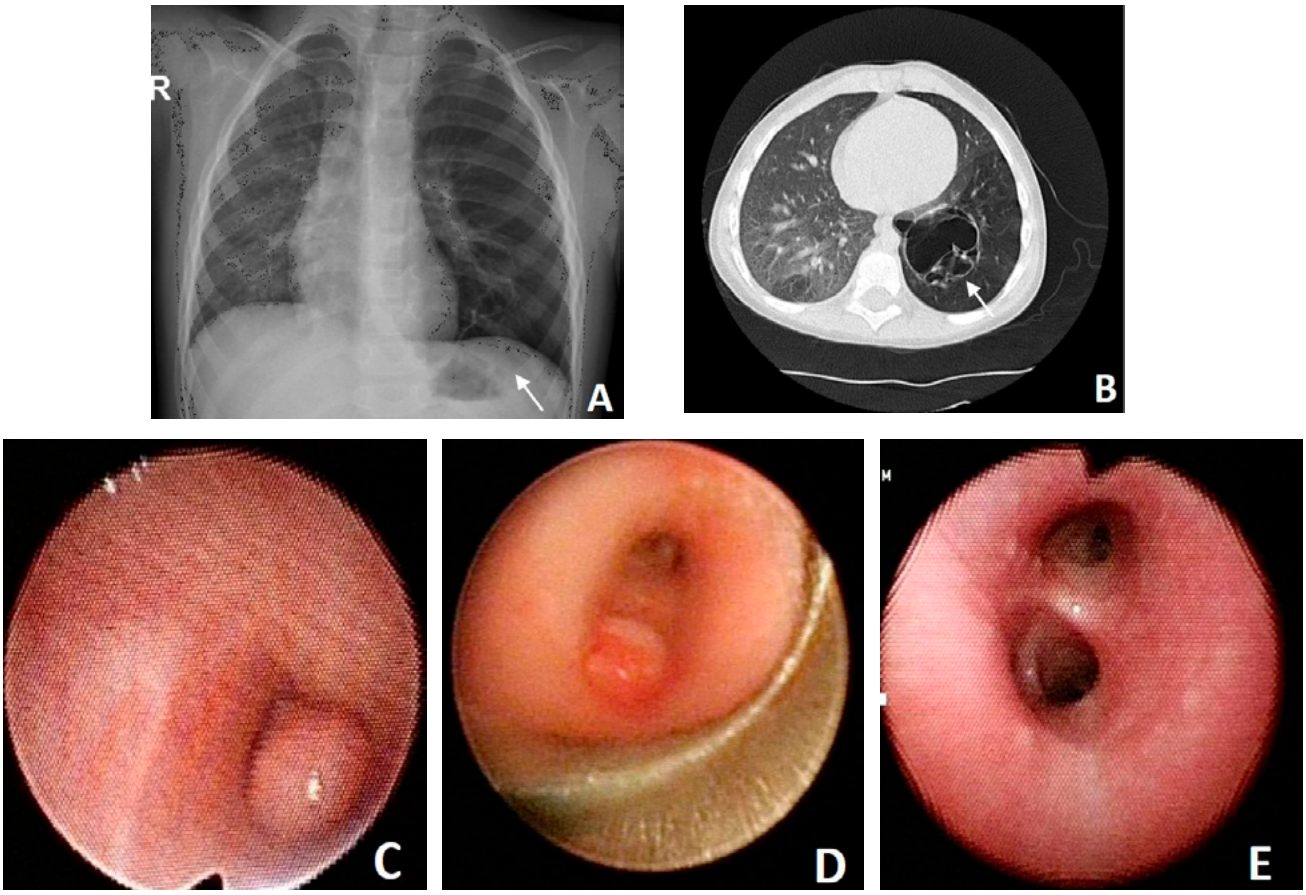
Endobronchial findings were unchanged after 2 weeks of observation, during which he developed however signs of a lower respiratory tract infection. A rigid bronchoscopy (Storz 4.0) was performed, aiming to remove the polyp endoscopically. With the use of a forceps the lesion was removed, opening the entrance of the upper lobe, lingula and the main part of the lower lobe, leaving a small residual mass at the apical segment of the LLL (Fig.1D). The postinterventional period was uneventful and he was discharged after 2 days.

Histopathological examination was consistent with an IBP, with a fibrovascular stroma with congested blood vessels and moderate inflammatory infiltrates, mainly lymphocytes and neutrophils and a few eosinophils. Some cystic glands were seen without any signs of malignancy. The stroma was lined with slightly irritated respiratory epithelium.

Cultures of BAL remained negative. BAL-cytology showed inflammatory cells but no malignant cells.

Follow-up bronchoscopy 1 and 6 weeks after intervention showed healing of the

Figure 1: A. Chest X-ray at first presentation showing hyperinflation of the left lung with a bullous lesion (arrow) projecting over the left heart border; B. Chest CT confirming multilocular cystic lesion (arrow) of 64 mm medio-basal in the left lower lobe and secondary hyperinflation of the left lower lobe; C. Pedunculated, round, pinkish mass in the left main bronchus; D. Residual mass in 1 of the four orificia of the left lower lobe 1 week after intervention; E. Normal left main bronchus 10 months after intervention.



left main bronchus. In the more distal airways of the LLL a smaller polyp was seen, however inaccessible for removal with rigid bronchoscopy. Ten months after the polyp removal a complete spontaneous resolution of the remaining lesion was seen on routine follow-up (Fig.1E). Repeat chest CT-scan showed also a favorable evolution with slight regression of the multilocular cystic lesion. Therefore, conservative management is applied.

Case 2

A one-year old boy was referred to our center for recurrent pneumoniae of the left lung. In November 2018 he was admitted for the first time with a respiratory syncytial virus (RSV) infection with surinfection in the lingula. He was admitted twice in January with an infiltrate in the LLL, accompanied by pleural effusion at the last episode (Fig.2A). He received intravenous antibiotics during the 3 consecutive hospitalizations, and required no supplemental oxygen therapy. Sweat test was normal.

At presentation in our clinic, a boy in good general health was seen, with diminished breath sounds on the base of the left hemithorax. CXRs previously performed showed a progressive increase in hyperinflation of the left lung with an increased pulmonary infiltrate.

Because of the hyperinflation, an inhaled foreign body was suspected, and a flexible bronchoscopy (Olympus 2.8) was performed revealing an almost complete occlusion of the left main bronchus by a peduncular mass, without the visualization of a foreign body (Fig.2C). Distal from this obstruction an inflammatory mucosa and purulent secretions were seen, for which intravenous antibiotics (amoxicilline-clavulanate) were started. Inflammatory markers were: CRP of 37,6 mg/L, sedimentation rate of 54 mm/h and normal WBC of 10400/µL. BAL-cultures remained negative. Tuberculin skin test was negative. Low-dose chest CT showed 2 densities in the left main bronchus (5- and 4-mm diameter at respectively 1 and 2 cm distal from the tracheal bifurcation), suggestive for papillomatosis (Fig.2B). No other papillomatous lesions in mouth or trachea were found however. Distal from these lesions atelectasis was seen with bronchiectatic changes in the LLL. Additionally, a hyperinflation of the left upper lobe and lingula was noted.

The endobronchial lesion was almost entirely removed by biopsy forceps with rigid bronchoscopy (Storz 3.5). The more distal airways had a normal anatomy with an edematous, inflammatory mucosa and some mucus plugs which were easily removed by BAL.

Histopathological examination showed normal edematous stromal tissue with normal seromucous glands with a marked infiltration by inflammatory cells, mainly lymphocytes and neutrophils, covered by cylindrical bronchial epithelium with enlarged nuclei, consistent with an IBP (Fig.2E). No signs of granuloma or malignancy were seen. Cultures were positive for *Neisseria species*, *Haemophilus parainfluenza* and *gram-positive cocci*.

Repeat ultra-low dose chest-CT 3 days after the intervention showed a marked regression of the hyperinflation in the left upper lobe. The infiltrates in the lingula were stable but bronchiectatic changes in the LLL and lingula were decreased. The lumen of the left main stem bronchus remained narrowed compared to the right side with an irregular lining, but no more endobronchial densities were observed.

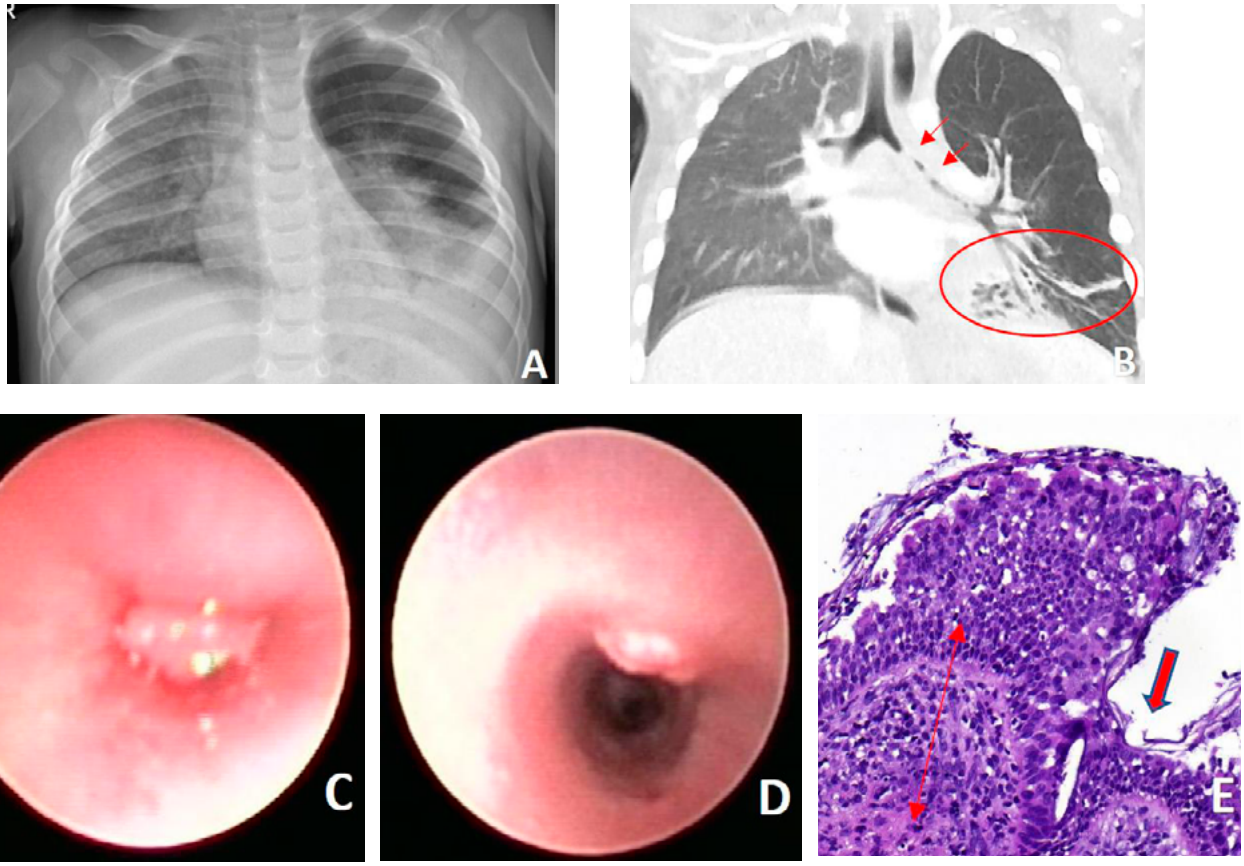
Repeat flexible bronchoscopy 1 week after the intervention showed a favorable evolution. Minimal inflammatory changes were seen in the area where the polyp was removed. Because of persistent purulent bronchial secretions, intravenous antibiotics were started for a period of 14 days, as respiratory cultures were positive for *Stenotrophomonas maltophilia*.

Bronchoscopy 4 weeks after the intervention showed again improvement, with the persistence of a small notch at the site of removal but no macroscopic signs of inflammation (Fig.2D). BAL fluid was positive for *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Stenotrophomonas maltophilia*, for which new antibiotic treatment was started (oral ciprofloxacine for 10 days). Two months after the intervention he developed again a productive cough with clinical deterioration. Findings at bronchoscopy were similar to the previous examination. A significant amount of *Haemophilus influenzae* was found in the BAL, without other gram negatives. Therefore, he was treated with amoxiclav orally.

The latest chest CT (low-dose), 3 months after intervention, revealed an almost complete resolution of the bronchiectatic changes and hyperinflation, with a normal caliber of the left main bronchus.

Literature review

Figure 2: A. Chest X-ray at admission with consolidation in left lower lobe with adjacent pleural effusion and hyperinflation; B. Chest CT at admission: 2 endobronchial densities of 5- and 4-mm in the left main stem bronchus (arrow) with distal bronchiectatic changes in the left lower lobe (circle) and hyperinflation of the left upper lobe and lingula; C. Complete occlusion of the left main stem bronchus by a pedunculated mass; D. Residual granular tissue at the site of intervention; E. Histopathology showing normal edematous stromal tissue with a marked infiltration by inflammatory cells (double arrow) circumscribed by cylindrical bronchial epithelium (full arrow).



Systematic review of literature revealed 16 English written articles describing IBP in children[2,4,5,14,26-37]. The diagnosis could not be acknowledged in 8 papers due to missing (5/8) or incomplete (3/5) histopathological description and were excluded from our review[14,26,29-31,34,35,37]. The remaining 8 articles report 18 pediatric patients diagnosed with an IBP[2,4,5,27,28,32,33,36]. Patient details, including our two cases, are summarized in Table 1.

According to the classification developed by Drennan and Douglas, IBP are a subtype of the bronchial papillomas, which also comprises the solitary bronchial papilloma (SBP) and multiple papillomatosis (MP). The differentiation between IBP, SBP and MP is based on their histopathological features[38]. SBP are defined by Zimmerman et al as "complexly arranged, cauliflower-like outgrowths from an epithelial surface composed of vessel-bearing connective tissue cores, with or without inflammatory cell infiltration, covered by a uni- or multilayered epithelium"[39]. MP are multiple, flat, nodular lesions due to continuous growth of the bronchial epithelium in response to an infection with the Human papillomavirus type 6 or 11[40]. A detailed overview comparing these 3 lesions is given in Table 2[27,39-43].

IBP are rarely encountered lesions in both the pediatric and adult population. Their true incidence is unknown[3].

Kut et al analyzed the medical records of 2555 children in 3 pediatric pulmonology centers in Turkey between 1997 and 2011, who underwent flexible bronchoscopy after presentation with chronic respiratory symptoms. In 10% endobronchial obstruction was diagnosed. Bronchial polyps were seen in only 4 patients, of which 3 were inflammatory in nature[37].

Pathophysiology

The majority (12/18) of IBP in our patient review has been described in premature children with a history of intubation and mechanical ventilation in the neonatal period[4,28,32,33]. Berman et al describe an IBP secondary to aspiration of a foreign body. In older children IBP may occur in patients with chronic inflammation of the bronchi as seen in patients with asthma and CF-related bronchiectasis[2,36]. In 2 other cases the etiology remained unknown (idiopathic)[4,5].

Clinical manifestation

Symptoms are nonspecific and depend on the size and location of the lesion[1]. In our patient review the most common symptoms include cough, dyspnea, chest pain or fever, which were reported in 22%, 22%, 11% and 17% respectively[2,4,5,27,28,36]. One patient presented hemoptysis and recurrent pneumoniae[36]. Ten neonates were ventilation dependent even before diagnosis[32,33].

Additional findings

CXR showed atelectasis in 14/18 patients and hyperinflation in 6/18[4,5,27,28,32,33]. One patient had only a small nodular lesion[2]. Supplementary CT was performed in 3/18 patients[4,5]. In all, CXR findings were confirmed and in 1 patient bronchiectatic changes were diagnosed. Endoluminal lesions were noted in 2 patients[4]. Chest CT-scan of the CF patient showed widespread bronchiectasis[36].

CT can provide more details about possible lung damage distal to the lesion. The distal findings can be divided in three subtypes based of the ball-valve principle, as described by Jackson and Jackson[1]. Complete obstruction or stop-valve leads to atelectasis in the distal area after absorption of the air by the circulating blood. This can also be seen with a check-valve when the valve allows air to leave the lung but not enter. However, if air can enter but cannot exit the lung, it leads to hyperinflation and occasionally emphysema. Lastly, it can result in suppurative lung disease like pneumoniae, bronchiectasis and even lung abscesses[1].

At bronchoscopy, several bronchial lesions can appear as endobronchial polyps. An extensive differential diagnostic overview is given in Table 3[37-44-51]. Basic patient characteristics and symptoms, imaging studies (CXR, chest CT-scan, fluodeoxyglucose-scan) and bronchoscopic aspects can help in the differentiation. In some cases, histological confirmation is needed to enable a distinction between the different entities[3].

Treatment

In the majority of the patients (11/18) the polyp was endoscopically removed[4,5,28,32]. Five underwent additional endoscopic cauterization, presumably to treat the minimal bleeding[33]. No other complications were reported. One patient underwent lobectomy after endoscopic removal of the polyp because of persistent atelectasis, whereas 4 underwent lobectomy or partial pneumectomy due to the extent of the lung damage [4,32,36]. Apart from a persistent air leak in one patient no post-operative complications were reported[36].

One patient, with negligible symptoms, had spontaneous expectoration of the lesions[2]. The IBP reported after inhalation of a foreign body was treated with oral and inhaled corticosteroids after endoscopic removal of the foreign body[27]. A nearly complete regression of the lesion was reported after 6 months.

Repeat bronchoscopy was performed in 9 patients, with no recurrence nor increase of the existing lesions[2,4,5,33]. All patients were asymptomatic at their last follow-up visit.

No malignant transformation of IBP was seen, in contrast to cases with other papilloma subtypes.

Discussion

To our knowledge this is the first article aiming to assemble and review all pediatric cases of inflammatory endobronchial polyps (IBP) reported in English literature.

Our first observation is that the terminology of IBP is used inconsistently, despite the clear definition earlier reported. Two original articles describe the endobronchial lesions as granulation tissue. However, histopathological findings are in line with IBP and they are therefore included in our review[32,33]. Two authors assumed their patient having an IBP based on macroscopic features, but lacked biopsy to confirm the diagnosis[14,34]. Four authors describe subjects with endobronchial inflammatory tissue, granulation tissue, organized inflammatory granulation tissue and inflammation, as being IBP, however their histopathological findings are not in line with the true definition of IBP, and are therefore excluded from our review[26,31,32,35]. As such, Peroni A. earlier described the distinction between inflammatory polyps and granuloma or granulomatous tissue. The latter being soft, flat lesions, usually multiple and covering the bronchial wall, rarely causing bronchial obstruction, as opposed to the IBP seen in our cases and other manuscripts. These friable and easily bleeding lesions have the tendency to resorb spontaneously. Most importantly, granuloma are not lined by bronchial epithelium, being the most important characteristic feature distinguishing them from IBP. Secondly, not all authors adhere to the classification developed by Drennan and Douglas earlier described, but follow the classification of lung tumors published by the World Health Organization. They consider IBP as tumor-like lesion whereas papillomas are categorized under the benign epithelial tumors and divided in 3 subtypes (squamous, glandular and mixed) corresponding with the solitary papilloma subtype in the classification by Drennan and Douglas[52].

Differences in nomenclature made it difficult to collect valuable data about IBP in literature. Cases were only included if histopathological features corresponded with the definition we used for IBP, regardless the nomenclature used in the manuscript. Abovementioned barriers could bias our results in a way that cases may be missed. However, to our opinion the classification of Peroni is fair as endobronchial granulomas are much more often seen in children, especially those with a tracheostomy[53]. They can probably be considered as an early stage of the polyps we have described in our cases. It remains however unclear why some lesions resorb spontaneously and others evolve to polyps.

Literature review showed a very low prevalence of IBP in children. Taking into account the rarity of IBP it is remarkable that we recently diagnosed 2 young patients in less than one year. Either their occurrence is really low and our consecutively diagnosed patients were found by coincidence, or the incidence is higher but remain undiagnosed as they do not always result in symptoms. This last hypothesis is suggested earlier by Freant et al.

Systematic review demonstrated that IBP are especially seen in children with a history of previous intubation. As this is an important risk factor for bronchial damage, varying from little granulation tissue to polyp formation or stenosis, in extremis leading to an acquired atresia [4,30,35]. It is likely that due to the small caliber of the airways in this population, polyps rapidly become symptomatic and require intervention. This was also speculated by McShane et al. A relationship between the duration or timing of the intubation, the onset of symptoms and the size of the polyps could not be demonstrated. As most of the histopathological findings in these polyps show squamous metaplasia, with or without local ulceration, the causative factor is believed to be an irritation of the bronchial wall. Predominantly IBPs are found in the right bronchial tree, probably due to anatomical features. However, the 2 cases we have reported have no history of intubation or foreign body aspiration and had IBP in the left bronchial tree. This finding hypothesis that other non-traumatic features can result in the development of IBP. The young age in our subjects and the absence of other systemic signs and symptoms suggest that an infectious process is most likely the initiating factor. However, its rarity in children with frequent respiratory infections suggests that another unidentified factor (genetic or environmental) is needed for the development of IBP. Therefore, we plead for a better reporting of children with IBP.

IBP are benign lesions, which do not metastasize nor infiltrate among adjacent normal cells. Nevertheless, they can cause significant respiratory symptoms and lung damage which, if not recognized and treated correctly in time, can lead to permanent lung disease or even death. Therefore, it is important to consider IBP in any patient with persistent symptoms of respiratory tract obstruction who does not respond to standard treatment[37,44]. Flexible bronchoscopy with biopsy is the optimal diagnostic tool. Bronchiectasis as a result of an IBP has been described once in literature and was seen in one of our patients. The patient reported by McShane required lobectomy due to the significant destruction of lung parenchyma distal to the lesion. The bronchiectatic changes seen in our case resolved almost completely soon after the removal of the polyp, suggesting that rapid diagnosis and intervention should be encouraged. Our first case is somehow unique, as this is the only child with IBP and associated bullous lesions in the lung ever reported. The multilocular lesion can be the consequence of the polyp, creating an overexpansion with barotrauma in that part of the lung distal from the obstruction. However, this does not explain the smaller unilocular lesion on the contralateral lung. We believe that this solitary lesion is rather found by accident. One adult case-report of a 68-year old woman, diagnosed with an inflammatory polyp in the right upper lobe, has been reported with a cystic lesion in the right upper long. This lesion regressed completely after endoscopic removal of the polyp[54]. This finding supports our advice to only remove the polyp and to avoid pulmonary resection at a first stage.

IBPs need to be differentiated from other endobronchial lesions, especially malignant tumors, as these are more prevalent in adults, but also found in children, and require a different follow-up. All endobronchial lesions present with similar clinical symptoms and radiographic and bronchoscopic features making it difficult to differentiate them without histological examination, which remains the gold standard for diagnosis.

In symptomatic patients, endoscopic removal by biopsy forceps is the most appropriate and safe treatment option. Caution should be taken if hemangioma is suspected because of the higher risk of bleeding. There is no experience in children with other endoscopic modalities such as cryotherapy, electrocautery or Nd-YAG-laser (Neodymium yttrium aluminum garnet) which are being used in adults for inflammatory polyps, but impossible to apply in children due to the size of instruments needed for this intervention. Two articles described a successful use of Nd-YAG laser in older children to treat endobronchial granulation tissue[14,55]. More research is needed before other treatment options than forceps biopsy can be advised in children for the treatment of IBP.

Only if endobronchial removal is impossible or lung damage is irreversible or too extensive, surgical intervention is indicated.

Keeping in mind that these lesions can resolve spontaneously, a conservative approach can be considered in children with few or no symptoms. This recommendation is mainly based on observations in the adult population where patients were successfully treated with oral or inhaled corticosteroids[7,10,11,21].

Follow-up bronchoscopy is indicated if the patient presents respiratory symptoms. Otherwise, literature review recommends to repeat this only once in the follow-up period. Given the young age of our cases, the evident lung damage demonstrated by CT scan, the re-occurrence of cough and the huge experience with bronchoscopy at our pediatric pulmonology unit, we performed more than once a bronchoscopy after removal of the polyp. This enabled us to treat respiratory infections accordingly to what BAL-cultures revealed. Isolation of non-classic gram-negative bacteria (*as Stenotrophomonas maltophilia and Pseudomonas aeruginosa*) are more often found in destructed lung tissue, as seen in children with CF and non-CF-bronchiectasis[56]. We performed a tuberculin skin test, sweat test and basic immunological screening to exclude underlying diseases in our patient, all of which were normal. As children of this young age cannot expectorate sputum and the value of cough swabs in non-CF-subjects is unknown, we are convinced that a repeat bronchoscopy in symptomatic children, who underwent resection of an endobronchial polyp, is justified.

Conclusion

Inflammatory polyps of the tracheobronchial tree are benign, mostly solitary lesions. They are extremely rarely reported in children and originate from chronic inflammation of the airway, secondary to trauma, infection or idiopathic. IBP should be considered in every child with persistent respiratory symptoms, unresponsive to standard treatment, especially if hyperinflation or atelectasis is seen on chest X-ray. Diagnosis and differentiation of other endobronchial masses should be based on histopathological features after endobronchial removal by biopsy forceps, which is the recommended therapeutic option in symptomatic patients. Bronchoscopic follow-up is only recommended in a patient with recurrent symptoms of cough who is unable to expectorate, to enable identification and correct treatment of pathogens. Otherwise clinical follow-up is recommended as the risk of recurrence or malignancy is negligible. If removal of the endobronchial polyp can be performed at an early stage, barotrauma in the more distal bronchial tree and parenchyma still can recover.

Table 1: Overview of all pediatric case reports.

AUTHOR (YEAR)	PATIENT DETAILS, HISTORY	SYMPTOMS AND PHYSICAL EXAMINATION AT PRESENTATION	RADIOGRAPHIC FINDINGS	FLEXIBLE BRONCHOSCOPY FINDINGS	HISTOPATHOLOGICAL EXAMINATION	SUSPECTED ETIOLOGY	MANAGEMENT	FOLLOW-UP
NAGARAJ ET AL (1980)	M, Born at 32 w, HMD	Ventilation dependent	Atelectasis of RML	Nodular lesion RB	Squamous metaplasia and granulation fibrosis*	Prior intubation	Bronchoscopic aspiration, excision and cauterization	AS at 11 m Normal FB
	F, Born at 29 w, IRDS	Ventilation dependent	Atelectasis of RML and RLL	Large polypoid lesion in RB	Squamous metaplasia and granulation fibrosis	Prior intubation	Bronchoscopic aspiration, excision and cauterization	AS at 16 m Normal FB
	F, Born at 29 w HMD	Ventilation dependent	Atelectasis of RL	Nodular lesion mostly in RB	Squamous metaplasia and granulation fibrosis	Prior intubation	Bronchoscopic aspiration, excision and cauterization	AS at 18 m Normal FB
	F, Born at 28 w, IRDS	Ventilation dependent	Atelectasis of RLL and RML	Nodular lesion in RB	Squamous metaplasia and granulation fibrosis	Prior intubation	Bronchoscopic aspiration, excision and cauterization	AS at 12 m Normal FB
	F, Born at 29 w, IRDS	Ventilation dependent	Atelectasis of LL	Nodular lesion in LB	Squamous metaplasia and granulation fibrosis	Prior intubation	Bronchoscopic aspiration, excision and cauterization	AS at 11 m Normal FB
MILLER ET AL (1981)	5-w, F Born at 25.5 w BPD	Ventilation dependent	Progressive hyperinflation of RLL, mediastinal shift and compression of RUL	-	Polypoid granulation tissue with ulceration and squamous metaplasia of the overlying epithelium, Multiple lesions	Prior intubation	Right lower lobectomy	Extubated after 3 w, AS at 6 y
	9-w, M Born at 25 w BPD	Ventilation dependent	Progressive hyperinflation of RML and RLL, compression of RUL and mediastinal shift	-	Polypoid granulation tissue at junction of RML and RLL bronchi, squamous metaplasia, focal ulceration of overlying epithelium	Prior intubation	Right middle and lower lobectomy	Extubated after 12 days, Further unknown
	7-w, M Born at 30 w, BPD	Ventilation dependent	Hyperinflation of RML and atelectasis of RUL	Multiple polyps in BI	Granulation tissue with surface ulceration and areas of squamous metaplasia	Prior intubation	Endoscopic resection and fulguration	Extubated after 4 days, Further unknown
	2-m, F Born at 29 w,	Ventilation dependent	Hyperinflation RML and RLL	2 polyps in BI	Granulation tissue with focal mucosal ulcerations	Prior intubation	Transbronchial resection with	Extubated after 5 m,

	BPD						subsequent lobectomy of RML and RLL	Further unknown
ARGÜELLES M. ET AL (1983)	10-y, M, Bronchial asthma	Expectoration of a solid, soft, smooth, rosaceous body (1x0.3 cm) Sibilant rales diffuse	XR: small left perihilar nodular lesion; Small irregular area in RUL	Multiple reddish, oval, polypoid tumors; 1-10 mm; Lower tracheal and main bronchi walls	Polypoid, solid body of soft gray-pink tissue; Lined by columnar epithelium with focal squamous metaplasia; central stroma of loose connective tissue with many capillary vessels, chronic inflammatory infiltration; thickened basal membrane	Asthma	-	Spontaneous expectoration of IBP for 1 y, max 1.8 cm long. Normal FB 1 m after latest expectoration 3-y AS
BERMAN ET AL (1984)	17 -y, F, smoker, Suspicion bronchial asthma	Central nocturnal chest pain for 3 m; sore throat, cough and pleuritic chest pain for 1 w Diminished breaths sound on the left	XR: LLL collapse, mediastinal shift to the left	Fleshy, friable mass filling left mainstem bronchus Notion of foreign body distal to bronchial growth	Corrugated ciliated pseudo-epithelium, occasionally dipping into the stroma to form mucous glands. Focal squamous metaplasia. Neovascularization in stroma with eosinophilic and chronic inflammatory cell infiltrates	Foreign body	Prednisone 20 mg/day and beclovent (2 puffs 4x/day) Removal foreign body	Nearly complete regression after 6 m
ROBERTS ET AL (2001)	15-y, F CF colonized with *Pseudomonas aeruginosa* Polypoidal disease	Frequent chest infections with chest pain and hemoptysis.	CT: widespread bronchiectasis, worst in RUL with mediastinal shift.	-	Multiple endobronchial polyps up to 4 mm throughout bronchi and bronchioles, filling bronchiectatic airways. Cellular, chronically inflamed fibro-connective tissue stroma, lined by stratified columnar ciliated epithelium Mostly lymphocytes and plasma cells	Stagnation of purulent secretions, chronic inflammation	Partial pneumectomy	Well at 7 m with significant reduction of infections

MCSHANE ET AL (2002)	7-w, F Born at 30 w	Intermittent respiratory distress	XR: Hyperinflated RL CT: Overexpansion of all lobes of the RL	3-mm polyp, arising from a long stalk, attached to membranous part of the termination of the RB, obstructing the RBI	Polyp comprising arborizing capillaries which rose from its stalk, xanthomatous histiocytes (center) and inflamed granulation tissue (periphery)	Prior intubation	Endoscopic removal by rigid bronchoscope	AS with normal FB at 9 m
	2.5-y, M Born ad term	Intermittent cough, wheeze and pyrexia for 3 w	XR: RML and RLL collapse	Polypoid lesion in RBI	2-mm polyp, comprising arborizing capillaries interspersed with fibroblastic stroma with marked acute and chronic inflammatory cell infiltrate Granulation tissue on surface	Prior Intubation	Endoscopic removal	Normal FB at 1 w AS at 7 y
	6-w, M Born at 27 w	Persistent RL collaps	Complete collapse of RL with blind ending RMB	3-mm polyp obstructing RMB	Polyp comprising arborizing capillaries interspersed with loose fibroblastic stroma within moderate acute and chronic inflammatory cell infiltrate, granulation tissue on surface	Prior intubation	Endoscopic removal	Asymptomatic at 4 years
	12-y, M	Cough and pyrexia for 6 m	XR: Left basal consolidation CT: Probable obstructive lesion causing collapse of the LLL	Obstruction of LLL bronchus by polypoidal gelatinous lesion	Edematous stroma covered by respiratory-type mucosa and focal squamous epithelium, Mild acute and chronic inflammatory cell infiltrate 22-mm lesion	Unknown	Lobectomy	AS at 16 ys
CLUBLEY ET AL (2007)	2-m, M, Born at 28+5 w	Tachypnea and poor feeding	XR: complete opacification of left hemithorax, hyperinflation of the RL	Pedunculated polyp arising from proximal BI, prolapsing in and out bronchus with respiration	4-mm polyp, predominantly granulation tissue, ulcerated surface partially covered with residual metaplastic squamous epithelium, inflammatory infiltrate	Prior Intubation	Endobronchial removal by grasping forceps	AS at 6 m

FATIMI ET AL (2012)	14-y, Fe	Dyspnea and respiratory distress High-grade fever, rhinorrhea and cough for 1 m Tachypnea, hyper-resonant lower left lung with mild rhonchi	XR: Hyperlucent LL with decreased volume, left hemi-diaphragm raised CT: Intraluminal soft tissue opacity in LMB, mucuspluggs and atelectatic changes	Large soft tissue mass, completely occluding LLL	Polypoidal tissue, broad fibro-cellular stroma, covered by double layer of respiratory type ciliated epithelium and mucus secreting glands, chronic inflammation with lymphocytes and plasma cells, proliferating vessels	Unknown	Bronchoscopic resection	Normal FB after 5 m AS after 2 y
ROELS ET AL (2019)	2-y, M Born at 36+1 w	Cough and fever for 1 day Diminished breath sound on left hemithorax	XR: beginning infiltrates in RL, hyperinflation of LL, bullous lesion in LLL CT: unilocular bullae (19mm) in RLL and multilocular bullae (64mm) in LLL	Pedunculated, round, pinkish mass in LMB	fibrovascular stroma with congested blood vessels, moderate inflammatory infiltrates, mainly lymphocytes and neutrophils and with a few eosinophils. Cystic glands without signs of malignancy. Lined with slightly irritated respiratory epithelium	Unknown	Removal by biopsy forceps leaving residual mass at apical segment of LLL	Spontaneous resolution of remaining lesion at FB after 10 m
	1-y, M	Recurrent pneumoniae LLL Diminished breath sound on the base of the left hemithorax	XR: progressive hyperinflation of the LUL and consolidation in LLL CT: 2 densities in LMB, atelectasis and bronchiectasis in LLL. Hyperinflation LUL and lingula	Complete occlusion LMB by pedunculated mass	normal edematous stromal tissue with normal seromucous glands and infiltration by inflammatory cells, mainly lymphocytes and neutrophils, lined by cylindrical bronchial epithelium with enlarged nuclei	Unknown	Endoscopic removal by biopsy forceps	Stable residual notch at removal site after 2 m; Almost complete resolution of chest CT

Used abbreviations: LL: left lung; LLL: left lower lobe; LUL left upper lobe; RL: right lung; RLL: right lower lobe; RML: right middle lobe; RUL: right upper lobe, RB: right bronchus; LB: left bronchus; BI: bronchus intermedius; RBI: right bronchus intermedius; RMB: right main bronchus; LMB: left main bronchus. W: weeks; m: months; y: years. F: female; M: male. XR: chest radiography; CT: computed tomography, FB: flexible bronchoscopy. BPD bronchopulmonary dysplasia. IBP: inflammatory bronchial polyps. HMD: hyaline membrane disease. IRDS: infant respiratory distress syndrome. * inflammation and fibrosis. AS: asymptomatic.

Table 2: characteristic features distinguishing bronchial papilloma subtypes.

	Solitary papilloma	**Inflammatory polyp**	**Multiple papillomatosis**
Prevalence	Rarest type	Rare	Rare
Population	Males > 50 years	Predominantly adults	Juvenile and adult onset
Etiology	Assumed genetic predisposition	Chronic bronchial inflammation	Viral origin (HPV)
Location	Proximal airways	Main bronchi or their principle branches close to their origin or bifurcation	Primarily larynx, 2% trachea
Bronchoscopic features	Pedunculated, large base, sharp border Raspberry or blackberry shape or cauliflower like	Pedunculated, usually solitary More or less reddish, velvety appearance, signs of superficial vessels	Flat nodular masses
Histological features - Superficial epithelial lining - Stromal component	 Monolayered or multi-layered, keratosed or nonkeratosed Squamous, glandular or mixed epithelium Fibrous stroma ± infiltration with inflammatory cells	 Regular respiratory mucosa Fibrous connective tissue of thin collagenous fibers, very vascular; Loose oedema with inflammatory cells	 Bronchial epithelium with thickened basal cell layers Fibrovascular core
Evolution - recurrence	Spreads exophytically	Spontaneous regression after removal of causative factor No recurrence	Tendency to spread, recur and heal spontaneously
Malignancy	Common	Non reported	More often in adult onset and radiated juvenile patients

Table 3: Overview of endobronchial lesions in children.

Benign endobronchial tumors
- Hamartoma
- Hemangioma
- Papilloma
- Inflammatory pseudotumor (plasma cell granuloma)
- Leiomyoma
- Mucus gland tumor
- Granular cell tumor
- Juvenile xanthogranuloma
- Lipoblastoma
- Chondroma
- Schwannoma

Malignant endobronchial tumors
- Adenoma
- Carcinoid (typical or atypical)
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Bronchogenic carcinoma
- Rhabdomyosarcoma
- Leiomyosarcoma
- Lymphoma (ALCL, PPL)

Congenital malformations
- Bronchogenic cyst[50] *

Infectious diseases
- Tuberculosis
- Atypical mycobacteria
- Fungi
- Hydatid cyst membrane[46] *

Other
- Granulation tissue
  - Foreign body reactions
- Endometriosis[48] *
- Tracheobronchopathia osteochondroplastica[49] *
- Sarcoidosis

* Casereports

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Publieksprijs België	86,52€

Bexsero: het eerste vaccin tegen meningokokken van serogroep B.

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

BEXSERO

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

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL** Bexsero suspensie voor injectie in voorgevulde spuit Meningokokken groep B-vaccin (rDNA, component, geadsorbeerd) - EU/1/12/812/001 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]
Zuigelingen van 3 tot en met 5 maanden	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 miltdisfunctie. 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. **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 EUROSTATION II Victor Hortaplein, 40/40 B-1060 Brussel Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **Luxemburg** Direction de la Santé – Division de la Pharmacie et des Médicaments Villa Louvigny – Allée Marconi L-2120 Luxembourg Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/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** 03/2019 (v09) **AFLEVERINGSWIJZE** Op medisch voorschrift.

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Deformational plagiocephaly as a marker for developmental delay

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Key words

Deformational plagiocephaly, developmental delay, child, literature study

Abstract

Objective: Deformational plagiocephaly (DP) and brachycephaly (included in the definition of DP) have become more frequent since the 'back to sleep' campaign was launched in 1992. Many caregivers are concerned that this has had an influence on the child's development as some recent studies have shown an association between DP and developmental delay. This literature study summarizes the available evidence and aims to clarify whether an association between DP and developmental delay is possible.

Study design/Methods: A literature study was conducted. Three major databases (MEDLINE, EMBASE and CINAHL) were systematically searched in February 2019. The final studies were selected based on specific exclusion and inclusion criteria. Exclusion criteria comprised study type, prematurity and language. Inclusion criteria used were study type, age of subjects, conditions and developmental outcomes. We rated each selected study on the basis of its methodological quality using a relevant scoring system.

Results: 1,276 articles were found following a literature search (after the exclusion of duplicates). 25 final articles were selected on the basis of a number of exclusion and inclusion criteria. The quality of the studies was restricted due to confounding and bias such as selection bias. Most studies had a moderate to high methodological quality. 17 studies showed a positive association between DP and developmental delay (including 4 studies of a high quality). 8 studies found no-association (including one study of high quality).

Conclusion: There appears to be an association between DP and developmental delay in children younger than 2 years old. Follow up and monitoring of development is needed in children with DP. Future studies should focus more on older children to investigate whether such delay persists.

What is known on this topic

DP is a common condition in young children for which parents often seek counsel. Many studies up until now have found an association between DP and developmental delay. No causal relationship has yet been proven.

What this study adds

This literature review brings together the relevant studies about this important topic to give an overview of our current knowledge on this issue. The review allows giving evidence based advice to counsel parents of infants with DP.

Introduction

Deformational plagiocephaly (DP), also known as 'positional plagiocephaly' or 'non-synostotic plagiocephaly', is a frequent form of cranial asymmetry in infants. The deformation of the skull is produced by extrinsic forces acting on an intrinsically normal skull. As a result the head is marked by a typical and visible unilateral flattening. The word 'plagiocephaly' originates from the Greek words 'plagios' meaning oblique, and 'kephale' meaning head. In addition to cranial asymmetry, other characteristics of DP are unilateral occipital flattening, ipsilateral ear shift and a potential facial asymmetry.

A clear differentiation has to be made between a positional etiology, where the head shape is asymmetrical because of pressure related deformation, and 'craniosynostosis' or 'synostotic plagiocephaly', where premature fusion of the cranial sutures results in asymmetrical growth.

DP is the result of the impact of chronic pressure on the same part of the malleable and fast-growing skull of infants, this additionally shapes the brain differently . These stressors can also cause brachycephaly which is the non-oblique version of plagiocephaly, namely flattening of the occipital bone. In this study, positional plagiocephaly and brachycephaly are aggregated as their causes and treatments are alike.

Since the 'back to sleep' campaign was initiated in 1992 by the American Academy of Paediatrics, the prevalence and incidence of DP have increased. This campaign strongly recommended the supine sleep position for all infants, in order to prevent Sudden Infant Death Syndrome (SIDS). The prevalence of DP currently varies between 13% and 48% of children under 1 year of age . Common age of detection is 4 months, while the abnormality can disappear at 2 years of age . Incidence rates are 6.8% at 1 year and 3.3% at 2 years of age .

There are various risk factors that influence the evolution of head shape such as male gender, preterm delivery, maternal age, twin pregnancy, the use of car seats, bouncy seats, swings and individual developmental risk factors . DP is more frequent in infants with torticollis, head preference to one side, decreased activity levels, hypotonia and limited neck movements. During the first 3 months of life the skull is most malleable and has the fastest growth. Moreover infants spend the majority of their time in a supine position. The first months of life also represent an important period in development, in which developmental problems can occur. Between the age of 4 to 6 months the child develops improved head control. This results in more frequent head movements and a spontaneous improvement of the head shape in the case of flattening.

Until recently DP was considered a purely aesthetic problem which had no influence on the infant's health and development. Treatments to improve head shape include firstly the repositioning of the sleep position to avoid pressure on the affected side of the skull as much as possible. Additional treatment options are physiotherapy and helmet therapy. Physiotherapy improves neck muscle strength and spontaneous head movements. In helmet therapy a custom fitted cranial molding orthosis is used and has to be worn almost 100% of the time.

In the last couple of years, several studies showed that DP is associated with delay in different developmental categories such as cognition, language and motor

skills. These developmental delays can persist through preschool age where special education services may be needed . Yet there is no proof of a causal relationship between DP and developmental delay. No solid evidence was found that the treatment of DP shortens the developmental delay. Moreover, there are only a few studies that have researched the severity of DP and its association with developmental delay. At present it remains unclear if a physician who examines an infant with DP, should actively look for signs of developmental delay or monitor the psychomotor development during follow up.

In this literature study, we assessed all available studies on the possible association between developmental delay and DP to provide the most up to date information for a practicing physician.

MATERIALS AND METHODS

Study selection

A structured study of the published literature was conducted, according to the Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines also known as the PRISMA guidelines (Figure 1).

Three major databases (MEDLINE, EMBASE and CINAHL) were systematically searched in February 2019. No publication date or language restrictions were applied in this search. In MEDLINE, the following search terms 'Plagiocephaly, Nonsynostotic' (MeSH), 'Plagiocephaly'(MeSH), 'Craniosynostoses' (MeSH) and 'Brachycephaly'(MeSH) were used. Additionally, the search terms 'Developmental disabilities', 'Intellectual disabilities' and 'Motor skill disorders' were added to the search string. In EMBASE 'Plagiocephaly' was used as Emtree term as well as a search term. In the CINAHL database 'Plagiocephaly' was used as MeSH term as well as a search term.

All retrieved publications were checked for duplicates and screened based on title and abstract to remove all irrelevant manuscripts. Additionally, reference lists of relevant publications were searched to identify all relevant studies for systematic analysis. The age limit was set between 0 and 18 years. All studies investigate deformational plagiocephaly or brachycephaly and its association with development. The developmental outcomes are 'gross/fine motor skills', 'language' and 'cognition'. Letters, recapitulations and reviews were excluded. Studies focussing exclusively on premature infants were excluded as well. Study designs included in the penultimate selection were randomized-controlled trials, observational studies, cohort studies, case-control studies, cross-sectional studies and case series. Finally, all manuscripts were screened for eligibility by full-text assessment based on the study selection criteria (Supplementary Table 1 and 2).

Data extraction and study quality

All selected articles that fulfilled the inclusion and exclusion criteria were examined for methodological quality and susceptibility to bias. A specific data extraction and quality control form was used for this purpose (Supplementary Table 3).

For each article, several aspects were investigated: (1) the source population; (2) exposure; (3) outcome; (4) methods used to deal with possible biased results; (5) methods used to deal with confounding; (6) the use of statistics, including an assessment of the power of the tests used; and (7) the declaration of conflicts of interest. Each article was ranked based on these seven quality criteria (0 or 1 for each criteria) from having a low, moderate or strong quality (Table 1). No meta-analysis was carried out due to the heterogeneity of the studies investigated. Most studies applied different methods to measure plagiocephaly and used a wide variety of developmental assessments.

Statistical analysis

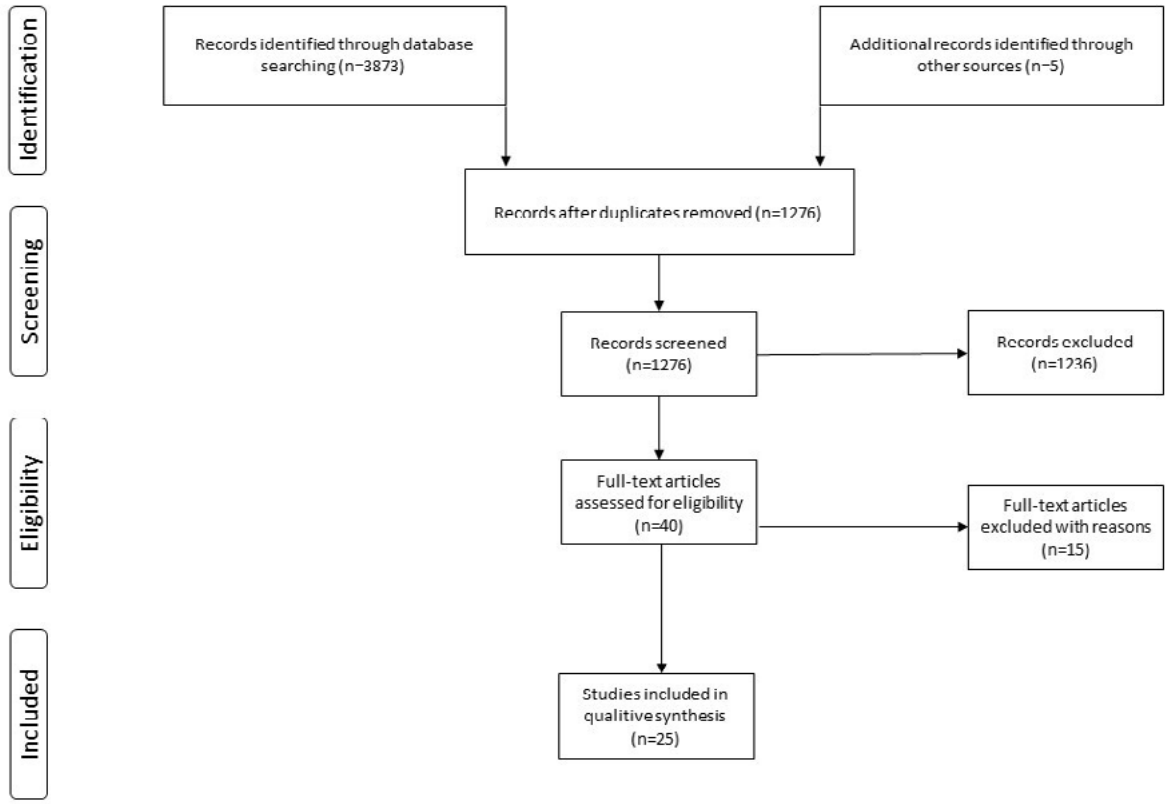
The one-sample Kolmogorov-Smirnov test was used to evaluate the normality of the sample size, methodological quality and age range of the studies used in the final analysis. The Fisher's exact test was used to compare the characteristics of good quality studies (5-7 points) with those of the studies of a lower quality (0-4) based on the methodological quality control form. A p-value of 0.05 was considered statistically significant.

RESULTS

PRISMA procedure

The initial screening resulted in a total of 3,873 records and 5 additional records were retrieved through other sources. By removing the duplicates, 1,276 records were retained. These records were screened and assessed based on title and abstract. Eventually 25 articles that met the inclusion and exclusion criteria were

Figure 1: PRISMA Flow Diagram



Supplementary Table 1: Inclusion criteria

Study design	Randomized-controlled trials
	Cohort studies
	Case-control studies
	Cross-sectional studies
	Observational studies
	Case series
Subjects	Age: 0-18 years
Conditions	Deformational plagiocephaly or brachycephaly
Outcomes	Developmental outcomes: gross motor, fine motor, language and cognition

Supplementary Table 2: Exclusion criteria

Exclusion	Letters
	Reviews
	Recapitulations
	Only prematurity population
	Language: Italian

Supplementary Table 3: Data extraction and quality control form

Domain	Tool item must address
Methods for selecting study participants	Appropriate source population (cases, controls and cohorts) and inclusion or exclusion criteria.
Methods for measuring exposure variables	Appropriate measurement methods for exposure(s). Appropriate explanation of how the measurement was taken.
Methods for measuring outcome variables	Appropriate measurement methods for outcome(s). Parental surveys, Parental interviews and Prescreening Developmental Questionnaire 2 (PDQ-II) are not appropriate measurement methods for the outcome.
Design-specific sources of bias (excluding confounding)	Appropriate methods outlined to deal with any design-specific issues such as recall bias, interviewer bias, biased loss to follow or blinding. All studies can't be fully blinded due to the fact that Plagiocephaly is visible to the examiner.
Methods to control confounding	Appropriate design and/or analytical methods. Standardized controls, non-matched controls (other than age and sex matched) are not appropriate.
Statistical methods (excluding control of confounding)	Appropriate use of statistics for primary analysis of effect. Small sample or power < 0.8 is not appropriate. Comparing to a standardized control group or no control group at all is not appropriate. Student t-test is not appropriate.
Conflict of interest	Declarations of conflict of interest.

Table 1: Articles used in this review ranked in order of quality

Author	Source population	Measurement exposure	Measurement outcome	Dealing with bias	Dealing with confounding factors	Statistics	Conflict of interest	Overall level of evidence .../7	Study type	Study size (case | control)		Age in months (range, or other)	Outcome
Zhao[19] 2017								6	Case control	393	390	0 – 18	Association
Collett[20] 2013								6	Longitudinal	224	231	7 – 36	Association
Collett[1] 2012								6	Case control	20	21	7 – 9	Association
Collett[21] 2011								6	Longitudinal	227	232	7 – 18	Association
Kennedy[22] 2009								6	Case control	27	27	3 – 8	No association
Linz[23] 2018								5	Longitudinal	51	15	6 – 12	No association
Wermke[24] 2017								5	Case control	51	15	5 – 7	No association
Speltz[25] 2010								5	Case control	235	237	4 – 11	Association
Hussein[26] 2018								4	Retrospective	155	0	4 – 36	Association
Fontana[11] 2016								4	Longitudinal	27	0	4 – 11	Association [(i)]
Knight[12] 2013								4	Retrospective	21	0	5 – 12	Association [(ii)]
Hutchison[27] 2010								4	Longitudinal	129	0	3 – 4 years	No association [(iii)]
Kordestani[28] 2006								4	Longitudinal	110	0	3 – 10	Association
Hashim[29] 2014								4	Case control	16	18	3 – 12	No association
Hutchison[30] 2012								4	Longitudinal	126	0	3 – 12	No association [(iii)]
Hutchison[31] 2009								4	Retrospective	287	0	4 – 7	Association
Fowler[13] 2008								4	Case control	49	50	4 – 13	Association [(iv)]
Balan[32] 2002								4	Case control	15	15	6 – 17	Association
Korpilahti[16] 2012								3	Longitudinal	61	0	3 – 4 years	Association
Siatkowski[33] 2005								3	Retrospective	40	0	5 – 13	Association [(v)]
Hutchison[34] 2004								3	Longitudinal	7	193	1 – 24	No association
Panchal[35] 2001								3	Retrospective	63	0	8 – 11	Association
Shamji[36] 2012								2	Retrospective	80	0	4 – 9	Association [(vi)]
Steinbok[7] 2007								2	Longitudinal	278	0	3–16m & 8–9 years	No association
Miller[14] 2000								1	Retrospective	254	0	School aged	Association

[(i)] Association for language and motor. No association for cognition, [(ii)] Association for motor, [(iii)] Decrease over time, [(iv)] Association for tone, [(v)] Constriction of a hemifield, [(vi)] Left-sided PD

selected to perform the qualitative synthesis. One Italian study was excluded due to the language barrier . The selected 25 articles are shown in Table 1. The articles are ranked by methodological quality from high (6-7 points), moderate (3-5 points) to low quality (0-2 points). The majority of the studies have moderate (17 studies) to high quality (5 studies). All studies contained selection bias because plagiocephaly is visible to the examiner. In addition, 19 of the 25 studies contained confounding bias because either no control variables were used or the control variables were limited to the patient's age and gender. Fourteen of the 25 studies did not apply appropriate statistical techniques because: (1) they used standardized samples as controls; (2) they only used a standardized t-test; or (3) the statistical analysis was likely to be affected by a type II error. Older studies (9 studies) did not include an explicit declaration of conflict of interest in the text. Eight studies used a parental survey or a parental interview to measure the developmental delay in children, which is susceptible to reporting bias. Three studies did not have a detailed explanation of how the plagiocephaly was measured. All studies elaborated extensively on how the study population was selected. Older studies tend to be of lower quality.

Study population and methodological quality

Table 1 summarizes the data assembled, which concerns study type, sample size, age and outcome ranging from best quality to worst. The mean sample size is 175 patients (SD ±190). The mean methodological quality is 4 (SD ±1.35). Lower and upper age ranges were not normally distributed with a median lower age range of 4 months, a median upper age range of 12 months and an interquartile range of 3 and 4 months, respectively.

At the methodological level the studies consist of 8 case-control studies, 7 retrospective studies, 6 longitudinal studies without controls and 4 longitudinal studies with controls. The top-ranked studies tend to be longitudinal studies with appropriate controls. The second-ranked studies are longitudinal studies without controls. Cross Sectional studies and retrospective studies are ranked as third best (Supplementary Table 4).

Three significant differences were found between the studies of higher (5-7) and lower (0-4) methodological quality ($p<0.05$). Significant differences were found for the categories 'Conflict of interest ($p=0.02$)', 'Statistical quality ($p=0.002$)' and 'Confounding factors ($p=0.005$)'. No significant differences were found for the categories 'Measurement of outcome (0.26)', 'Measurement of exposure ($p=0.52$)', 'Publication date ($p=0.20$)' and 'Longitudinal studies ($p=1.00$)'.

Supplementary Table 4: Study type ranking

1) Longitudinal studies (with controls)	2) Longitudinal studies (without controls)	3) Cross sectional studies / retrospective studies	4) Case series / Case control studies
Collett[20] 2013 (association) 6	Fontana[11] 2016 (association for language & composite motor, no association for cognition) 4	Hussein[26] 2018 (association) 4	Collett[1] 2012 (association) 6
Collett[21] 2011 (association) 6	Hutchison[27] 2010 (association) 4	Knight[12] 2013 (association for motor) 4	Kennedy[22] 2009 (no association) 6
Linz[23] 2017 (no association) 5	Kordestani[28] 2006 (association) 4	Hutchison[31] 2009 (association) 4	Wermke[24] 2017 (no association) 5
Hutchison[34] 2004 (no association) 3	Hutchison[30] 2012 (association) 4	Siatkowski[33] 2005 (association) 3	Zhao[19] 2017 (association) 6
	Korpilahti[16] 2012 (association) 3	Shamji[36] 2012 (association in left-sided PD) 2	Speltz[25] 2010 (association) 5
	Steinbok[7] 2007 (association) 2	Panchal[35] 2001 (association) 3	Hashim[29] 2014 (no association) 4
		Miller[14] 2000 (association) 1	Fowler[13] 2008 (association for tone) 4
			Balan[32] 2002 (association) 4

Study measurements and outcomes

The 25 studies measured psychomotor development in three different ways.

A. BSID II & III

Nine studies used the Bayley Scales of Infant Development (BSID II or III) (Table 2). All of the studies that used BSID II or III had a moderate to high methodological quality. They all showed a positive association for all three categories (language, motor and cognition) between developmental delay and DP except for 2 studies which showed no association with cognition and mental development .

Table 2: Analysis of studies using BSID II or III ranked according to quality

BSID II or III	Association	Quality
Collett[20] 2013	Association: all (language, motor and cognitive), most for language and cognitive	6
Collett[1] 2012	Association: all, most for cognitive and motor	6
Collett[21] 2011	Association: all, most for language and cognitive	6
Speltz[25] 2010	Association: all, most for motor and language	5
Hussein[26] 2018	Association: motor and cognitive	4
Fontana[11] 2016	Association: language and motor. No association for cognition.	4
Knight[12] 2013	Association: only motor	4
Kordestani[28] 2006	Association: motor and mental	4
Panchal[35] 2001	Association: motor and mental	3

B. Parental Surveys

Eight studies were based on parental surveys (Table 3). Four of these showed a positive association. One study showed a positive association for only left-sided DP and another one only for tone. Two studies showed no association between DP and developmental delay. Fowler et al. conducted a parental survey as well as a neurological scale (Table 4). Miller et al. and Steinbok et al. [7] both had a school aged population but show different outcomes. Both studies are of low methodological quality and the measurement method is poor. Hutchison et al. show no correlation in 3-4 year olds with a study of moderate quality.

Table 3: Analysis of studies using parental surveys ranked according to quality

Parental surveys	Association	Quality
Parent-completed age-appropriate Ages and Stages Questionnaires:		
- Hutchison[31] 2009	- Association	4
- Hutchison[27] 2010	- Association	4
- Hutchison[30] 2012	- Association	4
- Fowler[13] 2008	- Association: tone	4
PDQ-II (Revised Denver II Prescreening Questionnaire):		
- Hutchison[29] 2004	No association	3
Survey questionnaire: cosmetic and cognitive outcomes:		
- Shamji[36] 2012	Association: left-sided DP	2
Questionnaire survey parents: cosmetic appearance, learning problems:		
- Steinbok[7] 2007	No association	2
Interview parents about special medical/ educational problems:		
- Miller[14] 2000	Association	1

C. Additional neurocognitive outcome measurements

Eight studies investigated the neurocognitive developments such as motor (1 study), language (3 studies), neurological (2 studies), auditory (2 studies) and visual (1 study) (Table 4). The motor scale study showed no association. This study is of good methodological quality but is a case control study. The 2 language studies that were of high methodological quality (5/7) showed no association. The language study showing a positive association was of moderate quality (3/7). Both neurological studies showed positive associations. Auditory scales showed mixed results. One was positive and the other one was negative. Visual scales revealed an association for 'constriction of a hemifield' and the study of DP. Korpilahti et al. included an older population of 3-4 year olds which showed an association for language and has a moderate quality.

Table 4: Additional neurocognitive outcome measurements ranked according to quality

BSID II or III	Association	Quality
Motor scales:		
AIMS & PDMS: - Kennedy22 2009	No association	6
Language scales:		
Art-index: - Linz23 2018	No association	5
Fundamental frequency (fo) for vocal control: - Wermke[24] 2017	No association	5
Reynell Developmental Language Scales III, the Renfrew Naming Task, the Finnish version of MacArthur Communicative Development: - Korpilahti[16] 2012	Association	3
Neurological scales:		
Chinese version of the Infant Neurological International Battery (Infanib): - Zhao[19] 2017	Association	6
Modified Hammersmith infant neurologic assessment: - Fowler[13] 2008	Association: tone	4
Auditory scales:		
Even related potentials: - Hashim[29] 2014 - Balan[32] 2002	- No association - Association	4 4
Visual scales:		
Standardized binocular arc perimetry in the horizontal plane: - Siatkowski[33] 2005	Association: constriction of a hemifield	3

DISCUSSION

In this review 17 out of the 25 studies showed a clear association between DP and developmental delay in young children aged less than 2 years. The delay is most pronounced in the assessment of motor and language skills. Even though the biomechanical cause of DP is clearly understood (pressure on the occipital part of a malleable skull with resultant flattening), the underlying aetiology is still less evident. It is hypothesized that DP is caused by developmental delay which may be a source of reduced head movement. The identification of DP could thus be an early marker for delayed psychomotor development and a reason for closer clinical follow up. Especially when other risk factors for developmental delay are present such as socioeconomic risk factors or premature birth. At present the literature that guides clinicians in the care of these patients is fairly limited and does not provide clear answers to the relevant clinical questions: whether the developmental delay is still present later in life and how severe the delay associated with DP is.

The question of a link between the severity of the DP and the severity of the developmental delay can be answered with a degree of certainty. Nine studies used the Bayley Scale of Infant Development (BSID II or III), a well validated measurement of the mental and motor development. In this assay, an examiner tests the behaviour of infants from 1 to 42 months of age in three domains: cognition, motor skills, and behavioural skills. Of these 9 studies, 4 were of high methodological quality. The studies detected a delay in motor development (9/9), cognitive development (5/9) and language development (5/9). No study could correlate the severity of the DP with the severity of the developmental delay. In comparison with the other studies in this review, these studies were homogenous in nature, yet only include children at a young age, so no prognosis can be made for the development later in life.

This is the second systematic review on the relationship between DP and developmental delay. One earlier review was published in 2017 and included 22 studies . Our findings correlate with their study as the authors conclude that plagiocephaly is a marker of an increased risk of developmental delay. In this context, all clinicians should closely monitor infants with plagiocephaly to detect developmental delay at an early stage. A prompt referral to a specialized physiotherapist could at least improve the motoric component of the developmental delay and could often also subsequently improve skull shape.

This review shows that the studies on this topic are usually small, with a mean cohort size of 175 patients. In comparison, prospective observational studies in the field of cardiology or obesity include thousands of patients . Secondly, the studies are of poor methodological quality. Of the 17 studies that showed a positive association between DP and developmental delay just 4 were of a high methodological quality. Thirdly, the studies in this review report only on young children, so a clear answer on how long the delay persists is difficult to formulate. The subjects of the studies reviewed in this paper range in age between 0 and 2 years. Four studies have investigated the long-term effects of DP (one until the age of 9 years). Two studies found an association between DP and developmental delay; and two studies did not. Yet these 4 studies (Steinbok et al. [7], Miller et al. [14], Korpilahti et al. [16], Hutchison et al.[15]) focussing on children from 3 years onward were either based on parental surveys rather than validated neurocognitive development test and/or were of low methodological quality. Hutchison et al.[15] even showed a decrease in correlation over time. The long-term follow-up of these children is challenging due to the fact that many are lost to follow up and that measuring developmental delay in older children and adolescents is time consuming. Future studies that focus on the evolution of developmental delay and DP later in life are still needed to settle the debate.

One of the limitations of this literature review is that the selected studies showed: (1) selection bias due to the non-blinding of the examiners; (2) recall bias due to participants not recalling the information correctly; (3) sampling bias due to low response rates and a lack of follow-up; (4) confounding bias because no control variables were used or the control variables were limited to the patient's age and sex; and (5) reporting bias in parents' questionnaires and surveys. Moreover, a small sample size and a lack of power calculations are present in most studies.

The second limitation is that only 4 studies focussed on children older than three years of age. These studies showed an equivocal outcome. The longitudinal study with the best quality from Hutchison et al. [15] showed a decrease in association, which may indicate that the developmental delay is transient. However, more research in older children is needed to confirm that this delay is transient, a matter which is crucial for parents and clinicians.

The third limitation of this review is the nature of quality control forms to assess the methodology of the studies. Despite the use of a validated scoring system, the interpretation of some criteria remains subjective. To address this limitation the used criteria were clearly specified and an explanation was provided for each individual score.

The strength of this study is that no restrictions were made on publication dates and only one study was excluded due to a language barrier (Italian). Three reliable and extensive databases were searched in depth.

CONCLUSION

This literature study summarizes current knowledge concerning the relationship between DP and developmental delay. An extensive literature search was conducted and all articles were rated in a systematic way to establish their quality. The study objective was to determine whether there is an association between DP and developmental delay. Its findings show that such association indeed exists in the group of children under the age of 2. However, for older children with DP less evidence is available whether their development is delayed in comparison with the normal population, suggesting that this delay can be transient. Future studies should focus on older children to investigate whether such delay persists or not. No study could correlate the severity of DP with the severity of developmental delay.

In conclusion, DP is associated with early developmental delay. Clinicians would be prudent to monitor all children with DP closely, in order to address any apparent developmental delay promptly. Specialized physiotherapy, revalidation centres and home counselling of the parents can be valuable treatment options for both DP and developmental delay, as better motors skills and increased activity will improve skull shape. In all cases in which extra risk factors, such as premature birth and difficult socioeconomic circumstances, are present adequate clinical paediatric follow-up is highly recommended.

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DÉNOMINATION DU MÉDICAMENT: HEMANGIOL 3,75 mg/ml, solution buvable. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** 1 ml de solution contient 4,28 mg de chlorhydrate de propranolol correspondant à 3,75 mg de propranolol base. Liste des excipients : Hydroxyéthylcellulose, Saccharine sodique, Arôme fraise (contient du propylène glycol), Arôme vanille (contient du propylène glycol), Acide citrique monohydraté, Eau purifiée. Excipient à effet notoire : 1 ml de solution contient Propylène glycol 2,60 mg. **FORME PHARMACEUTIQUE :** Solution buvable. Solution buvable limpide, incolore à légèrement jaune, avec une odeur fruitée. **INDICATIONS THERAPEUTIQUES :** HEMANGIOL est indiqué dans le traitement des hémangiomes infantiles proliférátifs nécessitant un traitement systémique : Hémangiomes entrainant un risque vital ou fonctionnel, Hémangiomes ulcérés douloureux et/ou ne répondant pas à des soins simples, Hémangiomes avec un risque de cicatrices permanentes ou de défiguration. Le traitement doit être instauré chez les enfants âgés de 5 semaines à 5 mois (voir rubrique 4.2 du RCP complet). **POSOLOGIE ET MODE D'ADMINISTRATION :** Le traitement doit être instauré par un médecin expérimenté dans le diagnostic, le traitement et la prise en charge des hémangiomes infantiles, dans un environnement clinique contrôlé dans lequel des installations adéquates pour la prise en charge des réactions indésirables, y compris celles nécessitant des mesures d'urgence, sont disponibles. Posologie : La posologie est exprimée en propranolol base. La dose initiale recommandée est de 1 mg/kg/jour, répartie en deux prises séparées de 0,5 mg/kg. Il est recommandé d'augmenter la dose jusqu'à la dose thérapeutique, sous surveillance médicale, de la manière suivante : 1 mg/kg/jour pendant 1 semaine, puis 2 mg/kg/jour pendant 1 semaine, puis 3 mg/kg/jour en dose d'entretien. La dose thérapeutique est de 3 mg/kg/jour, administrée en 2 prises séparées de 1,5 mg/kg, le matin et en fin d'après-midi, avec un intervalle d'au moins 9 heures entre deux prises. HEMANGIOL doit être donné pendant ou juste après un repas pour éviter le risque d'hypoglycémie. Si l'enfant ne mange pas ou vomit, il est recommandé de ne pas administrer la dose. Si l'enfant recrache une dose ou ne prend pas tout le médicament, il convient de ne pas lui administrer une autre dose et d'attendre la dose suivante prévue. Au cours de la phase de titration, chaque augmentation posologique doit être réalisée sous surveillance médicale dans les mêmes conditions que pour l'administration de la dose initiale. Après la phase de titration, la dose sera réajustée par le médecin en fonction de l'évolution du poids de l'enfant. Une surveillance clinique de l'état de l'enfant et un réajustement de la posologie doivent être effectués au moins une fois par mois. Durée du traitement : HEMANGIOL doit être administré pendant une période de 6 mois. L'arrêt du traitement ne nécessite pas de diminution progressive de la dose. Chez la minorité de patients qui présentent une rechute des symptômes après l'arrêt du traitement, celui-ci peut être réintroduit dans les mêmes conditions avec une réponse satisfaisante. Populations pédiatriques : En l'absence de données d'efficacité clinique et de sécurité, HEMANGIOL ne doit pas être utilisé chez le nourrisson âgé de moins de 5 semaines. Il n'y a pas de données d'efficacité et de sécurité dans les essais cliniques menés avec HEMANGIOL permettant de recommander l'instauration d'un traitement par HEMANGIOL chez le nourrisson et l'enfant âgé de plus de 5 mois. Enfants insuffisants hépatiques ou rénaux : En l'absence de données, l'administration du produit n'est pas recommandée chez l'enfant insuffisant hépatique ou rénal (voir rubrique 4.4 du RCP complet). Mode d'administration : Voie orale. HEMANGIOL doit être administré directement dans la bouche de l'enfant à l'aide de la seringue pour administration orale graduée en mg de propranolol base fournie avec le flacon de solution buvable (voir les instructions d'utilisation à la rubrique 3 de la notice). Le flacon ne doit pas être agité avant utilisation. Si nécessaire, le médicament peut être dilué dans une petite quantité de lait pour bébé ou de jus de pomme et/ou d'orange adapté à l'âge de l'enfant. Le produit ne doit pas être versé dans un biberon plein. Le mélange peut être effectué avec une cuillérée à café (environ 5 ml) de lait pour les enfants pesant jusqu'à 5 kg ou avec une cuillerée à soupe (environ 15 ml) de lait ou de jus de fruit pour les enfants pesant plus de 5 kg et administré dans un biberon. Le mélange doit être utilisé dans un délai de 2 heures. HEMANGIOL et le repas doivent être donnés par la même personne afin d'éviter le risque d'hypoglycémie. Si plusieurs personnes sont impliquées, une bonne communication est essentielle pour garantir la sécurité de l'enfant.**CONTRE-INDICATIONS :** Prématuré n'ayant pas atteint l'âge corrigé de 5 semaines (l'âge corrigé étant calculé en soustrayant le nombre de semaines de prématurité de l'âge réel) • Nouveau-né allaité par sa mère traitée par des médicaments contre-indiqués avec le propranolol • Hypersensibilité à la substance active ou à l'un des excipients • Asthme ou antécédent de bronchospasme • Blocs auriculo-ventriculaires des second et troisième degrés • Maladie du sinus (y compris bloc sino-auriculaire) • Bradycardie au-dessous des limites suivantes : Age : Fréquence cardiaque (battements/min) – 0-3 mois :100 – 3-6 mois : 90 – 6-12 mois : 80 • Hypotension artérielle au-dessous des limites suivantes : Age : Pression artérielle (mm Hg) – 0-3 mois: 65/45 – 3-6 mois : 70/50 – 6-12 mois : 80/55• Choc cardiogénique • Insuffisance cardiaque non contrôlée par un traitement • Angor de Prinzmetal • Troubles artériels périphériques sévères (syndrome de Raynaud) • Enfants prédisposés à l'hypoglycémie • Phéochromocytome. **EFFETS INDESIRABLES :** Résumé du profil de tolérance : Dans les essais cliniques conduits dans les hémangiomes infantiles proliférátifs, les effets indésirables les plus fréquemment rapportés chez les enfants traités par HEMANGIOL ont été des troubles du sommeil (16,7%), des infections respiratoires majorées telles que bronchite et bronchiolite associées à une toux et une fièvre, des diarrhées (16,5%) et des vomissements (11,5%). Globalement, les effets indésirables rapportés au cours du programme d'autorisation temporaire d'utilisation et dans la littérature ont été des hypoglycémies (et les événements associés tels que des crises convulsives hypoglycémiques) et des infections respiratoires majorées associées à une détresse respiratoire. Liste tabulée des effets indésirables : Le tableau suivant présente les effets indésirables rapportés, quelles que soient la dose et la durée du traitement, dans trois études cliniques conduites chez 435 patients traités par HEMANGIOL à la dose de 1 mg/kg/jour ou de 3 mg/kg/jour sur une durée maximale de traitement de 6 mois. La fréquence des effets indésirables est définie en utilisant la convention suivante : très fréquent (≥ 1/10) ; fréquent (≥ 1/100 à < 1/10) ; peu fréquent (≥ 1/1000 à < 1/100) ; rare (≥ 1/10 000 à < 1/1000) ; très rare (< 1/10 000) ; fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Compte tenu de la taille de la base de données des essais cliniques, les catégories Rare et Très rare ne sont pas représentées. Au sein de chaque classe de systèmes d'organes, les effets indésirables sont présentés par ordre décroissant de gravité. **Infections et infestations :** Très fréquent : Bronchite. Fréquent : Bronchiolite. **Troubles du métabolisme et de la nutrition :** Fréquent : Diminution de l'appétit. **Affections psychiatriques :** Très fréquent : Troubles du sommeil. Fréquent : Agitation, Cauchemars, Irritabilité. **Affections du système nerveux :** Fréquent : Somnolence. Fréquence indéterminée : Crise convulsive hypoglycémique. **Affections cardiaques :** Peu fréquent : Bloc AV. Fréquence indéterminée : Bradycardie. **Affections vasculaires :** Fréquent : Extrémités froides. Fréquence indéterminée : Hypotension artérielle, Vasoconstriction, Syndrome de Raynaud. **Affections respiratoires, thoraciques et médiastinales :** Fréquent : Bronchospasme. **Affections gastro-intestinales :** Très fréquent : Diarrhées, Vomissements. Fréquent : Constipation, Douleur abdominale. **Affections de la peau et du tissu sous-cutané :** Fréquent : Erythème, Erythème fessier. Peu fréquent : Urticaire, Alopécie. Fréquence indéterminée : Dermatite psoriasiforme. **Investigations :** Fréquent : Diminution de la pression artérielle. Peu fréquent : Diminution de la glycémie, Diminution de la fréquence cardiaque, Neutropénie. Fréquence indéterminée : Agranulocytose, Hyperkaliémie. Description d'effets indésirables sélectionnés : Concernant les infections des voies respiratoires inférieures telles que la bronchite ou la bronchiolite, une aggravation des symptômes (y compris de bronchospasme) a été observée chez des patients traités par HEMANGIOL en raison de l'effet bronchoconstricteur du propranolol. Ces effets ont dans de rares cas conduit à l'arrêt définitif du traitement (voir rubrique 4.4 du RCP complet). Les troubles du sommeil recouvrent l'insomnie, un sommeil de mauvaise qualité et l'hypersomnie. Les autres affections du système nerveux central ont principalement été observées en début de traitement. Des diarrhées ont été fréquemment rapportées sans être systématiquement associées à une maladie gastro-intestinale infectieuse. La survenue de diarrhées semble dose-dépendante entre 1 et 3 mg/kg/jour. Aucun cas n'a été d'intensité sévère et n'a conduit à l'arrêt du traitement. Les événements cardiovasculaires rapportés au cours des études cliniques ont été asymptomatiques. Lors des 4 heures de surveillance cardiovasculaire réalisée pendant les jours de titration, une diminution de la fréquence cardiaque (d'environ 7 bpm) et de la pression artérielle systolique (< 3 mm Hg) a été observée après l'administration du médicament. Un cas de bloc cardiaque auriculo-ventriculaire du second degré chez un patient avec des troubles de la conduction sous-jacents a entraîné l'arrêt définitif du traitement. Des cas isolés de bradycardie symptomatique et d'hypotension artérielle ont été rapportés dans la littérature. Les baisses de la glycémie observées au cours des études cliniques ont été asymptomatiques. Toutefois, plusieurs cas d'hypoglycémie associée à une crise convulsive hypoglycémique ont été rapportés au cours du programme d'autorisation temporaire d'utilisation et dans la littérature, notamment en cas de jeûne lors d'une maladie concomitante (voir rubrique 4.4 du RCP complet). Le traitement concomitant par corticoïdes systémiques peut majorer le risque d'hypoglycémie (voir rubrique 4.5 du RCP complet). Une hyperkaliémie a été rapportée dans la littérature chez quelques patients avec un hémangiome ulcéré étendu (voir rubrique 4.4 du RCP complet). 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, EUROSTATION II, Place Victor Horta, 40/ 40, B-1060 Bruxelles, Boîte Postale 97 B-1000 Bruxelles Madou, Site internet: www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be, Luxembourg : Direction de la Santé – Division de la Pharmacie et des Médicaments, Allée Marconi – Villa Louvigny, L-2120 Luxembourg, 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 :** Pierre Fabre Dermatologie 45 place Abel Gance F- 92100 Boulogne. **NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ :** EU/1/14/919/001. **DATE DE MISE À JOUR DU TEXTE :** 01/2019. 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1. D.P. Krowchuk et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. Pediatrics Volume 143, number 1, january 2019: e20183475
2. Nécessitant un traitement systémique

Congenital cytomegalovirus infection after reactivation in a seropositive mother: innocent infection or not?

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Key words

'congenital CMV infection', 'cytomegalovirus', 'non-primary infection', 'prevention'

Abstract

Congenital cytomegalovirus (CMV) infection is the most common congenital infection worldwide. Most neonates are asymptomatic at birth even though they can develop symptoms later in life. Symptomatic patients can be treated with valganciclovir if diagnosis is established within 2-3 weeks after birth. Most healthcare practitioners focus on prevention of CMV seroconversion in seronegative women during pregnancy. Recent data have shown that reactivation of cytomegalovirus in seropositive women, is responsible for the greatest portion of symptomatic congenital CMV infections in neonates. It is therefore of the utmost importance that prevention strategies are taught to all pregnant women.

Introduction

Congenital CMV infection is the most common congenital infection worldwide. It has a very broad spectrum of symptoms, but is often missed because most infants are asymptomatic at birth. Symptomatic congenital CMV infection is most frequently seen after a primary infection of the mother during pregnancy. Nevertheless, most infants become infected as a result of a secondary (non-primary) maternal CMV infection through reactivation or reinfection with a new viral strain. These neonates can become symptomatic shortly after birth or get diagnosed after several years when symptoms become apparent. It is very important that this latter group receives a timely diagnosis and the correct follow-up.

Case presentation

We present a newborn girl, born at a gestational age of 38 weeks and 2 days. It was a second uncomplicated pregnancy that required a caesarian section because of breech presentation. Apgar scores were 8 - 9 - 9 at respectively 1 - 5 - 10 minutes.

Birth weight was 2350 g (< P3), length was 45 cm (< P3) and head circumference was 31 cm (< P3). She had mild hypoglycemia postnatally that recovered spontaneously after introduction of feeding. On first clinical examination petechiae were found. Peripheral blood count showed thrombopenia of 74 000/µL (150 000 – 450 000/µL).

The symmetric growth restriction in combination with thrombopenia warranted further investigations such as TORCHES screening (toxoplasmosis, rubella, cytomegalovirus, herpes simplex and syphilis). CMV (cytomegalovirus) PCR (polymerase chain reaction) on saliva was positive and the diagnosis of congenital CMV infection was confirmed by PCR on urine. Maternal CMV IgM and IgG were determined before this pregnancy and showed IgG positivity and negative IgM (CMV immunity).

The baby was transferred to our center for additional investigations: peripheral blood count (PBC), liver enzymes, cranial ultrasound, magnetic resonance imaging (MRI) of the brain, hearing and ophthalmological evaluation.

The thrombopenia was confirmed on PBC. Liver enzymes were normal. Automated brain stem response (ABR) revealed a unilateral hearing loss on the left side of 50 decibel (dB). On cranial ultrasound bilateral ventricle dilatation, diffuse calcifications and striatal vasculopathy were seen (figure 1). MRI of the brain was abnormal with gyration disorders, white matter abnormalities, periventricular cysts, calcifications, moderate hydrocephalus and cerebellar hypoplasia (figure 2). Ophthalmological screening was normal.

After all additional investigations we classified the child as severe symptomatic and therapy was offered to the parents. After consent of the parents, therapy with valganciclovir was started at 16 mg/kg/dose, twice daily for a duration of 6 months.

The blood platelets gradually normalized during hospital stay. Follow up for hearing, vision and neurological development was initiated.

Discussion

Congenital cytomegalovirus (cCMV) infection is the most common, yet under-recognised, congenital infection worldwide with a reported prevalence in the developed world being approximately 7 per 1000 births [1-4]. Congenital CMV has a significant long-term impact on affected children, being the major cause of non-hereditary sensorineural hearing loss and major infectious cause of neurodevelopmental abnormalities in infants born in developed countries. Long-term sequelae are more common in symptomatic children (approximately 50%) but they are also found in around 13% of the asymptomatic children [2].

Congenital CMV infection has a very broad spectrum of presentation. Most infants, approximately 85-90%, are asymptomatic at birth. Those children will have normal clinical examination and additional investigations after birth. However, about 10-15% of asymptomatic children will develop sensorineural hearing loss (SNHL) [2]. In contrast, symptomatic infants have 40-60% chance of suffering from permanent sequelae like SNHL, cognitive impairment, retinitis and cerebral palsy [5, 6].

Diagnosis is made by isolating cytomegalovirus through culture or by detecting the virus DNA through polymerase chain reaction (PCR) in the neonate. Both urine and saliva samples can be used for the postnatal diagnosis of cCMV with a high sensitivity (93-100%) and specificity (> 97%), if they are collected in the first 2-3 weeks of life. Dried blood spots (DBS) collected at birth have a low sensitivity and are therefore not the gold standard [5, 7]. Nonetheless they can be used to retrospectively differentiate between a congenital CMV infection and a postnatally acquired CMV infection (for example through breast-feeding) [2, 8, 9].

After diagnosis is confirmed, additional investigations are performed to classify the children into symptomatic or asymptomatic cCMV infection. Symptomatic disease can be divided into mild/moderate symptomatic disease, severe focal symptomatic organ disease (i.e. hepatitis, pneumonitis, colitis, bone marrow suppression) or symptomatic central nervous system (CNS) disease, which includes microcephaly, radiological abnormalities on MRI or ultrasound, chorioretinitis of SNHL [9].

Figure 1: Cranial ultrasound shows bilateral ventricle dilatation (white asterisk), diffuse calcifications (yellow arrow) and striatal vasculopathy.

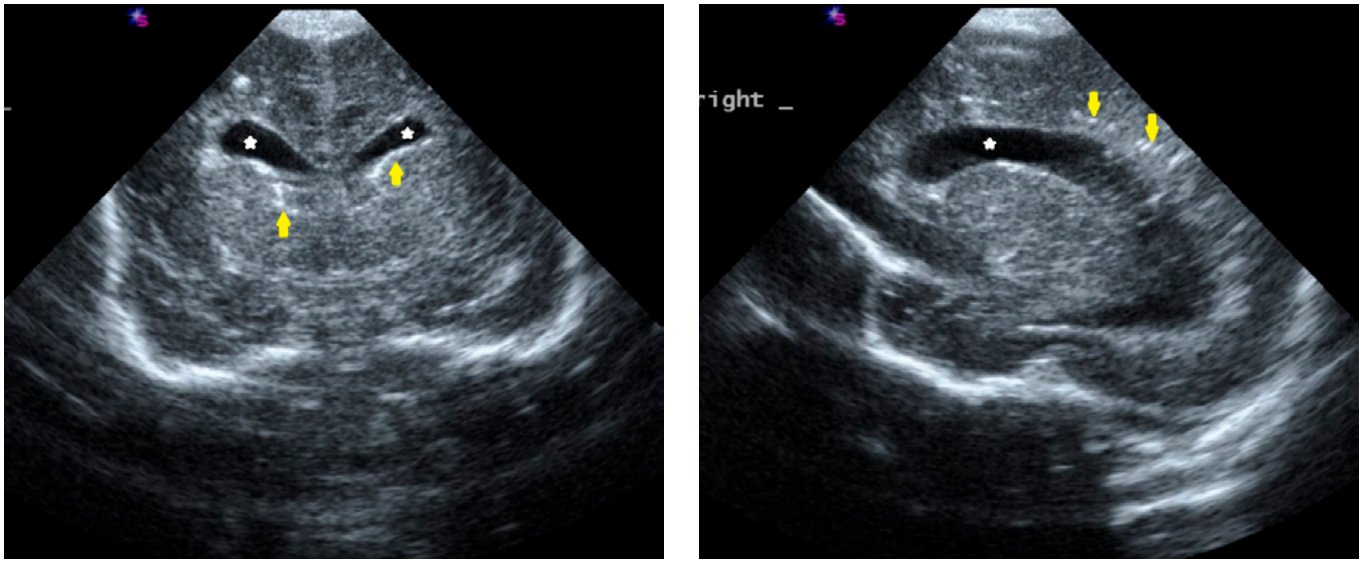
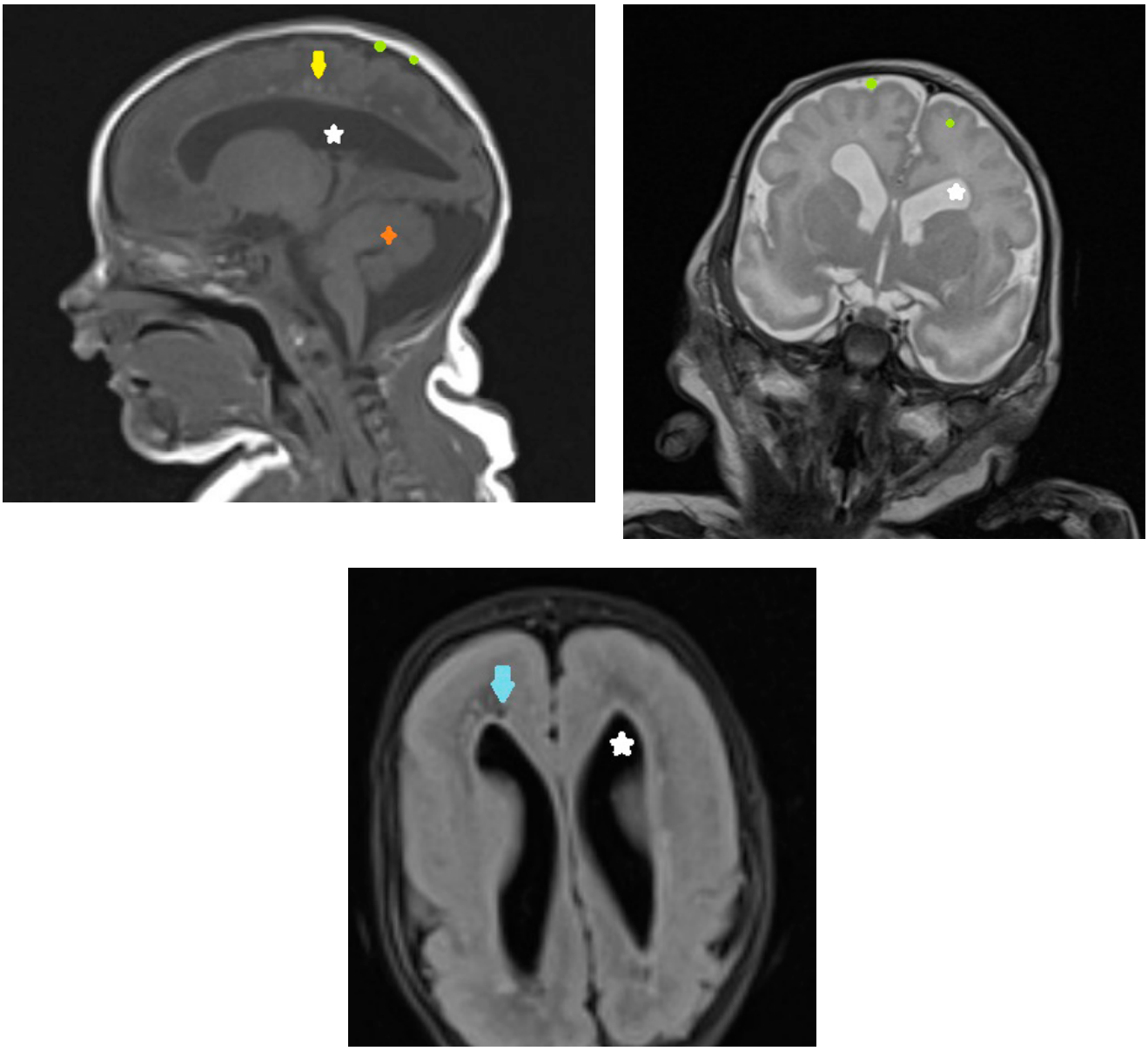


Figure 2: Magnetic resonance imaging (MRI) shows gyration disorders (green orb), white matter abnormalities, periventricular cysts (blue arrow), calcifications (yellow arrow), moderate hydrocephalus (white asterisk) and cerebellar hypoplasia (orange asterisk).



At present, treatment is only recommended for symptomatic CNS disease or severe focal organ disease. The therapy consists of oral valganciclovir during 6 months. It has been shown that this is more beneficial for long-term hearing and neurodevelopmental outcomes than 6 weeks of intravenous therapy. If valganciclovir is started, regular monitoring for possible myelosuppression is recommended throughout the course. In case of isolated sensorineural hearing loss, no evidence is available that the antiviral therapy provides any benefit, which is why it is generally not recommended [5]. Asymptomatic children are currently not eligible for therapy, since there is no evidence of any beneficial effect. However, until recently asymptomatic infants were not included in treatment trials. There is an ongoing study from the United States (with ClinicalTrials.gov Identifier NCT03301415) that will hopefully bring us some new insights [8].

Most of the congenital CMV infections are found after a primary maternal CMV infection during pregnancy. Mothers can become infected by two sources, which are sexual activity and contact with young children since transmission happens through contact with infectious bodily fluids such as saliva and urine. The risk of transmission from mother to fetus is the highest when the primary infection occurs in the first trimester of gestation [10]. It is uncommon to determine a mononucleosis-like illness with prolonged fever, malaise, adenopathy, skin rash, pharyngitis and abnormal hepatic transaminases in pregnant women with a primary CMV infection. Only 10% of women who seroconvert during pregnancy report a febrile illness, which is why most primary maternal CMV infections are undetected [11]. The diagnosis of maternal primary CMV infection can be made by determining CMV antibodies. The most straightforward confirmation is the conversion of CMV IgG antibody from negative to positive, but this is an unlikely scenario since you need paired serum samples that can pinpoint the infection during pregnancy. If serum samples show seropositivity for both CMV IgM and IgG, further evaluation is required by testing for avidity of CMV IgG antibody. If there is a low avidity of IgG, a primary infection is most likely. In case of high avidity, the infection has been active for a few months or longer. Nonetheless, these diagnostic tools have their limitations and cannot always accurately determine the timing of infection onset [11].

Non-primary or recurrent maternal CMV infection causes fetal infection in about 1.2% which is a much lower transmission risk than in primary infections (30-35%) [12, 13]. No symptoms have been associated with recurrent CMV infection. The pathogenesis of this phenomenon is not yet completely understood. It may be a reactivation of endogenous virus or a reinfection with a new virus strain, ultimately leading to vertical transmission to the fetus [1, 3, 6]. In Belgium, screening for CMV antibodies prior to or in the beginning of pregnancy is not unusual nor standard practice. Seroimmunity is confirmed by negative CMV IgM and positive IgG antibodies. Since symptoms are rare in secondary CMV infections, serology is usually not tested again during pregnancy. This means the diagnosis of a non-primary CMV infection is predominantly made postnatally, when an infant shows symptoms.

Recent evidence indicates that secondary CMV infections in pregnant women with preconceptional immunity contribute to a much greater proportion of symptomatic cCMV than was previously thought [14, 15]. Initially, little was known about non-primary CMV infections but data have shown that about two-thirds to three-quarters of all cCMV infections occur in infants born to mothers with pre-existing seroimmunity [5]. This may seem odd because the risk of mother-to-fetus transmission is much higher in primary infections compared to non-primary infections, but it can be explained by the simple fact that there are more seropositive than seronegative (pregnant) women in the world, especially in low and middle income countries, and by the fact that preconceptual immunity only provides partial protection against viral transmission [6,15]. To illustrate, some developing countries reach a prevalence rate of almost 100% in early childhood [11]. In Europe, the seropositivity rate of CMV in pregnant women ranges between 30-95%, with demographic features such as ethnic group, age, parity and social economic class as the main influential factors. One prospective study from Belgium reported a CMV seroprevalence rate of 30% in pregnant women. These women however, were predominantly expecting a first child and had a high education level [16, 17].

In this article, we present a case of a severe symptomatic CMV infection after non-primary infection.

Prevention of maternal CMV infections is difficult. There are currently no vaccines available to prevent CMV infection in pregnant women and treatment options during pregnancy are limited [1,10]. Several non-randomized studies about cytomegalovirus hyper immune globulin (HIG) suggest that it might prevent intrauterine CMV transmission in women with primary CMV infection, but other randomized studies cannot confirm this finding [5].

An international surveillance study in Europe (2017) revealed that there is limited consensus about the diagnosis and management of congenital CMV infection among experts. This led to an under-reporting of infected infants in the registries. Furthermore, it could mean that a lot of newborns with congenital CMV have not been timely diagnosed. Since early recognition and treatment are imperative for symptomatic infants and audiological and ophthalmological follow-up should be organized for all infected children, this means healthcare providers should be further informed to provide a better recognition of the disease. In addition, universal screening programs could help identify the infants in the neonatal period [18].

The most efficient way to prevent congenital CMV is to educate (pregnant) women about cytomegalovirus and to reduce their risk by limiting their exposure to children's saliva and urine [19]. A mixed interventional and observational controlled study from Revello et al (2015) concluded that providing seronegative women information about CMV and reinforcing hygienic recommendations, reduced the risk of seroconversion significantly (1.2% vs 9%). Hygienic recommendations included washing hands after exposure to young children's bodily fluids and surfaces touched by children, avoiding kissing children on the mouth or cheeks and not sharing utensils, food, drinks, etc [10]. Another study from Amin et al (2018) proved that a young child's saliva was the main source for spreading CMV in the household, more than the child's urine. This can be explained by the fact that a child's urine is contained in a diaper, whereas saliva is not, which is why it can spread to other surfaces in the house and consequently infect the pregnant mother. Informing women on this mode of transmission could help reduce the risk of seroconversion [20]. Not only seronegative women should be educated in this way, seropositive women would also benefit from this important prenatal education [4, 15].

Conclusion

Congenital CMV infection is responsible for permanent disability (such as hearing loss, vision loss, cerebral palsy and/or cognitive impairment) in thousands of children each year. Currently, there are no vaccines available to prevent intrauterine transmission of CMV from the mother to the fetus. If a symptomatic infant is suspected during pregnancy, prenatal MRI and detection of CMV PCR on amniotic fluid are available, but there is no antiviral treatment until the child is born. Prevention can therefore be the key to reducing the burden of congenital CMV infections. Until recently, prevention strategies were mainly focused on the reduction of primary CMV infections. Nowadays, these strategies are emphasizing the importance of increasing the public awareness of congenital CMV infection by educating both medical professionals and mothers of childbearing age, underscoring the importance of basic hygiene and inducing behavioral changes in CMV seronegative and – equally important – seropositive women.

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Current rotavirus vaccines: effective and safe

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Question

Are current rotavirus vaccines safe and effective in preventing diarrhoea in infants and children?

Context

Rotavirus infections were a common cause of diarrhoea-related hospital admissions before the rota-virus vaccine was introduced in Belgium. Infections with rotavirus can still induce severe diarrhoea in children which could lead to complications including death. However, in low childhood mortality countries such as Belgium deaths due to rotavirus are rare.

Two rotavirus vaccines are globally available and prequalified by the World Health Organisation (WHO). Both the monovalent vaccine Rotarix (RV1, GlaxoSmithKline) and the pentavalent vaccine RotaTeq (RV 5, Merck) are currently approved for use in Belgium. Several other vaccines are available but are only licensed in single countries in Asia. The first ever licensed rotavirus vaccine, RotaShield (RR-TV, Wyeth Laboratories) was withdrawn from use following reports of intussusceptions. Later observations suggested that this risk was age-related and more common in infants who were over 90 days old when receiving the first dose.

Criteria for study selection

This Cochrane review included trials in children comparing rotavirus vaccines which were prequali-fied by the WHO versus placebo or no vaccine. The main outcomes reported by the review are severe cases of rotavirus diarrhoea, severe all-cause diarrhoea, all-cause death, serious adverse events and intussusception specifically.

Summary of the results

The authors identified fifty-five trials with a total of 216,480 participants. Thirty six trials assessed Rotarix and 15 trials assessed RotaTeq. The remaining four trials investigated Rotavaq, a vaccine not available in Belgium. The review authors performed separate analyses for high- and low-mortality countries as determined by the WHO. This Cochrane Corner, aimed at Belgian paediatricians, will therefore only discuss the results for low-mortality countries on the two vaccines available in Belgium.

Rotarix

At one year follow up, vaccination with Rotarix reduced the number of severe cases of rotavirus diar-rhoea by 84% compared to placebo with the risk decreasing from 13 cases per 1000 participants to 2 per 1000 (95% CI^: 1-3 per 1000; 43,799 participants, 7 studies, high-certainty evidence). The num-ber of severe cases of all cause diarrhoea was lowered by 41% (24 per 1000 vs 4 per 1000 (95% CI: 3-5); 36,002 participants, 9 studies, moderate-certainty evidence). At two years follow-up, Rotarix vaccination resulted in a 82% reduction of severe rotavirus diarrhoea cases (41 per 1000 vs 24 per 1000 (95% CI: 19-30); 28,051 participants, 3 studies, high-certainty evidence) and a 37% reduction of all-cause diarrhoea cases (moderate-certainty evidence). There was no increased risk of serious ad-verse events (high-certainty evidence) or intussusception (low-certainty evidence).

RotaTeq

At one year follow up, RotaTeq vaccination decreased the number of severe rotavirus diarrhoea cases from 17 cases per 1000 to 1 per 1000 (95% CI: 1-5 per 1000), a 92% reduction (4132 participants, 5 studies, moderate-certainty evidence). In children followed for up to two years after vaccination, severe cases of rotavirus diarrhoea were reduced by 82% (25 per 1000 vs 4 per 1000 (95% CI: 2-10); 7318 participants, 4 studies, moderate-certainty evidence). The review authors did not identify any studies reporting on severe all-cause diarrhoea after RotaTeq vaccination. No increased risk for seri-ous adverse events (high certainty evidence) or intussusception (low-certainty evidence) was detect-ed.

Conclusion

In the first two years, Rotarix prevents more than 80% of severe rotavirus diarrhoea cases. The evi-dence concerning the efficacy of RotaTeq for severe rotavirus diarrhoea is slightly less certain, but it probably also prevents 82 to 92% of cases. Rotarix probably prevents 37 to 41% of severe cases of all-cause diarrhoea. No studies were identified that reported this outcome for RotaTeq. Rotavirus vac-cination with either Rotarix or RotaTeq does not increase the number of serious adverse events and may have little or no effect on the number of intussusception cases.

Implications for practice

The review supports the WHO recommendations for the use of these rotavirus vaccines and Rotarix and RotaTeq are shown to have similar efficacy and safety profiles. Although the safety data exclude a risk of intussusception of the magnitude seen with RotaShield, the review underlines the importance of continued surveillance for intussusception or other serious adverse events in countries where ro-tavirus vaccination has been introduced systematically.

REFERENCE:

Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diar-rhoea: vaccines in use. Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.pub4.

Access the full text of these reviews via the Cebam Digital Library for Health (www.cebam.be/nl/cdlh or www.cebam.be/fr/cdlh)

^ **CI:** confidence interval

NOUVEAU: LINGETTES PAMPERS® AQUA PURE

La pureté de l'eau avec la facilité d'une lingette

Les nouvelles lingettes Pampers® Aqua Pure ont été développées pour offrir une lingette la plus humide possible qui assure à la fois un soin efficace et la meilleure protection de la peau.

Les lingettes Pampers® Aqua Pure contiennent 99% d'eau purifiée, du coton bio et une lotion à effet tampon de pH unique pour un soin en douceur tout en protégeant la peau sensible de bébé

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- Conviennent à la peau des nouveau-nés
- organic cotton — A base de coton bio
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- 0% alcool, parabène, phénoxyéthanol, colorant, parfum

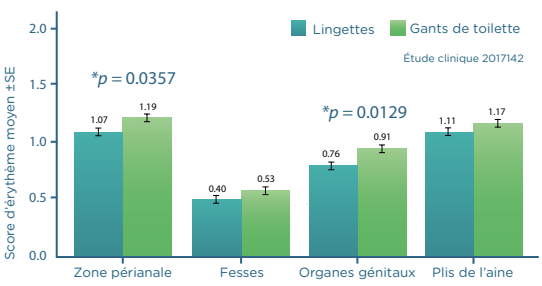
Une nouvelle étude clinique démontre que les lingettes Pampers® Aqua Pure sont au moins aussi douces qu'un gant de toilette imbibé d'eau

En collaboration avec l'ESPD, Pampers a mené une étude chez 130 bébés évaluant l'effet des lingettes pour bébé sur le siège en comparaison avec un gant de toilette imbibé d'eau du robinet.

Cette étude a été réalisée en parallèle en aveugle et à répartition aléatoire (ce qui signifie que les examinateurs ignoraient quels étaient les soins appliqués). Après une phase de repos d'une semaine durant laquelle seul l'usage d'eau du robinet et du gant de toilette était autorisé, les deux types de soins ont été comparés pendant une période de deux semaines en mesurant les scores d'érythème sur 4 sites.

Après deux semaines d'utilisation, il a été démontré que les lingettes Pampers® Aqua Pure sont au moins aussi douces qu'un gant de toilette imbibé d'eau. La peau nettoyée avec des lingettes a également présenté un pH significativement inférieur en comparaison à la peau nettoyée à l'aide d'un gant de toilette imbibé d'eau du robinet, ce qui pourrait procurer des bénéfices à long terme pour la santé de la peau.

Score d'érythème moyen par site



Composants d'origine végétale qui ont été testés dermatologiquement

- Benzoate de sodium
- EDTA
- PEG-40 Huile de ricin hydrogénée
- Acide citrique
- Citrate de sodium
- Caprylate sorbitan

Effet tampon de pH

La lotion contient un système à effet tampon à base d'acide citrique conçu pour préserver l'équilibre naturel du pH de la peau.[1] Des études scientifiques ont démontré que l'une des principales causes de l'érythème fessier est le déséquilibre du pH qui se produit lorsque le lange est souillé. Les langes sales (combinaison urine et selles) contiennent souvent des enzymes digestives qui irritent la peau. Pour contrer cet effet, les lingettes pour bébé Pampers contiennent une lotion spécialement conçue, dotée d'un effet tampon permettant de ramener rapidement le pH de la peau à des valeurs normales comprises entre 4,5 et 6,0.

Les lingettes Pampers® Aqua Pure sont :

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sans parabène
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[1] Données internes de P&G

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- Bervoets L, Van Noten C, Van Roosbroeck S, Hansen D, Van Hoorenbeeck K, Verheyen E, et al. Reliability and Validity of the Dutch Physical Activity Questionnaires for Children (PAQ-C) and Adolescents (PAQ-A). Arch Public Health. 2014;72(1):47.

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DÉNOMINATION DU MÉDICAMENT: HEMANGIOL 3,75 mg/ml, solution buvable. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** 1 ml de solution contient 4,28 mg de chlorhydrate de propranolol correspondant à 3,75 mg de propranolol base. Liste des excipients : Hydroxyéthylcellulose, Saccharine sodique, Arôme fraise (contient du propylène glycol), Arôme vanille (contient du propylène glycol), Acide citrique monohydraté, Eau purifiée. Excipient à effet notoire : 1 ml de solution contient Propylène glycol 2,60 mg. **FORME PHARMACEUTIQUE :** Solution buvable. Solution buvable limpide, incolore à légèrement jaune, avec une odeur fruitée. **INDICATIONS THERAPEUTIQUES :** HEMANGIOL est indiqué dans le traitement des hémangiomes infantiles proliférátifs nécessitant un traitement systémique : Hémangiomes entrainant un risque vital ou fonctionnel, Hémangiomes ulcérés douloureux et/ou ne répondant pas à des soins simples, Hémangiomes avec un risque de cicatrices permanentes ou de défiguration. Le traitement doit être instauré chez les enfants âgés de 5 semaines à 5 mois (voir rubrique 4.2 du RCP complet). **POSOLOGIE ET MODE D'ADMINISTRATION :** Le traitement doit être instauré par un médecin expérimenté dans le diagnostic, le traitement et la prise en charge des hémangiomes infantiles, dans un environnement clinique contrôlé dans lequel des installations adéquates pour la prise en charge des réactions indésirables, y compris celles nécessitant des mesures d'urgence, sont disponibles. Posologie : La posologie est exprimée en propranolol base. La dose initiale recommandée est de 1 mg/kg/jour, répartie en deux prises séparées de 0,5 mg/kg. Il est recommandé d'augmenter la dose jusqu'à la dose thérapeutique, sous surveillance médicale, de la manière suivante : 1 mg/kg/jour pendant 1 semaine, puis 2 mg/kg/jour pendant 1 semaine, puis 3 mg/kg/jour en dose d'entretien. La dose thérapeutique est de 3 mg/kg/jour, administrée en 2 prises séparées de 1,5 mg/kg, le matin et en fin d'après-midi, avec un intervalle d'au moins 9 heures entre deux prises. HEMANGIOL doit être donné pendant ou juste après un repas pour éviter le risque d'hypoglycémie. Si l'enfant ne mange pas ou vomit, il est recommandé de ne pas administrer la dose. Si l'enfant recrache une dose ou ne prend pas tout le médicament, il convient de ne pas lui administrer une autre dose et d'attendre la dose suivante prévue. Au cours de la phase de titration, chaque augmentation posologique doit être réalisée sous surveillance médicale dans les mêmes conditions que pour l'administration de la dose initiale. Après la phase de titration, la dose sera réajustée par le médecin en fonction de l'évolution du poids de l'enfant. Une surveillance clinique de l'état de l'enfant et un réajustement de la posologie doivent être effectués au moins une fois par mois. Durée du traitement : HEMANGIOL doit être administré pendant une période de 6 mois. L'arrêt du traitement ne nécessite pas de diminution progressive de la dose. Chez la minorité de patients qui présentent une rechute des symptômes après l'arrêt du traitement, celui-ci peut être réintroduit dans les mêmes conditions avec une réponse satisfaisante. Populations pédiatriques : En l'absence de données d'efficacité clinique et de sécurité, HEMANGIOL ne doit pas être utilisé chez le nourrisson âgé de moins de 5 semaines. Il n'y a pas de données d'efficacité et de sécurité dans les essais cliniques menés avec HEMANGIOL permettant de recommander l'instauration d'un traitement par HEMANGIOL chez le nourrisson et l'enfant âgé de plus de 5 mois. Enfants insuffisants hépatiques ou rénaux : En l'absence de données, l'administration du produit n'est pas recommandée chez l'enfant insuffisant hépatique ou rénal (voir rubrique 4.4 du RCP complet). Mode d'administration : Voie orale. HEMANGIOL doit être administré directement dans la bouche de l'enfant à l'aide de la seringue pour administration orale graduée en mg de propranolol base fournie avec le flacon de solution buvable (voir les instructions d'utilisation à la rubrique 3 de la notice). Le flacon ne doit pas être agité avant utilisation. Si nécessaire, le médicament peut être dilué dans une petite quantité de lait pour bébé ou de jus de pomme et/ou d'orange adapté à l'âge de l'enfant. Le produit ne doit pas être versé dans un biberon plein. Le mélange peut être effectué avec une cuillérée à café (environ 5 ml) de lait pour les enfants pesant jusqu'à 5 kg ou avec une cuillerée à soupe (environ 15 ml) de lait ou de jus de fruit pour les enfants pesant plus de 5 kg et administré dans un biberon. Le mélange doit être utilisé dans un délai de 2 heures. HEMANGIOL et le repas doivent être donnés par la même personne afin d'éviter le risque d'hypoglycémie. Si plusieurs personnes sont impliquées, une bonne communication est essentielle pour garantir la sécurité de l'enfant.**CONTRE-INDICATIONS :** Prématuré n'ayant pas atteint l'âge corrigé de 5 semaines (l'âge corrigé étant calculé en soustrayant le nombre de semaines de prématurité de l'âge réel) • Nouveau-né allaité par sa mère traitée par des médicaments contre-indiqués avec le propranolol • Hypersensibilité à la substance active ou à l'un des excipients • Asthme ou antécédent de bronchospasme • Blocs auriculo-ventriculaires des second et troisième degrés • Maladie du sinus (y compris bloc sino-auriculaire) • Bradycardie au-dessous des limites suivantes : Age : Fréquence cardiaque (battements/min) – 0-3 mois :100 – 3-6 mois : 90 – 6-12 mois : 80 • Hypotension artérielle au-dessous des limites suivantes : Age : Pression artérielle (mm Hg) – 0-3 mois: 65/45 – 3-6 mois : 70/50 – 6-12 mois : 80/55• Choc cardiogénique • Insuffisance cardiaque non contrôlée par un traitement • Angor de Prinzmetal • Troubles artériels périphériques sévères (syndrome de Raynaud) • Enfants prédisposés à l'hypoglycémie • Phéochromocytome. **EFFETS INDESIRABLES :** Résumé du profil de tolérance : Dans les essais cliniques conduits dans les hémangiomes infantiles proliférátifs, les effets indésirables les plus fréquemment rapportés chez les enfants traités par HEMANGIOL ont été des troubles du sommeil (16,7%), des infections respiratoires majorées telles que bronchite et bronchiolite associées à une toux et une fièvre, des diarrhées (16,5%) et des vomissements (11,5%). Globalement, les effets indésirables rapportés au cours du programme d'autorisation temporaire d'utilisation et dans la littérature ont été des hypoglycémies (et les événements associés tels que des crises convulsives hypoglycémiques) et des infections respiratoires majorées associées à une détresse respiratoire. Liste tabulée des effets indésirables : Le tableau suivant présente les effets indésirables rapportés, quelles que soient la dose et la durée du traitement, dans trois études cliniques conduites chez 435 patients traités par HEMANGIOL à la dose de 1 mg/kg/jour ou de 3 mg/kg/jour sur une durée maximale de traitement de 6 mois. La fréquence des effets indésirables est définie en utilisant la convention suivante : très fréquent (≥ 1/10) ; fréquent (≥ 1/100 à < 1/10) ; peu fréquent (≥ 1/1000 à < 1/100) ; rare (≥ 1/10 000 à < 1/1000) ; très rare (< 1/10 000) ; fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Compte tenu de la taille de la base de données des essais cliniques, les catégories Rare et Très rare ne sont pas représentées. Au sein de chaque classe de systèmes d'organes, les effets indésirables sont présentés par ordre décroissant de gravité. **Infections et infestations :** Très fréquent : Bronchite. Fréquent : Bronchiolite. **Troubles du métabolisme et de la nutrition :** Fréquent : Diminution de l'appétit. **Affections psychiatriques :** Très fréquent : Troubles du sommeil. Fréquent : Agitation, Cauchemars, Irritabilité. **Affections du système nerveux :** Fréquent : Somnolence. Fréquence indéterminée : Crise convulsive hypoglycémique. **Affections cardiaques :** Peu fréquent : Bloc AV. Fréquence indéterminée : Bradycardie. **Affections vasculaires :** Fréquent : Extrémités froides. Fréquence indéterminée : Hypotension artérielle, Vasoconstriction, Syndrome de Raynaud. **Affections respiratoires, thoraciques et médiastinales :** Fréquent : Bronchospasme. **Affections gastro-intestinales :** Très fréquent : Diarrhées, Vomissements. Fréquent : Constipation, Douleur abdominale. **Affections de la peau et du tissu sous-cutané :** Fréquent : Erythème, Erythème fessier. Peu fréquent : Urticaire, Alopécie. Fréquence indéterminée : Dermatite psoriasiforme. **Investigations :** Fréquent : Diminution de la pression artérielle. Peu fréquent : Diminution de la glycémie, Diminution de la fréquence cardiaque, Neutropénie. Fréquence indéterminée : Agranulocytose, Hyperkaliémie. Description d'effets indésirables sélectionnés : Concernant les infections des voies respiratoires inférieures telles que la bronchite ou la bronchiolite, une aggravation des symptômes (y compris de bronchospasme) a été observée chez des patients traités par HEMANGIOL en raison de l'effet bronchoconstricteur du propranolol. Ces effets ont dans de rares cas conduit à l'arrêt définitif du traitement (voir rubrique 4.4 du RCP complet). Les troubles du sommeil recouvrent l'insomnie, un sommeil de mauvaise qualité et l'hypersomnie. Les autres affections du système nerveux central ont principalement été observées en début de traitement. Des diarrhées ont été fréquemment rapportées sans être systématiquement associées à une maladie gastro-intestinale infectieuse. La survenue de diarrhées semble dose-dépendante entre 1 et 3 mg/kg/jour. Aucun cas n'a été d'intensité sévère et n'a conduit à l'arrêt du traitement. Les événements cardiovasculaires rapportés au cours des études cliniques ont été asymptomatiques. Lors des 4 heures de surveillance cardiovasculaire réalisée pendant les jours de titration, une diminution de la fréquence cardiaque (d'environ 7 bpm) et de la pression artérielle systolique (< 3 mm Hg) a été observée après l'administration du médicament. Un cas de bloc cardiaque auriculo-ventriculaire du second degré chez un patient avec des troubles de la conduction sous-jacents a entraîné l'arrêt définitif du traitement. Des cas isolés de bradycardie symptomatique et d'hypotension artérielle ont été rapportés dans la littérature. Les baisses de la glycémie observées au cours des études cliniques ont été asymptomatiques. Toutefois, plusieurs cas d'hypoglycémie associée à une crise convulsive hypoglycémique ont été rapportés au cours du programme d'autorisation temporaire d'utilisation et dans la littérature, notamment en cas de jeûne lors d'une maladie concomitante (voir rubrique 4.4 du RCP complet). Le traitement concomitant par corticoïdes systémiques peut majorer le risque d'hypoglycémie (voir rubrique 4.5 du RCP complet). Une hyperkaliémie a été rapportée dans la littérature chez quelques patients avec un hémangiome ulcéré étendu (voir rubrique 4.4 du RCP complet). 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, EUROSTATION II, Place Victor Horta, 40/ 40, B-1060 Bruxelles, Boîte Postale 97 B-1000 Bruxelles Madou, Site internet: www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be, Luxembourg : Direction de la Santé – Division de la Pharmacie et des Médicaments, Allée Marconi – Villa Louvigny, L-2120 Luxembourg, 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 :** Pierre Fabre Dermatologie 45 place Abel Gance F- 92100 Boulogne. **NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ :** EU/1/14/919/001. **DATE DE MISE À JOUR DU TEXTE :** 01/2019. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne du médicament http://www.ema.europa.eu.). **MODE DE DELIVRANCE :** Médicament soumis à prescription médicale.

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Pierre Fabre DERMATOLOGIE

1. D.P. Krowchuk et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. Pediatrics Volume 143, number 1, january 2019: e20183475
2. Nécessitant un traitement systémique

Publieksprijs België	86,52€

Bexsero: het eerste vaccin tegen meningokokken van serogroep B.

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

BEXSERO

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

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]
Zuigelingen van 3 tot en met 5 maanden	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 temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Personen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van personen met complementdeficiëntie, asplenie of miltdisfuncties. Personen met familiale complementdeficiënties (bijvoorbeeld C3- of C5-deficiënties) en personen die behandelingen ondergaan die de terminale complementactivatie remmen (bijvoorbeeld eculizumab) hebben een hoger risico op een invasieve ziekte veroorzaakt door ***Neisseria meningitidis*** groep B, zelfs als deze personen antilichamen ontwikkelen na vaccinatie met Bexsero. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. **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 EUROSTATION II Victor Hortaplein, 40/40 B-1060 Brussel Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **Luxemburg** Direction de la Santé – Division de la Pharmacie et des Médicaments Villa Louvigny – Allée Marconi L-2120 Luxembourg Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/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** 03/2019 (v09) **AFLEVERINGSWIJZE** Op medisch voorschrift.

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

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