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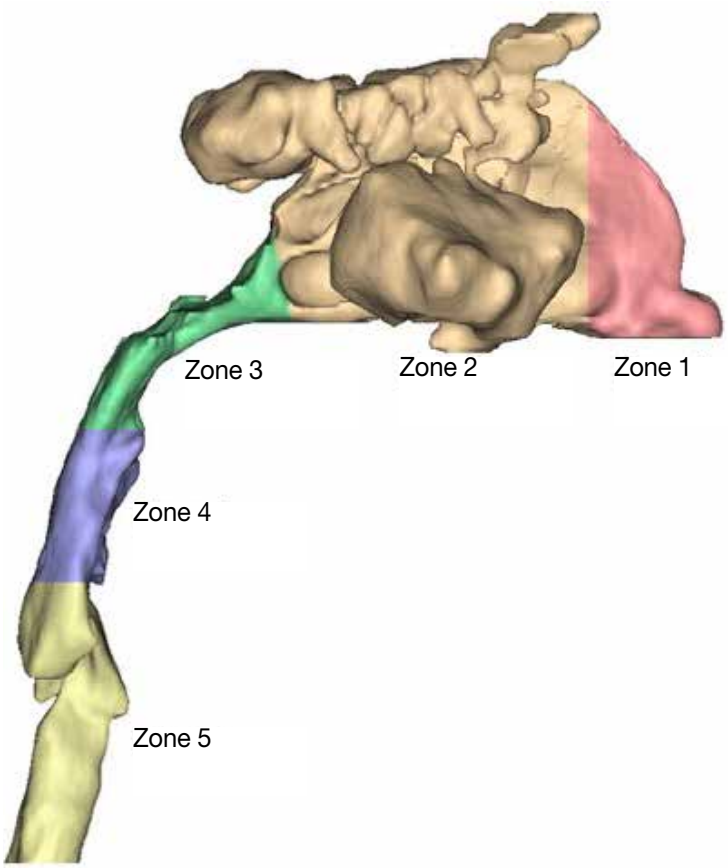

Article

Made in Belgium

Focus on Symptoms

Paediatric Cochrane Corner

Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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A la vie

Editorial

Dear colleagues,

While spring is in the air and climate is changing, our Journal continues to be a tower of strength providing news in science and clinical care to our readership. We also share sad moments with our members.
On March 7th 2019 professor José Ramet died. In the tribute in this issue he is described as a : “fine man, friendly, accessible, wise, engaged, a natural charm, stylish, a good sense of humour and a good doctor”.
Dr Pierre Bauche passed away on February 9th 2019. He was one of the pioneers of the Groupement Belge des Pédiatres Francophones (GBPF) and an inexhaustable energetic pediatrician. Pierre Philippet, current president of the GBPF is calling him: “une personalité incontournable et attachante, passioné, généreux et fidèle à ses convictions”.
On behalf of the whole paediatric community we present to their families our deepest condolences.
This issue features original articles covering different topics in general paediatrics.
A case report draws our attention on how gastro-intestinal complaints may result in a nephrologic diagnosis. A nice multi-centre initiative attempts to document the number of gastro-intestinal endoscopic procedures perfomed in children in Belgium, in the North of the country and Brussels. An interesting guideline is proposed on vaccination, antibiotic prophylaxis and other preventive measures for children with a functional or anatomical asplenie. A useful tool is presented for the evaluation of malnutrition in hospitalised children.
Following the previous article about Mycobacterial infections in children, Interferon Gamma Release Assay, is highlighted as a useful diagnostic tool.
Innovative imaging techniques to predict treatment outcome in paediatric obstructive sleep apnoea are described in our current Made in Belgium.
In the second contribution in: “Focus on Symptoms” , a very clear algorithmic approach guides us to solve the problem of thrombocytopenia in children.
In the Cochrane Corner Section the sensitivity and the specificity of the CRP measurement at the initial evaluation of an infant with suspected late-onset infection is discussed.
On March 21-22, 2019 the annual congress of the Belgian Society of Paediatrics was a very big succes, with almost 800 attendees. The plenary session hosted by our pediatric trainees was an instant hit. They highlighted how technology and applications could impact the future of medicine and paediatric clinical practice. The new formula in which different subspecialties participated in a multidisciplinary fashion seemed to be appreciated by many colleagues. On behalf of the editorial board we want to warmly congratulate the organizing and scientific committee, presided by prof Gunnar Buyse, UZ Leuven. We kindly invite all the colleagues and scientists who gave a presentation or a short communication to prepare a manuscript for submission to our Journal. The abstacts of the symposium are published in the Supplement of the BJP and can be found on our website: www.bvk-sbp.be.

Be our guest and enjoy reading!

Samy Cadranel and Marc Raes, chief editors.

President's Address

Dear Colleagues,
Dear Friends,

As newly-elected president of the Belgian Society of Paediatrics I first of all want to thank and especially to congratulate professor Ann Malfroot who was our captain during the previous 4 years. She not only continued the work of her famous predecessors , but succeeded to further increase the attractiveness of our national society. Stimulating the optimalization of our website, she increased the visibilty of the BVK-SBP. A warm and sincere “dankuwel – merci” is more than deserved!
Futhermore I would like to thank all of them who gave me their confidence and support to take over this task as president of the Belgian Society of Paediatrics. Starting from what the Belgian pediatrician, in training or confirmed, but particulary from what our children growing up in a more and more complex world need, we have to reflect with our different societies VVK, GBPF, Belgian Academy and the BVK-SBP not only what we can offer each of us but how we could work much more and closer together and were we can find synergies and even merge on different areas. Being very busy all of us, we have to avoid double or duplication of work and efforts, we have to integrate and balance our forces, we have to share our ideas and initiatives on a regular base, we have to create time and place for our young(er) colleagues, with special attention to the changing ideas about work-life balance. With respect for the past and keeping in mind that existing societies can be a trademark, we need to have the courage to think out of the box to furher optimise the organisation of our discipline, taking into account the complexity of health care in Belgium with regional differences, regulatory realities, “culture-related” traditions and linguistic diversity. We have to try to unify the somewhat fragmented landscape of Pediatrics in Belgium.
I am very pleased and greatfull that many colleagues are prepared to engage themself , by thinking over and realizing these intentions, to provide our children and adolescents and their families the best possible comprehensive health care available. We Pediatricians play a specific and irreplaceable role at the clinical and scientific level in the care and cure of our up-growing children and their families. We need to continue to meet each other not only on video’s but also in real life time by time, as during our very interesting and entertaining Yearly Congresses , to have animated discussions, to work out joint scientific initiatives, to share our knowledge and seek harmony and cooperation with other health care professionals and disciplines, to convince policy and decision makers when necessary, to advocate children’s rights, to look across our national border, we also need to continue to work on the visibility and acknowledgement of our paediatric discipline and expertise.
For all that: “united forces” are needed with the mental , practical and financial support of all colleagues, young and old, in training or confirmed, in primary, secondary, tertiary and/or academic care, as much as possible!
I invite all of you to continue to support your own beautiful and fascinating medical profession.

Marc Raes,
President BVK-SBP

Uw vragen of commentaar
Vos questions ou commentaires

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SOCIÉTÉ BELGE DE PÉDIATRIE

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Obituary

PROF. DR. JOSÉ RAMET
1955 – 2019

Professor Ramet died on March 7, 2019. He was a fine man, friendly, accessible, wise, engaged, a natural charm, stylish, a good sense of humour and a good doctor.

In the last years he has suffered much from the disease that affected his physical capacities. His mind remained painfully clear until the last moment. His death makes us sad. His place is empty now. We are upset but appeased as he finally finds rest. We think back to him with sadness and good memories at the same time. That is what Portuguese call 'saudade'.

José Ramet was appointed in 2005 as professor at the university of Antwerp and as head of the department of paediatrics at the Antwerp university hospital. Before that he worked as a children's intensivist at the Brussels university hospital where, in 1983, he was the founder of the paediatric intensive care unit.

He was a good clinician, a fascinating teacher, a stimulating scientist and a tough manager. A quick insight into problems, focus on the essential, thorough knowledge of the subject, always at least a plan B, tough in discussions, a bit suspicious and never fully revealing himself. And he was a man with a vision and ambition that reached beyond the local Antwerp affairs. His ideal was to improve the fate of sick children and the quality of paediatrics. He had realized that only representative, national and supranational, organizations can influence a policy. When José was convinced of the rightness of a cause his commitment was absolute. He went for his goal with determination, an iron will and hard work. He also knew that relationships are important to achieve your goal. He understood like no other the art of establishing and maintaining contacts. He was a man who could bring people together. In the end everyone in the paediatric world knew José Ramet.

He has held various positions: President of the European Board of Paediatrics, Secretary General of the European Academy of Paediatrics, President of the Belgian Society of Paediatrics, President of the Society of Paediatric and Neonatal Intensive Care. In 2012 he was nominated as the first Executive Director of the European Academy of Paediatrics. He was the founder of a number of innovative initiatives such as the Belgian Resuscitation Council and the Belgian Paediatric Clinical Research Network. He was honoured in 2006 as Honorary Fellow of the Royal College of Paediatrics and Child Health and in 2010 he received the Angel Ballabriga prize for achievements in paediatrics.

José was particularly proud of these achievements. But more than that we remember the José for who family, loyal friendship, concern for collaborators were so important. The sparkle in his eyes when he talked about his sons or his sisters, the joy and pride when his parents came to visit. His love and immense respect for Françoise, his wife. From his desk chair, the photograph of his wife and children was in the centre of his vision. On the wall a picture of the distant New York where his youngest son is working. The pride about the career of his oldest son. The sweet joy about his grandchildren. His unconditional trust in Ingrid, his loyal secretary, who followed him from the beginning of his career. The delicate attentions towards collaborators with some difficulty. And then his humour, the roguish, warm smile.

How we wish you were here José.

Anne Malfroot, Stijn Verhulst, Samy Cadranel, Mark Wojciechowski

PIERRE BAUCHE
(31 MARS 1932 – 9 FÉVRIER 2019)

Le Docteur Pierre Bauche est décédé le 9 février 2019 à Bruxelles.

Borain d'origine, et issu de l'Université de Liège, Pierre Bauche a été pionnier dès les années 60 en s'expatriant à Paris pour parfaire sa formation. Revenu s'installer à Liège, il s'est totalement dévoué à ses petits patients, tout en restant en perpétuel questionnement sur sa pratique. A côté de sa carrière de clinicien attentif et dévoué, il a développé une énergie considérable à faire avancer le savoir au bénéfice de ses collègues. Au début des années 80, il a ainsi été parmi les fondateurs du Groupement Belge des Pédiatres de langue Française (GBPF). La première réunion scientifique du GBPF eut lieu le 16 mai 1981 à Wépion, et a été le début d'une longue série de réunions dont Pierre Bauche a été la cheville ouvrière quasi exclusive sur le plan scientifique jusqu'il y a une dizaine d'années. Son sens du contact, son enthousiasme et sa ténacité lui ont permis de convaincre bon nombre de personnalités nationales et internationales de venir partager leur savoir avec les pédiatres belges.Insatiable travailleur, il a participé à la création de la Société Européenne de Pédiatrie Ambulatoire (la SEPA), ou de l'Académie de Pédiatrie. Il a été à l'origine de nombreuses campagnes et enquêtes sur les vaccinations, le tabagisme chez l'enfant, …

Passionné, généreux et fidèle à ses convictions, Pierre Bauche restera dans les mémoires du monde pédiatrique belge comme une personnalité incontournable et attachante.

Pierre Philippet
Président du GBPF

Seminar Autoinflammatory Diseases:
Advances in Understanding and New Therapies

Saturday April 27, 2019

Faculty Club – Willem van Croy – Groot Begijnhof 14 – Leuven

Organized by the Departments of Pediatric Rheumatology, Rheumatology and Internal Medicine University Hospitals of Leuven campus Gasthuisberg

It is with great pleasure that we invite you to the Seminar of Autoinflammatory Diseases, to be held in Leuven on 27th April 2019.

The program brings lectures on the expanding spectrum of autoinflammatory diseases and new advances in treatment, by international experts in the field.

We look forward to welcome you in Leuven !

With kind regards

Carine Wouters en Lien De Somer

9:00 – 09:30	**Coffee and welcome** Carine Wouters - Leuven
9:30 –12:15	**New developments in autoinflammatory diseases** Marco Gattorno - Genoa, Italy
	Cells and cytokines in the innate immune response Patrick Matthys - Leuven,
	Monogenic autoinflammatory diseases
	Cryopyrin-associated autoinflammatory diseases: advances in insight and therapies Helen Lachmann - London, UK
	Familial Mediterranean Fever: what is known in 2018? Ahmed Gül - Istanbul, Turkey
	Interferonopathies: an evolving entity Alexandre Belot - Lyon, France
12.15 – 13.30	**Lunch**
13.30 – 15.00	**Non-monogenic autoinflammatory diseases**
	Still's disease revisited Carine Wouters - Leuven
	Vasculitis : new entities and therapies Paul Brogan - London, UK
	The skin: a window into autoinflammatory diseases Antonio Torello - Madrid, Spain
15:00	**Concluding remarks and closing** Carine Wouters - Leuven

Accreditation has been requested

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Save the date

June 14, 2019

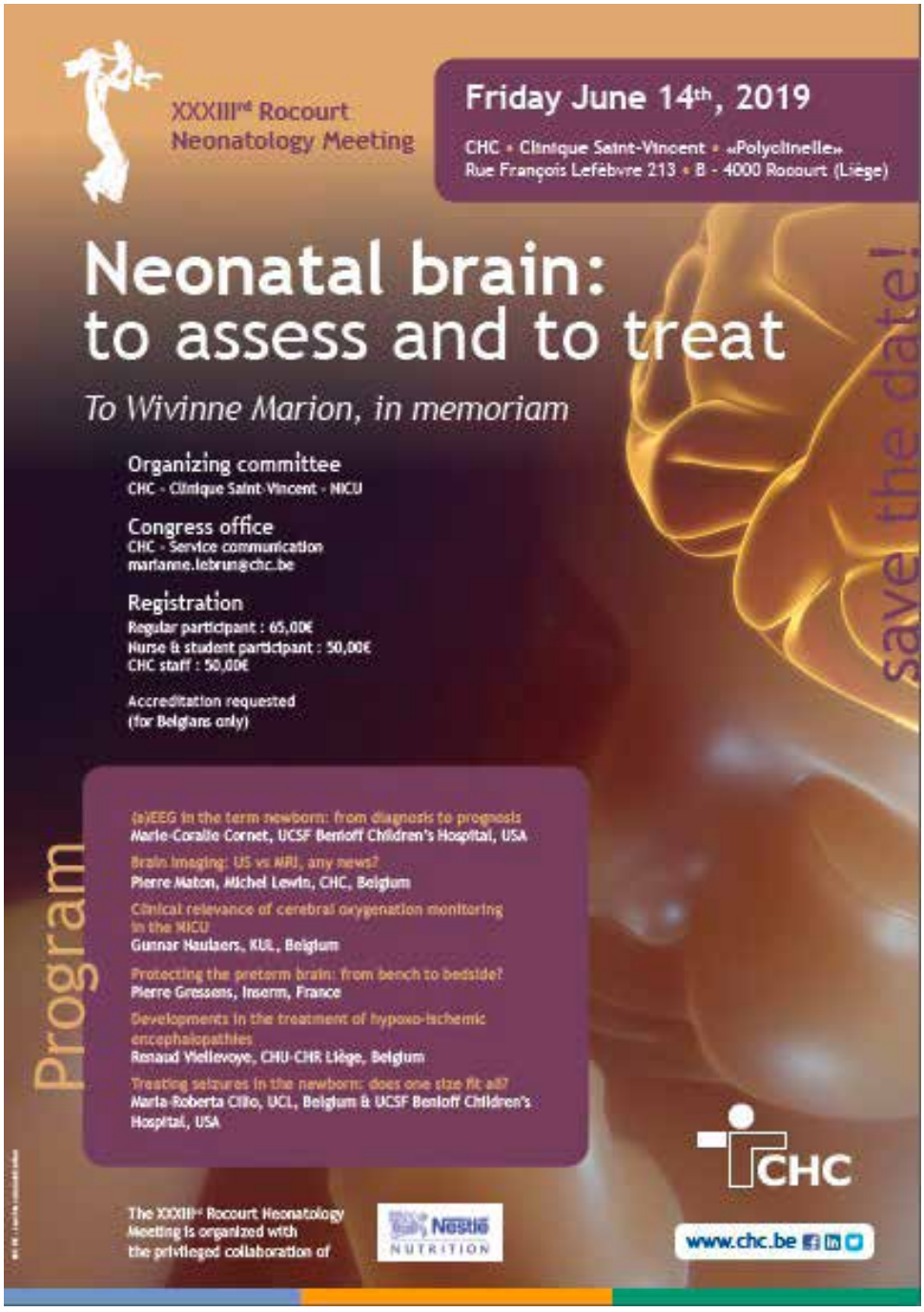
XXXIIIrd neonatal meeting

Dear colleagues,

It is our great pleasure and honor to invite you to our XXXIIIrd neonatal meeting,
this year devoted to neonatal neurology.

Practical informations about inscriptions and timetable will follow soon.
We really look forward to meeting you on this occasion dedicted to a very special person.

Pierre Maton



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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 Produktkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. ▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden. Zie rubriek "Bijwerkingen" voor het rapporteren van bijwerkingen. 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	Noodzaak niet vastgesteld [d]
Adolescenten (11 jaar of ouder)en volwassenen*	Twee doses, elk van 0,5 ml	Niet minder dan 1 maand	Noodzaak niet vastgesteld [d]

[a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor 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). Individuen 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 individuen met complement deficiëntie, asplenie of miltdisfuncties. 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 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 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 injectie 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 06/2018(v05) **AFLEVERINGSWIJZE** Op medisch voorschrift.

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

BE/BEX/0011/16a(1) – July 2018 - V.U.: GlaxoSmithkline Pharmaceuticals n.v., av Pascal 2-4-6, 1300 Wavre

Save the date

September 20, 2019

6th ABC of Pediatric Dermatology

Dear colleague,

It is with great pleasure that we invite you to the 6th ABC of Pediatric Dermatology, to be held in Affligem (Essene) on 20th September 2019.

Both dermatologists and pediatricians encounter children with skin problems on a daily basis.

The aim of this course is to provide the participants with detailed up-to-date knowledge of common skin conditions and clinical clues to arrive at the diagnosis of rarer and more serious conditions. This year again the lectures will be delivered by leading experts in respective fields, chosen to inspire as well as educate.

In order to facilitate interactions, the number of participants is limited.

Registration forms will be treated on a strictly first come first served basis.

Participation is not guaranteed until full payment of the registration fee is received.

Thanks to our main sponsors (Eucerin, Nestlé, Pampers & Pierre Fabre) and several co-sponsors the registration fee for dermatologists and pediatricians can be kept down to the symbolic amount of 40 €.

The course is free to trainees and members of the ESPD and ISPD.

We look forward to welcoming you to our symposium.

Dr. D. Van Gysel, Aalst

Dr. A. Hulsmann, Breda

Affligem (Essene)

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GROUPEMENT BELGE DES PEDIATRES DE LANGUE FRANÇAISE
79ème réunion – 27 avril 2019 – Sart-Tilman, Université de Liège
QUAND PLAQUETTES ET GLOBULES
SANG-MÊLENT & BROUILLENT LA FORMULE :
L'HEMATOLOGIE PEDIATRIQUE BENIGNE

08H00 *Accueil – visite des stands, café, croissants*
08H30 *Ouverture des secrétariats*
08H55 *Ouverture de la réunion scientifique – Dr Lucie Rouffiange*

Matinée

1ère session – Modérateurs : Dr Pierre Philippet – Dr Anna Vanderfaeillie

LIGNEE ROUGE

09H00 **Conduite à tenir devant une anémie : comment s'y retrouver ?** – *Dr Laurence Dedeken, HUDERF*
09H30 **L'anémie hémolytique : comment s'orienter ? –** *Dr Nathalie Aladjidi, CHU Bordeaux*
10H00 **La drépanocytose : quelles nouveautés pour son traitement ?** – *Dr Françoise Bernaudin, CHI Créteil*
10H30 **FLASH : L'anémie ferriprive** – *Dr Annelyse Bruwier, GHdC*
10H40 *Discussion*

11H00 *Pause Café - Visite des stands*

2ème session – Modérateurs : Dr Marc Alexander – Dr Catherine Heijmans

LIGNEE BLANCHE

11H30 **Neutropénie : quand faut-il s'inquiéter ?** – *Dr Alina Ferster, HUDERF*
12H00 **Lymphopénie : quand penser à un déficit immunitaire ?** – *Dr Benoit Florkin, SUHOPL, CHR Liège*
12H25 **Hyperéosinophilie : quand investiguer ?** – *Dr Pierre Philippet, SUHOPL, CHC Liège*
12H50 *Discussion*

13H00 *Lunch- Visite des stands*

Après-midi

14H00 **SESSION GBPF**
"Pediavox : les actualités pédiatriques belges" – Dr Pierre Philippet (président du GBPF)

3ème session – Modérateurs : Dr Francis Veyckemans – Dr Pierre Peters

HEMOSTASE

14H20 **Quand s'inquiéter devant un bilan de coagulation perturbé ?** – *Dr An Van Damme, UCL Saint-Luc*
14H50 **Hémophilies : quoi de neuf Docteur ? –** *Dr Phu-Quoc Lê, HUDERF et Hôpitaux Iris Sud*
15H20 **Quel bilan de coagulation en cas d'AVC ou de thrombose ? –** *Dr Jean-Marc Minon, CHR Liège*
15H40 **FLASH : Bilan pré-op chez l'enfant : oui ou non ? –** *Dr Francis Veyckemans, CHRU Lilles*
15H50 *Discussion*

16h00 *Pause café – Visite des stands*

4ème session – Modérateurs : Dr Lucie Rouffiange – Dr Jean-Luc Hennecker

16H15 **PTI : quelles avancées en 2019 ?** – *Dr Samuel Balbeur, CSPO et UCL Saint-Luc*
16H45 **Aplasie médullaire : un nouveau diagnostic ?** – *Dr Christophe Chantrain, SUHOPL, CHC Liège*
17H15 **Et les transfusions dans tout ça ?** – *Dr Pierre Demaret, CHC Liège*
17H45 *Discussion*

18H00 *Fin de la réunion scientifique*

Liste des orateurs

- Dr ALADJIDI Nathalie, CHU Bordeaux
- Dr BALBEUR Samuel, CSPO et UCL Saint-Luc
- Dr BERNAUDIN Françoise, CHI Créteil
- Dr BRUWIER Annelyse, GHdC
- Dr CHANTRAIN Christophe, SUHOPL, CHC Liège
- Dr DEDEKEN Laurence, HUDERF
- Dr DEMARET Pierre, CHC Liège
- Dr FERSTER Alina, HUDERF
- Dr FLORKIN Benoit, SUHOPL, CHR Liège
- Dr MINON Jean-Marc, CHR Liège
- Dr PHILIPPET Pierre, SUHOPL, CHC Liège
- Dr LÊ Phu-Quoc, HUDERF et Hôpitaux Iris Sud
- Dr VAN DAMME An, UCL Saint-Luc
- Dr VEYCKEMANS Francis, Hôpital Jeanne de Flandre CHRU Lilles

Liste des modérateurs

- Dr ALEXANDER Marc, HUDERF
- Dr HEIJMANS Catherine, Hôpital de Jolimont et HUDERF
- Dr HENNECKER Jean-Luc, Hôpital Notre Dame de Grâce Gosselies
- Dr PETERS Pierre, CHU Sart-Tilman Liège
- Dr PHILIPPET Pierre, SUHOPL, CHC Liège
- Dr ROUFFIANGE Lucie, SUHOPL, CHC Liège
- Dr VANDERFAEILLIE Anna, CHU Saint-Pierre Bruxelles
- Dr VEYCKEMANS Francis, Hôpital Jeanne de Flandre CHRU Lilles

A single Belgian centre experience with the Interferon Gamma Release Assay in the diagnosis of Mycobacterial infections in Children.

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Key words

Interferon gamma release assay, tuberculosis, nontuberculous mycobacteria, children

Abstract

OBJECTIVE

Tuberculosis (TB) is an infectious disease, caused by Mycobacterium tuberculosis, difficult to diagnose particularly in children. Identification of mycobacteria by culture, takes 2-8 weeks. Tuberculin skin test (TST) is since many years the diagnostic test but has several disadvantages. The interferon gamma release assay (IGRA) was developed to diagnose TB infection in peripheral blood. It detects in vitro interferon production from peripheral blood lymphocytes after stimulation with mycobacterial antigens and could offer several practical and theoretical advantages over TST. In Belgium there is little experience with the clinical use of IGRA in children. We report data from our paediatric centre.

Methods

All IGRAs performed between March 2015 and December 2017 in children with suspected TB or close contact with an active TB were retrospectively reviewed and compared to the data in the medical files.

Results

In total 42 IGRAs were performed in 30 children, with a median age of 3 years. Twenty-nine IGRAs were performed as a first line assessment, 13 were done in a follow up setting. Eleven subjects had a positive IGRA. Six cultures confirmed mycobacterial disease of which 2 for Mycobacterium tuberculosis. A significant association was shown between IGRA and TST results ($p < 0.005$) as well as with combined imaging (X-ray, bronchoscopy, ultrasound) ($p=0.018$).

Conclusions

IGRA results contributed in the confirmation or rejection of mycobacterial infection or disease in children. The results correlated well with the results of the TST, even in the youngest subjects < 5 years of age.

Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. Although the incidence of TB seems well controlled in Belgium as in the vast majority of the EU member states, TB incidence rates among foreign-born patients remain several times higher than among natives [1-3]. TB incidence is 10 times higher in the biggest Belgian cities, and after decades of decline, TB case rates increased in Brussels in 2016 (+3/100.000 cases in 2 years' time) [1]. As the majority of the EU countries are committed to pursue elimination of TB, continuing efforts to ensure optimal diagnosis, treatment and prevention of TB are needed [4].

Discrimination between latent TB infection (LTBI) defined as tuberculous contamination without clinical or radiological signs of disease and active TB disease with clinical signs and symptoms and/or radiographic changes is important for diagnosis and management [1-4].

The occurrence of TB in children is an important health indicator in low-incidence countries, because it represents recent transmission of Mycobacterium tuberculosis from an adult with infectious TB [5]; however, children often present as the index case [6]. Compared to adults, childhood TB is more at risk for rapid progression from LTBI to active TB disease after contact with a contagious person.[7] On the other hand, diagnosis is especially challenging in children due to the wide clinical spectrum of TB disease in children, the more frequent occurrence of disseminated disease, and the higher prevalence of extra-pulmonary manifestations with higher prevalence of non-tuberculous mycobacteria (NTM) compared to adults. [6,8,9,10]. Identifying children with TB disease from LTBI may be difficult because over half of them have few or no symptoms [5, 11]. Moreover, the unspecific nature of TB disease signs may mimic several common childhood diseases, including pneumonia and other bacterial and viral infections, and even cancer such as lymphoma [3, 11].

Abnormalities on chest radiograph are mostly present in case of pulmonary TB disease, but are not as specific as in adults [11]. Moreover, bacteriological confirmation in children is not obvious and only about 1/5 of childhood TB is culture-confirmed in the European Union [2]. The mean reason for this is the pauci-bacillary nature of the disease in children. Respiratory samples are difficult to obtain because children, who in contrast to adults, do not expectorate easily, and samples must be obtained by using induced sputum, gastric aspiration to collect swallowed sputum and/or broncho-alveolar lavage during bronchoscopy [4, 12]. Due to the growth characteristics of the mycobacteria, cultures can take up to 8 weeks and hamper rapid diagnosis.

The tuberculin skin test (TST) is historically the most used for diagnosing primary infection with Mycobacterium tuberculosis, however its use and interpretation has some drawbacks and limitations [7]. Availability of the tuberculin solution is not generalized in Belgium, intradermal injection must be done by an experienced health care worker and the child must be presented again 48 to 72 hours later to read the reaction. Interpretation is not clear cut. The test can be falsely negative in persons

infected with Mycobacterium tuberculosis less than 10 weeks preceding skin testing, in children incubating a viral infection, in children under immunosuppression including corticosteroids and in HIV infected persons.[13] In neonates and very young children, the reaction is weaker than in older children and adults. The test is not specific for Mycobacterium tuberculosis infection, but is also positive after Bacille Calmette Guérin (BCG) vaccination complicating interpretation in individuals with BCG, and there is cross reaction with NTM.

Interferon-gamma release assays (IGRAs) have the potential to overcome some TST limitations [7, 14]. Some are commercially available (QuantiFERON TB Gold® and T-SPOT.TB®). IGRAs detects in vitro interferon-gamma release in a whole blood sample after stimulation of lymphocytes with antigens specific to Mycobacterium tuberculosis. There are limited data on the use of IGRAs in children under the age of 3, especially in very young children under the age of 1. Some data on the use in South Africa, USA and Japan support the use of IGRA to evaluate LTBI especially in young BCG vaccinated children [6, 7, 15, 16]. It has also been shown that IGRA has greater sensitivity in children older than 5 years of age, to prove a TB disease [6].

On the other hand, studies are ongoing in children less than 5 years of age 7. An in-house IGRA was developed at the Laboratory of Vaccinology and Mucosal Immunity (U.L.B.) combining the interferon gamma (IFN-γ) response of blood mononuclear cells to 4 different stage-specific mycobacterial antigens: protein purified derivate (PPD), the heparin binding haemagglutin (HBHA), the early secreted antigen-6 (ESAT-6) and the culture filtrated protein-10 (CFP-10)[17,18,19,20].

It was shown that using these different antigens, differentiation could be made between a non-infected subject (negative response on PPD), an infection probably associated with the presence of metabolically active bacteria (positive response to ESAT-6 and CFP-10) or a latent infection (positive response to HBHA) or a BCG vaccinated individual (isolated positive PPD response) 20.The in-house IGRA was developed to enhance the diagnostic accuracy in children compared to the known commercialized QuantiFERON-TB Gold® (use of 3 stimulating antigens: ESAT-6, CFP-10, and TB7.7) or the T-SPOT.TB® (use of 2 stimulating antigens: ESAT-6 and CFP-10), with the hope to differentiate healthy-infected children from those with active TB.[20,21] In immunocompromised patients, like in human immunodeficiency virus (HIV) infected patients the in-house IGRA is potentially more sensitive than the QuantiFERON-TB Gold® in-Tube [22].

As already stressed , the TST is unreliable in distinguishing Mycobacterium tuberculosis infection

from infection with NTM and previous BCG-vaccination. Extra-pulmonary NTM disease is easier to diagnose, because NTM cultured from outside the lungs has been suggested to represent clinically significant disease in almost all cases.[23] The IGRA uses Mycobacterium tuberculosis specific antigens (ESAT-6 and CFP-10), which are located in the specific genomic area, called the region of difference (RD1).[23] This RD1 is not present in the majority of NTMs and the vaccine strain Mycobacterium bovis BCG, thus in the vast majority of individuals infected with NTM and in BCG vaccinated persons the IGRA should be negative. RD1 is present in mycobacteria belonging to the Mycobacterium tuberculosis complex (including Mycobacterium tuberculosis, Mycobacterium africanum, Mycobacterium bovis), so that IGRA will potentially show positive results in diseases caused by these strains. Except for the latter strains, IGRA shows better specificity worldwide with

no cross reactivity with most NTM and no BCG cross reactivity. Due to this specificity of the IGRA, studies have shown that it can be used, in contrast to TST, to discriminate between Mycobacterium tuberculosis and NTM infection/disease or BCG vaccination [23].

Data on the clinical use of IGRA in general are lacking in low incidence TB countries such as Belgium. We explore the clinical value of this in-house IGRA in improving diagnosis and management of Mycobacterium tuberculosis infections and diseases in children.

Methods

Data collection

Included subjects were children aged 17 years or younger, referred to the Paediatric Pulmonology Clinic of the UZ Brussel, a reference centre for tuberculosis and infectious diseases. Patients had a suspected Mycobacterium tuberculosis infection or disease or a close contact with an active TB or were in a follow-up under TB treatment, in a period of 21 months between March 2015 and December 2017.

Close contact was defined in accordance with the guidelines from the European Union standards of care, which means families, congregate settings like migrants' shelters, schools and prisons.4 A written informed consent was obtained for the blood collection and the IGRA assay, by the parents and the patients.

The IGRAs and TST were performed at diagnosis time. Follow up IGRAs were considered separately.

Introduction of IGRA in our clinic -as described below- was new and experimental at the beginning of this study. Therefore it was decided that IGRA results would not influence treatment decisions at diagnosis time.

Results of IGRA, medical information and laboratory findings were gathered in a retrospective way from the electronic record system of the UZ Brussel.

This retrospective study has been approved by the ethics committee of the UZ Brussel (B.U.N. 143201835682).

IGRA testing

Heparinized blood was taken on Monday, Tuesday or Wednesday, and sent to the Laboratory of Vaccinology and Mucosal Immunity, allowing processing of freshly collected blood within a maximum delay of 4 hours after blood drawing. Findings were send back to the UZ Brussels by e-mail. Requested blood volume was 9 ml for children under the age of 4 years and 18 ml for children older than 4 years.

An in-house IGRA, developed at the Laboratory of Vaccinology and Mucosal Immunity (U.L.B.), was used, which was funded by a research grant "Fonds Van de Voorde" from the Foundation King Baudouin, and by the Fund for Scientific Research. Any referral to IGRA in the results and discussion refers to this in-house IGRA.

The peripheral blood mononuclear cells were purified from the fresh blood samples and stimulated with staphyloccocal enterotoxin B (SEB) as a positive control and with antigen free medium as a negative control. The mononuclear cells were also stimulated during 96 hours with 4 different protein mycobacterial antigens: PPD, HBHA, ESAT-6 and CFP-10 as previously reported. Production of IFN-γ by the patient's cells after stimulation was respectively measured for the 4 antigens to characterize the response per antigen [18, 19, 20]. In selected patients, IGRA was repeated during follow-up, in case of unfavourable course of the disease.

Other testing

Imaging

A chest radiography (chest X-ray) was performed in the paediatric radiology department of the UZ Brussel, in children with suspected respiratory involvement. If needed in the diagnostic work-up, a Computed Tomography (CT) of the chest and a flexible fiberoptic bronchoscopy (Olympus) were performed. Pulmonary findings were defined as any abnormality in the imaging. In one patient is was based on clinical signs, in the absence of abnormal imaging findings.

In case of extra-pulmonary suspicion of mycobacterial infection, imaging according to the location was demanded. This could be an ultrasonography, a CT or a Positron emission tomography (PET) CT.

Tuberculin Skin Test

TST was performed by the Mantoux method using 0.1 ml or 2 IU of tuberculin RT 23 from Statens Serum Institute purified protein derivate (PPD). Inoculation is performed by an experienced nurse. Seventy two hours after inoculation interpretation is performed by one of the paediatric pulmonologists by measuring size and type of induration. TST was evaluated according to the national criteria (> 10 mm induration positive suggesting TB; 5-9 mm positive suggesting TB if < 5 years old, close contacts, clinical symptoms, presence of immunodeficiency or suggesting NTM if soft induration type III or IV; < 5 mm induration negative) [11,24] .

Microbiology

In patients with suspected active disease, sampling for cultures was obtained. According to the clinical picture, biopsy, gastric aspiration and/or bronchial alveolar lavage were performed. Cultures were analysed in the microbiology lab using mycobacterium-specific culture media.

Statistics

Data were analysed using the SPSS software package, version 24. Descriptive statistics were used to describe the study population characteristics. Outcomes for most of the investigations were dichotomized and cross tabulations with Chi square tests were performed.

Results

Population

Thirty patients with a median age of 3 years old (mean age 4.8 years with a range from 2 weeks to 17 years) with complete medical files were included during the study period. Twenty subjects were under the age of 5 years, of which 3 patients were less than 1 year old. There were more boys (n=17 or 56%).

None of the patients had received a BCG vaccination, except one boy, who was

vaccinated at birth in Burundi 7 years before inclusion in our study. In 2 patients BCG vaccination status was unknown, but they did not show any post-BCG scar during physical examination.

Underlying risk factors for Mycobacterium tuberculosis disease were found in 5 patients: 2 patients under corticosteroid treatment (1 patient with inflammatory bowel disease (IBD) and 1 patient with Still's disease), 1 patient with IBD under Imuran®, 1 patient with an inborn immunodeficiency (X-linked Chronic Granulomatous Disease) and 1 patient with a newly diagnosed HIV infection without antiretroviral treatment at the moment of the sampling. One patient had CF disease associated with higher risk for NTM disease.[10]

A first IGRA was performed in 11 patients because of pulmonary signs (Table 1), in 12 patients because of extra-pulmonary signs (Table 2), in 3 patients because of both pulmonary and extra-pulmonary signs (Table 1 and 2) and in 4 patients after close contact with a subject with an active tuberculosis infection (Table 3). A second IGRA was performed for different reasons (Table 4): (i) in IBD patient (Imuran® meanwhile ceased) with a milliary tuberculosis, for treatment follow up, (ii) and in 3 brothers with Mycobacterium bovis disease worsening under treatment and undercurrent viral infections.

All patients underwent one or more TST, and 12 of them had a positive TST.

Further imaging analysis was performed in all patients with symptoms. These included a chest X-ray in 17 patients and an ultrasound in 13 patients.

Other imaging techniques used were CT of the lungs in 9 patients, CT of the brain in 1 and PET CT in 1. Seventeen patients underwent a bronchoscopy.

Microbiological analysis was done in 24 patients of which 6 yielded positive results: 2 for Mycobacterium tuberculosis, 2 for Mycobacterium avium, 1 for Mycobacterium haemophilium and 1 for Mycobacterium bovis. All subjects with positive cultures presented with extra-pulmonary signs, except the one with Mycobacterium bovis infection, who also had ganglio-pulmonary involvement.

7 patients had a final diagnosis of TB disease, 1 patient of a Mycobacterium tuberculosis infection (LTBI) and 4 patients with a NTM disease (Table1 and 2).

After first line assessment, treatment (prophylactic or curative) with tuberculostatic agents was started in 12 patients, based on positive TST and imaging findings: 7 patients started because of extra-pulmonary signs, 2 patients because of pulmonary signs and 3 patients because of pulmonary and extra-pulmonary signs. Moreover 5 patients were treated having normal TST: 2 received prophylactic treatment after a close contact, while 3 were started on tuberculostatic agents having a normal TST, but very suggestive radiological signs. The IGRA was also negative in these last 5 patients with negative TST. Thirteen patients did not receive any treatment having negative TST, all 13 had negative IGRA for mycobacteria. Follow-up of these 13 patients confirmed absence of TB (by TST control and clinical evolution).

IGRA results

A total of 42 IGRAs were performed in 30 subjects. Twenty-nine were performed as a first line assessment, 13 were done as a follow up during treatment.

Twenty subjects were considered as having a negative IGRA testing: they had absence of response for the 4 mycobacterial antigens or were only responsive for the PPD antigen. Ten patients were considered as having a positive IGRA with a significant response to at least 2 or more of the 4 tested mycobacterial antigens.

There was a significant association between the TST and the IGRA results (chi square test $p < 0.005$). Only 1 patient of 2 years old with no adenopathies, a normal chest X-ray, but a productive cough, showed a positive TST of 12 mm and a negative IGRA (Table 1 patient *). The child was in close contact with his grandfather with pulmonary TB disease. The child was treated based on the positive TST and TB disease was never culture confirmed in the child. On the other hand, in 1 BCG vaccinated HIV-infected patient (Table 1 patient **) and high TB suspicion on chest imaging, negative TST was supported by negative IGRA, as well as in 1 patient with IBD (Table 1 patient ***) and denied TB diagnosis in both. Association between TST and IGRA was very helpful in confirming or denying TB in the immunosuppressed patients, and also in the difficult age group < 5 years and even below <1 year.

In the pulmonary involvement group a positive IGRA was significantly associated with the combined results of chest X-ray and bronchoscopy (chi square test p 0.018). If a negative IGRA was present a significant association with the combined results of chest X-ray and bronchoscopy (chi square test p 0,030) was observed. There was no association between IGRA results and the combined imaging findings of chest X-ray and TST as in the classical clinical screening (chi square test $p > 0.05$). No association was found when IGRA results were compared with either chest X-ray or bronchoscopic findings solely.

In the extra-pulmonary involvement group, a significant association was found between IGRA results and the combined results of the ultrasound and culture obtained by biopsy (chi square test p 0.007) as well as between IGRA results and the combination of TST and the ultrasound (chi square test p 0.035). Four patients (Table 2 patient °, °°, °°° and °°°°) showed positive cultures for NTM (Mycobacterium avium [2], Mycobacterium haemophilium [1], and Mycobacterium bovis [1]). TST was positive in all 4, however IGRA showed absence of response to ESAT-6 and to CFP-10 in the Mycobacterium avium, Mycobacterium haemophilium cases. In the Mycobacterium bovis patient there was a moderate response to CFP-10, due to the presence of RD1 in the wild-type bovis strains.[23]

There was no significant association (chi square test $p > 0.05$) between any of the microbiological analysis and IGRA results.

All patients with positive IGRA were treated, while 7 of the patients with a negative IGRA also received treatment.

Four children in this series had a close contact with an TB disease (Table 3): imaging examinations were normal, no microbiological examinations were performed. TST and IGRA were negative in all. Two very young children (2 months and 1 year old) were put on prophylactic treatment because of high risk for contamination and developing disease. In the other 2 patients with less close contact, it was decided not to start treatment because TST as well as IGRA did not show any positivity. None of these patients developed a LTBI or TB disease.

Follow up IGRA

It is feasible to repeat IGRA during follow-up of the disease, in case of unfavourable course, to control response. Follow up IGRAs performed for clinical degradation showed stable results and excluded new acquisition of Mycobacterium tuberculosis infection or progression of mycobacterial disease. Degradation could be attributed to viral infections (proven intercurrent varicella and influenza infection)[25, 26]. Treatment remained unchanged. Due to the small cohort no statistical analysis was performed.

Discussion

Age distribution of the studied population is comparable with the general Mycobacterium tuberculosis infected paediatric population in Belgium 1. Our study highlights that even in a low incidence country the index patient of a Mycobacterium tuberculosis infection (LTBI or TB) is often less than 5 years of age. This population is the most susceptible for Mycobacterium tuberculosis severe disease. Early diagnosis and treatment is very important in this group. However, confirmation or differentiation of LTBI and/or TB is especially challenging, and treatment is generally based on epidemiological, clinical and imaging findings: TST is still the most used test in this age group, despite many disadvantages 12. IGRAs are developed aiming to replace TST by a "simple" blood test which could offer practical and theoretical advantages over TST[17, 27].

In the United States of America the TST is already abandoned for children above the age of 5 years 6. In the age group less than 5 years old, data on clinical use of the IGRA are scarce[6, 17]. The immune system response itself is only recently being unravelled with significant difference in age-related responses. It has been shown that reliability of the IGRA increases with age as does the reliability for the TST 6. More than half of the patients included in this study were younger than 5 years of age. The age correlation was not investigated in this study, however a significant association between IGRA results and imaging findings was found in this very young study population with a median age of 3 years. This suggests that it would be safe to trust the long incubation time IGRA results even in children below 5 years of age18. Thereby the authors felt that IGRA results contributed to the diagnosis and to the decision to treat or not, instead of TST results only in difficult cases. Only in 1 patient of 2 years old TST was positive while IGRA result was negative. He was treated eventually because of additional clinical TB suspicion despite normal chest imaging. Diagnosis was eventually not confirmed by culture, we don't know if IGRA was falsely negative and we cannot explain why TST and IGRA results were discordant in this patient. A NTM infection could not be found and the patient's final diagnosis remained unclear (patient * Table 1). In 13 patients treatment was not started based on negative TST, negative IGRA results contributed to the decision not to treat.

Radiological abnormalities in pulmonary TB are known to be very broad and aspecific in Mycobacterium tuberculosis disease[11, 12]. This study showed that any abnormality seen on the chest imaging had no significant association to IGRA results. Only combined results of chest imaging and bronchoscopic findings were related to IGRA results. Chest imaging alone is not enough for diagnosis of TB in children in a low incidence country.

Co-existing diseases.

In this study population there were 5 patients with underlying risk factors to develop Mycobacterium tuberculosis disease. IGRA results were helpful in confirming or excluding TB diagnosis in even more difficult cases.

In 3 immunosuppressed patients and in 1 CF patient, IGRA results were important to confirm or to exclude the diagnosis of Mycobacterium tuberculosis infection. In 1 of these patients follow-up IGRAs were done and were consistent. Repeating IGRA in the follow up of difficult and/or complicated TB diseases is feasible and can give additional information. This is an advantage compared to TST, for which repeating tests are not recommend once they are positive.

Extra-pulmonary infections

Extra-pulmonary Mycobacterium tuberculosis infections may even be harder to diagnose than the classical pulmonary forms. The clinical symptoms that are present are even less specific and the infection usually is more spread than in localised pulmonary infections. Samples for culture are difficult to obtain, except in peripheral lymph nodes.

Extra-pulmonary localisations are more often linked with a NTM infection. NTM infections are difficult to identify as there is no test to prove this infection besides culture. TST is not accurate to confirm diagnosis, due to possible cross positivity with Mycobacterium tuberculosis8. In case of lymph node localisation, excision is mostly recommended to have final diagnosis, but culture is slow and can take up to 8 weeks. Four patients with Mycobacterium bovis (1), avium (2) and haemophilum (1) (Table 2, patient ° (= Table 1 patient *), °°, °°°, and °°°°) had a positive TST but response to stimulation in the IGRA assay was different: absence of reaction to ESAT-6 and CFP-10 in the Mycobacterium avium and haemophilum patients suggests absence of replication of RD1, present in Mycobacterium tuberculosis.[23] The fact that patient */°, infected with Mycobacterium bovis showed a moderate IGRA response to CFP-10 can be attributed to the presence of RD1 in Mycobacterium bovis wild-type strain, which hampers the differentiation with Mycobacterium tuberculosis strains. As explained in the introduction, this RD1 region including the ESAT-6 and CPF-10 antigens, specific for Mycobacterium tuberculosis complex strains, is deleted in the attenuated Mycobacterium bovis BCG vaccine strains but is present in the wild-type.[23] More research is needed to find out if IGRA can be used as a specific diagnostic tool to discriminate TB from NTM infections and BCG vaccination, a tool which will be of great value especially in paediatrics. Studies are ongoing with IGRA assay including stimulation with specific NTM antigens.

Close contacts

Young children less than 5 years of age, living in close contact with a contagious pulmonary TB subject are at particular risk of LTBI and TB. The risk of infection is greatest if the contact is close and prolonged such as contact of an infant with his contagious mother.[4] Preventive therapy is indicated for an LTBI or a contact in whom TB disease has been excluded if the patient is less than 5 years. Decision to start preventive therapy is not always easy if the contact is less close and is not living under the same roof, or in children older than 5 years. In this series, negative IGRA results together with negative TST, were helpful, considered afterwards in deciding not to treat 2 out of 4 children with close TB contact[13,27].

General

Our data suggest that IGRAs are as contributing as TST in the management of mycobacterial infections, in a low incidence country as Belgium. IGRA can have an additional role over TST in difficult situations such as immunosuppression and NTM infections, in close contact subjects or in situations where TST risks to be inconclusive.

Obstacles for the use of IGRA in Belgium are the cost of the testing materials and the laboratory costs. This study was financed by a scientific grant described in the acknowledgements. Cost-effectiveness studies on the implementation of IGRA in low incidence countries are ongoing, but results are inconsistent, and depend on the studied populations and the involved TB control program[13,27].

Limitations

The limitations of the study on the clinical value of IGRA in management of TB in children involve the retrospective design of the study, using the local database of the hospital. This means that the decision to perform imaging and bronchoscopic examinations or even microbiological testing was not made prospectively. This could affect the number of biopsies or punctures performed in the studied population. The small cohort presented could have an effect on the outcomes of chi square tests. Moreover, the retrospective nature of the study and the number of included patients could have affected the non-existing bond between the individual routine tuberculosis workup and the IGRA results.

Conclusion

The implementation of IGRA in the diagnosis of suspected mycobacterial infection is useful because of its promising characteristics. It seems to be as good as TST in the diagnosis of TB. IGRA was helpful in confirming or excluding TB diagnosis in even more difficult cases such as immunosuppression and very young children younger than 5 and even younger 1 year of age.

In the past diagrams with the implementation of this test were already made and current use in the United States of America is fully implemented these days. A more general use of this test could be interesting to better understand its implications and its strengths. A general recommendation could be made to use IGRA in screening before the start of an immunosuppressive therapy, in screening of close contact children, or as a standard routine test in patients known to have misleading clinical symptoms.

Table 1 : Subjects with pulmonary findings.

	Age	TST	Macroscopic				Microscopic	Treatment	Home –made IGRA						Contributing factors
			RX	US	CT	Broncho scopy			*IFN-γ concentrations (pg/ml)*					*conclusion*	
									SEB	*PPD*	*HBHA*	*ESAT-6*	*CFP-10*		
Age < 1 year	6 months	0	1	-	1	1	0	0	16378	0	0	0	0	0	-
	9 months	0	1	-	1	1	0	1	43708	42	0	18	0	0	Immunodef
TOTAL	2 patients	Negative	2 abnormal	-	2 abnormal	2 abnormal		1 treated	2 negative						
Age 1-5 years	1	0	1	-	1	1	0	1	9835	63	0	15	15	0	-
	1	1	1	1	1	1	0	1	55299	25593	305	5947	>9000	1	-
	1	1	1	1	-	1	*M. bovis*	1	40615	39312	234	<25	5102	1	-
	2 *	1	0	-	-	0	0	1	137734	1423	<25	<25	<25	0	-
	3	1	1	-	1	1	0	1	73911	27372	1050	<10	7116	1	-
	3	0	1	-	-	0	0	0	94651	<25	<25	<25	<25	0	-
	4	1	1	-	-	1	0	1	134063	52175	592	53	755	1	-
TOTAL	7 patients	5 positive	6 abnormal	2 abnormal	3 abnormal	5 abnormal	1 positive	6 treated	4 positive						
Age > 5 years	6 ***	0	1	-	1	-	0	0	75937	33	<25	<25	<25	0	IBD
	7 **	0	1	-	1	-	0	0	50519	<10	<10	<10	<10	0	HIV
	11	0	1	-	1	1	0	0	13329	69		<25		0	-
	14	0	1	-	1	1	0	0	10044	86	<10	<10	<10	0	-
	17	0	1	-	-	1	0	0	82316	59	<25	<25	<25	0	CF
TOTAL	5 patients	5 negative	5 abnormal	-	4 abnormal	3 abnormal	5 negative	5 non treated	5 negative						
TOTAL ALL	14 patients	5 positive	13 abnormal	2 abnormal	9 abnormal	10 abnormal	1 positive	7 treated	4 positive						

Legend: 1 is abnormal result, 0 is normal result. Subjects in grey have both pulmonary and extra-pulmonary findings and can be found in both tables 1 and 2.
Patient *, ** and *** are described in results and in discussion.

Table 2: Subjects with extra-pulmonary findings.

	Age	TST	Macroscopic				Microscopic	Treatment	Home –made IGRA						Contributing factors
			RX	US	CT	Broncho			*IFN-γ concentrations (pg/ml)*					*conclusion*	
									SEB	PPD	HBHA	ESAT-6	CFP-10		
Age <1 year	9 months	0	1		1	1	0	1	43708	42	0	18	0	0	Immunodef
TOTAL	1 patient	Negative	1 abnormal		1 abnormal	1 abnormal		1 treated						negative	
Age 1-5 years	1	0	-	1	-	-	-	1	27480	10	0	17	0	0	Still's disease
	1	1	1	1	1	1	0	1	55299	25593	305	5947	>9000	1	
	1°	1	1	1	-	1	*M. bovis*	1	40615	39312	234	<25	5102	1	
	1	0	0	1	-	-	0	0	490	<25	<25	<25	<25	0	
	2	0	-	1	-	-	0	0		0	0	0	0	0	
	2°°	1	0	1	-	-	*M. avium*	1	17326	710	94	0	0	1	
	3	1	0	1	-	-	*M. tuberculosis*	1	8053	21001	297	4615	9526	1	
	3°°°	1	0	1	1	-	*M. avium*	1	90661	7846	1133	<25	<25	1	
	4	0	0	1	-	-	-	-	21694	0	0	0	0	0	
	4	1	1	1	-	0	0	1	78616	36085	2125	<10	25	1	
	4	0	1	1	-	0	0	0	39364	397	27	0	0	-	
TOTAL	11 patients	6 positive	4 abnormal	11 abnormal	2 abnormal	2 abnormal	4 positive cultures	7 treated						6 positive	
Age > 5 years	7°°°°	1	0	1	-	-	*M.haemophilium*	1	77380	296	550	0	0	1	
	13	1	0	1	-	0	0	1	60757	3928	1576	15	213	1	
	15	1	1	-	1	0	*M. tuberculosis*	1	61849	103	122	<10	16	1	IBD - 8 months treatment
TOTAL	3 patients	3 positive	1 abnormal	2 abnormal	1 abnormal		2 positive cultures	3 treated						3 positive	
TOTAL ALL	15 patients	9 positive	6 abnormal	13 abnormal	4 abnormal	4 abnormal	6 positive cultures	11 treated						9 positive	

Legend table 2: 1 is abnormal result, 0 is normal result. Subjects in grey have both pulmonary and extra-pulmonary findings and can be found in both tables. Patients °, °°, °°° and °°°° are described in results and in discussion.

Table 3: Subjects with a close contact with an active tuberculosis infection.

	Age	TST	Macroscopic				Microscopic	Treatment prophylaxis	Home –made IGRA						Close contact
			RX	US	CT	Bronchoscopy			*IFN-γ concentrations (pg/ml)*					*conclusion*	
									SEB	PPD	HBHA	ESAT-6	CFP-10		
Age < 1 year	2 months	0	0	-	-	-	-	1 treated	31931	12	<10	<10	<10	0	Friend of the family
TOTAL patients	1 patient	negative	normal					1 treated						negative	
Age 1 -5 years	1	0	0	-	-	-	-	1 treated	51056	0				0	Great grandfather
	1 patient	negative	normal					1 treated						negative	
Age > 5 years	6	0	0	-	-	-	-	0	47130	2004	74	<25	<25	0	Father
	7	0	0	-	-	-	-	0	28042	286	64	<10		0	Father
TOTAL	2 patients	negative	normal					none						negative	
TOTAL ALL	4 patients	negative	normal	none	none	none		2 treated						negative	

Legend: 1 is abnormal result, 0 is normal result.

Table 4: Follow-up IGRA

			IFN-γ concentrations (pg/ml)				
Patient	Symptoms	Time treatment	SEB	PPD	HBHA	ESAT-6	CFP-10
A	extrapulmonary	8 m	61849	103	122	<10	16
		12 m	168855	685	377	0	61
B	Pulmonary	1m	20645	9833	952	<25	1344
		2m	49250	87434	>22500	<10	6887
		6m	7036	2748	747	0	433
C	Pulmonary and extrapulmonary	1m	16903	15154	1120	<25	422
		2m	32766	24300	7481	<25	894
		6m	3830	9038	902	<25	78
		12m	35736	23004	3796	<25	40
D	Pulmonary and extrapulmonary	1m	51059	19350	3775	163	3826
		2m	50993	18228	4139	<25	2179
		6m	4537	6031	799	<25	268
		12m	44021	20563	2683	<25	331

Legend: Follow up IGRAs in a IBD patient (A) under immunosuppression with a miliary tuberculosis for treatment follow up and in 3 brothers (B,C,D) with *Mycobacterium bovis* disease worsening under treatment and undercurrent viral infections

Conflicts of Interest

No author has any competing interests (financial or non-financial).

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Prevalence of malnutrition in hospitalised children and evaluation of implementation of the STRONGkids screening tool.

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Key words

malnutrition, hospitalised children, STRONGkids screening tool, biometric data

Abstract

OBJECTIVE

Malnutrition in hospitalised children in Belgium is an insufficiently recognised problem. Because of its serious consequences, it is important to detect and treat this problem in a timely manner.

The aim of this prospective observational study is to evaluate the prevalence of malnutrition and the implementation the STRONGkids screening tool in our tertiary hospital.

DESIGN AND SETTING

All children between one month and 16 years old (n = 548) hospitalised at the Paediatric Department and Paediatric Intensive Care Unit of the Antwerp University Hospital were included in the study. Weight and height were measured and given a STRONGkids score ranging from 0 to 5, adopting the definitions of acute and chronic malnutrition of the World Health Organisation. The use of the screening tool was evaluated on the last three days of months 1, 2, 3, 6, 9 and 12 after implementation.

RESULTS

Weight and height were measured in 83.8% of the patients admitted. For 70.3%, data was plotted in a growth chart. The overall prevalence of malnutrition was 23.2%, with 14.8% suffering from acute malnutrition and 17.6% chronic malnutrition. The STRONGkids score was applied in 61.3% of the admissions. There was a significant decrease in screening for malnutrition during weekends and/or holidays.

CONCLUSIONS

The percentages of acute and chronic malnutrition were higher than those found in similar research. Our data show that malnutrition in hospitalised children remains a problem, and the poor registration of biometric data is also concerning. More awareness is needed as a basis for standardised screening assessment.

Introduction

The prevalence of malnutrition in hospitalised children in developed countries is high.[1-6] In daily practice, however, it is still an insufficiently recognised problem. In Belgium, little research has been done. A study in 2011 described a prevalence rate of 18.4% in Belgium.[1] The results of a three-day national screening programme in the Netherlands in 2007 revealed a similar rate of 19%.[2] However, other studies show highly variable numbers for disease-related malnutrition, ranging from 6% to 51%, in other European countries, the United States of America and Canada.[3-7]

According to the World Health Organisation (WHO), malnutrition is the imbalance between supply of nutrients and energy and the demand of the body for maintenance, growth and development.[8] Preferably, malnutrition can be classified as low weight-for-height (acute malnutrition or 'wasting'), low height-for-age (chronic malnutrition or 'stunting') or a combination of both. It is of great importance to screen for malnutrition, given that it is associated with increased morbidity and mortality, as well as impaired growth and development.[9-10]

Registration of the prevalence of malnutrition using anthropometric data and the screening of children at risk of developing malnutrition using a screening tool are two essentials to adequately address the problem. Validated tools for this risk screening are scarce and implementation should be feasible. Three tools screening for this risk of developing malnutrition that are in use in Europe are the Paediatric Yorkhill Malnutrition Score (PYMS), the Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP) and the Screening Tool for Risk of Impaired Nutritional Status and Growth (STRONGkids). The PYMS and the STAMP include anthropometric measures (BMI compared with weight and height, respectively), while the STRONGkids includes a subjective clinical assessment of nutritional status. Therefore, risk classification differs markedly, with an overall agreement of about 40% between the three tools.[11]

The STRONGkids screening tool was developed in the Netherlands.[12] This tool scores the risk of malnutrition at admission and during hospitalisation. It has already been implemented in the Netherlands, proved its feasibility and has recently been validated in Belgium.[12,13]

The aim of our study was to evaluate the prevalence of malnutrition in our patient population and to evaluate the implementation of the STRONGkids screening tool at the Antwerp University Hospital (UZA). The purpose of introduction of this tool is to identify children who need to be referred to the dietician and/or clinical team for further nutritional review and follow up.

Materials and methods

Anthropometric and nutritional assessment

This is a prospective observational study in a tertiary hospital. All children admitted to the Paediatric Department and the Paediatric Intensive Care Unit (PICU) of the UZA were included during two periods of two months (June and July 2015 and December 2015 and January 2016). Inclusion criteria were: age between 1 month and 16 years and hospitalisation stay for more than 24 hours. Readmissions within 7 days were excluded. Age (months), sex, medical history, current use of medication, diagnosis (infectious, surgical, other) and length of hospital stay (days) were recorded for all included patients. 'Underlying disease' refers to the existence of any kind of (chronic) disease with a risk of malnutrition (see Figure 1). Weight and height were measured by the nursing staff at admission. CAE (Close Automation Electromécanique) measuring equipment was used for all children (PF77 and Charly 200). Head circumference was also measured for children less than 15 months of age. The data were plotted in the Flemish growth charts for the Belgian population.[14]

We generated standard deviation scores (SDS) for weight, height, weight for age (WFA), weight for height (WFH) and height for age (HFA) using the software program Growthvision. Acute malnutrition was defined as < -2 SDS WFA for children aged between 1 month and 1 year and < -2 SDS WFH for older children. Chronic malnutrition was defined as < -2 SDS HFA for all ages. Overall

malnutrition was defined as acute and/or chronic malnutrition, not counting patients twice. Combined malnutrition was defined as the existence of acute and chronic malnutrition in the same patient. The measurements were corrected for prematurity up to 2 years of age and for trisomy 21.

Screening for the risk of malnutrition

Next, for all children a STRONGkids score ranging from 0 to 5 was noted in the patient file at admission. Preferably this risk score is filled in by paediatricians or paediatric residents, otherwise by medical students under supervision. According to the criteria, a dietician was supposed to be contacted at a score of 4 or higher (Figure 1[15]).

Evaluation of implementation

Implementation of nutritional risk screening was required by the Joint Commission Information-accreditation (JCI). The STRONGkids screening tool was chosen to be implemented for this purpose. All nurses, dieticians and doctors were informed in advance. Our study protocol was also presented at staff meetings, and all paediatricians and paediatric residents were repeatedly informed about the implementation of the tool and how to use it.

The target was to screen for malnutrition within 24 hours of admission. We used the process evaluation tool of the Dutch Malnutrition Steering Group.[12] Evaluation of the implementation was performed at the following times during a time lapse of 12 months: the last 3 days of months 1 to 3, month 6, month 9 and month 12. We only conducted this evaluation in the Paediatric Department. We recorded the following items: whether the STRONGkids score was noted, if it was performed in a 24-hour timeframe after admission, by whom it was noted and whether the evaluation was correct. All scores were checked blindly by two of the authors.

Statistical analysis

Descriptive analysis was used to describe the study population and a Chi-square test was used to compare percentages. The Mann-Whitney U-test and Kruskal-Wallis test were used to compare continuous variables between two groups and between more than two groups, respectively. Post-hoc analysis for discontinuous and continuous variables was performed by the Z-test and the Bonferroni-test, respectively. Significance of the findings was set at $p < 0.05$.

The study was approved by the Ethics Committee of the UZA. No written informed consent was needed because implementation of the tool concerned standard care. Nevertheless, parents were informed by a brochure and could withdraw from participation at any time.

Results

Anthropometric and nutritional assessment

In total, 548 patients were included between June and July 2015 and between December 2015 and January 2016, with 230 patients (45.8%) included in the first period (June-July 2015) and 257 (54.2%) in the second (December 2015-January 2016). Three patients were excluded because the patient files were not available for review.

Baseline patient characteristics are shown in Table 1.

Weight was measured in 94.3% of all patients (Paediatric Department and PICU, 96.5% and 77% respectively). Weight and height were measured in 83.0% of the patients (Paediatric Department and PICU, 83.8% and 77.0% respectively). For 70.3% of these patients, data were plotted in a growth chart.

The overall prevalence of malnutrition was 23.2%, with 14.8% and 17.6% for acute and chronic malnutrition, respectively. There were significantly more patients with underlying disease in the chronic and overall malnourished groups compared to the acute malnourished group. In the group with overall malnutrition, there were significantly more patients with a history of prematurity. Concerning overall malnutrition, there was no significant difference ($p = 0.81$) in the duration of hospitalisation of patients with or without malnutrition. Surgical patients less commonly have malnutrition, whereas patients with underlying disease and patients admitted for gastroenterology or haemato-oncology are more frequently categorised as malnourished (Table 2).

Screening for the risk of malnutrition

Screening for the risk of malnutrition using the STRONGkids screening tool was performed in 61.3% of patients. Only 10.0% of the patients admitted to the PICU were screened, and these results were excluded. Overall, 26.5% of the children were classified as low risk. For 9 of the 14 patients with a high-risk score of 4 or 5,

Figure 1: STRONGkids screening tool[15]

(1) Subjective clinical assessment (1 point).
Is the patient in a poor nutritional status judged by subjective clinical assessment (diminished subcutaneous fat and/or muscle mass and/or hollow face)?
(2) High risk disease (2 points).
Is there an underlying illness with a risk of malnutrition or expected major surgery
(3) Nutritional intake and losses (1 point).
Are one of the following items present?
Excessive diarrhoea (≥5 per day) and/or vomiting (>3 times/day) the last few days?
Reduced food intake during the last few days before admission (not including fasting for an elective procedure or surgery)?
Pre-existing dietetically advised nutritional intervention?
Inability to consume adequate intake because of pain?
(4) Weight loss or poor weight gain? (1 point)
Is there weight loss or no weight gain (infants <1 year) during the last few weeks/months?

Overview of the item 'high risk disease' of the screening tool.

High risk disease
Anorexia nervosa
Burns
Bronchopulmonary dysplasia (maximum age 2 years)
Celiac disease
Cystic fibrosis
Dysmaturity/prematurity (corrected age 6 months)
Cardiac disease, chronic
Infectious disease (AIDS)
Inflammatory bowel disease
Cancer
Liver disease, chronic
Kidney disease, chronic
Pancreatitis
Short bowel syndrome
Muscle disease
Metabolic disease
Trauma
Mental handicap/retardation
Expected major surgery
Not specified (classified by doctor)

Nutritional risk score and recommendations for nutritional intervention.

Score	Risk for malnutrition and need for intervention	
	Risk	Intervention and follow-up
4–5 Points	High risk	Consult doctor and dietician for full diagnosis and individual nutritional advice and follow-up. Start prescribing sip feeds until further diagnosis.
1–3 Points	Medium risk	Consult doctor for full diagnosis; consider nutritional intervention with dietician. Check weight twice a week and evaluate the nutritional risk after one week.
0 Points	Low risk	No intervention necessary. Check weight regularly conform hospital policy and evaluate the nutritional risk after one week.

Table 1: Baseline patient characteristics

	Frequency (n)	Percentage (%)
Age (months)°	49.5 (1-191)	-
Hospital stay (days)°	3.0 (1.0-86.0)	-
Sex male/female	322/226	58.8/41.2
Underlying disease	281	51.3
Preterm infants	45	8.2
Admission category		
Infectious	105	19.2
Surgical	205	37.4
Haemato-oncology	50	9.1
Gastroenterology	53	9.7
Trauma	7	1.3
Pneumology	24	4.4
Nephrology	13	2.4
Metabolic disease	5	0.9
Endocrinology	25	4.6
Cardiology	1	0.2
Neurology	38	6.9
Other	22	4.0
Admission unit ward/PICU	487/61	88.9/11.1
Overall malnutrition	127	23.2§
Acute malnutrition	69	14.8
Malnutrition WFA	26	21.8*
Malnutrition WFH	43	12.4*
Chronic Malnutrition HFA	78	17.6*
STRONGkids		
Not performed	212	38.7
Low	145	26.3
Moderate	177	32.3
High	14	2.6

(PICU: paediatric intensive care unit, WFA: weight for age, HFA: height for age, WFH: weight for height)
° Median (range)
** WFA 26 out of 119, WFH 43 out of 346, HFA 78 out of 442*
§ Overall malnutrition was calculated as acute and chronic malnutrition (147 patients minus 20, because they were counted twice due to combined malnutrition (acute and chronic at the same time).

Table 2: Acute vs. chronic malnutrition

	Chronic % (n) N = 58	Acute % (n) N = 49	Combined % (n) N = 20	Sig.
Admission category				
Infectious	12.1 (7)	21.3 (10)	10.0 (2)	-
Surgical	32.8 (19)	23.4 (11)	30.0 (6)	-
Haemato-oncology	6.9 (4)	4.3 (2)	0.0 (0)	-
Gastroenterology	12.1 (7)	14.9 (7)	20.0 (4)	-
Underlying disease	77.0 (45)	42.0 (20)	95.0 (19)	§*
Prematurity	5.2 (3)	10.6 (5)	60.0 (12)	#*

(Sig: Significance)
° Median (range)
§ Significant difference between chronic and acute malnutrition
 # Significant difference between chronic and combined malnutrition
** Significant difference between acute and combined malnutrition*

Figure 2: Follow-up implementation

a dietician was consulted and nutritional interventions were initiated. The three risk group characteristics are shown in Table 3. Patients with a moderate or high-risk score were hospitalised for a significantly longer period of time in comparison to the low-risk group. Of the patients with a low-risk score, 57.9% were surgical. This differs significantly from the moderate and high-risk groups. No surgical patient had a high-risk score.

Evaluation of implementation

Figure 2 shows the tendency of notation of the STRONGkids score. Of all the scores, 82.6% were filled in by medical students (n = 46), compared to 17.4% by paediatric residents. All of the incorrect screenings were performed by medical students and were mostly underestimated.

Discussion

Anthropometric and nutritional assessment

This is one of few studies in Belgium that focuses on the prevalence of malnutrition in hospitalised children. The prevalence of malnutrition at admission in our tertiary hospital was 23.2%, with 14.8% suffering from acute malnutrition and 17.6% chronic malnutrition. Hospital stay was not prolonged in patients with malnutrition (acute, chronic, overall or combined).

The percentage of acute malnutrition is higher in comparison to the findings of Huysentruyt et al. in four Belgian hospitals (12.1%) and those of Joosten et al. in 52 Dutch hospitals (11%).[1,2] Their results were derived from combined research in secondary and tertiary hospitals. For chronic malnutrition, we found a prevalence of almost two times higher in contrast to the findings of Huysentruyt et al. in their tertiary hospital (9.5%),[1] while Joosten et al. reported a prevalence of 14% chronic malnutrition in the participating Dutch academic hospitals. Further findings by Joosten et al. show chronic malnutrition up to 18% in other European countries, which is more in line with our findings.[2] It seems likely that the highest prevalence of chronic malnutrition is to be found in tertiary hospitals, as more patients with severe and/or chronic disease are admitted there. This might explain our higher prevalence.

Acute malnutrition can occur at the same time as suffering from chronic malnutrition. In our study, these patients were placed in both groups. This is a possible explanation for our higher prevalence numbers for acute and chronic malnutrition. Nevertheless, when calculating overall malnutrition, no patients were counted twice. Furthermore, none of the studies mentioned above explained how they classified patients with both acute and chronic malnutrition. It is a combination measure, therefore, it could occur as a result of wasting, stunting, or both. This combined group in our study is characterised by significantly more patients with prematurity in their medical history. As a distinct number of these patients come from our Neonatal Intensive Care Unit, this seems an important

Table 3: Descriptives of the STRONGkids risk group

STRONGkids classification	Low % (n) N = 145	Moderate % (n) N = 177	High % (n) N = 14	Sig.
Age (months)°	68.2 (2-186)	36.6 (4-186)	7.8 (1-150)	#
Hospitalisation (days)°	3.0 (1-25)	4.0 (1-11)	4.0 (1-11)	#§
Admission category				
Infectious	12.4 (18)	19.8 (35)	7.1 (1)	-
Surgical	57.9 (84)	24.9 (44)	0.0 (0)	#§*
Haemato-oncology	0.0 (0)	15.3 (27)	21.4 (3)	#§
Gastroenterology	4.8 (7)	13.0 (23)	50.0 (7)	#§*
Underlying disease	42.1 (61)	61.6 (109)	85.7 (12)	#§
Malnutrition WFA	1.4 (2)	5.6 (10)	21.4 (3)	#§*
Malnutrition HFA	9.7 (14)	19.8 (35)	42.9 (6)	#§*
Malnutrition WFH	2.8 (4)	10.7 (19)	28.6 (4)	#§*
Chronic malnutrition	8.3 (12)	15.8 (28)	14.3 (2)	§
Acute malnutrition	2.8 (4)	11.3 (20)	21.4 (3)	§,#
Combined malnutrition	1.4 (2)	4.0 (7)	28.6 (4)	#*

(Sig: Significance, WFA: weight for age, HFA: height for age, WFH: weight for height)
° median (range)
§ Significant difference between the low and moderate-risk groups
 # Significant difference between the low and high-risk groups
** Significant difference between the moderate and high-risk groups*

finding. We believe mentioning this group could be more accurate in defining the different subtypes of malnutrition.

Only three patients were excluded because the patient files were not available for review. In total, a large group of patients was included. In this large group, both height and weight were measured for 83.8% of all patients admitted to the Paediatric Department. Only 70.3% of the measurements were noted in the growth chart. This poor registration of biometric data is striking, but above all disappointing. Also, more measurements should have been taken into account, like body mass index. SDS scores were digitally calculated but not shown in detail in the descriptive analysis. Joosten et al. and Huysentruyt et al. had more complete data. Joosten et al. included patients over three consecutive days, while Huysentruyt et al. targeted one hundred patients per hospital.[1,2] They conducted their studies during winter, while our periods were more widespread and unannounced, and therefore better simulated normal routines. Nevertheless, the final data seem comparable.

The anthropometric data were measured by nurses. Although the same calibrated weighing scales and height measurement tools were used for each measurement, data may be influenced by inter-observer variability. Moreover, ethnicity was not taken into account. Our patient population was composed of mostly native Belgians but they frequently have foreign backgrounds. Defining ethnicity and matching this with the appropriate growth curves was therefore impossible. Using the WHO Child Growth Standards might be considered in the future.

Screening for the risk of malnutrition

Data from the Netherlands, revealed that 80% of all children admitted to hospital are now screened for malnutrition. They show that due to this risk-screening with adequate intervention, the prevalence of malnutrition has dropped by 5% in 7 years (12% to 7%).[18] Despite notification of the importance and obligatory aspect of the screening for malnutrition by the hospital board, as well as introducing and repeating our study means, execution rate was low. In our study, 61.3% of the patients were screened for the risk of developing malnutrition. In the PICU, only 10.0% of the patients were screened. Because of these low numbers the data from the PICU on the STRONGkids score were excluded.

In contrast to other studies, there was no significant difference in length of hospital stay between patients with or without malnutrition.[1,2] However, when comparing the risk groups, hospital stay in the low-risk group was significantly shorter than in the group with moderate or high risk. Shortening the length of hospital stay is one main goal pursued to reduce health care costs. In this respect, defining patients with a high risk of malnutrition at admission could possibly reduce the length of hospital stay through early intervention. We also noted that almost all children who were categorised in the high-risk group had an underlying disease. Both findings are in line with the data of Hulst et al.[15] In addition, in Huysentruyt et al. most of the patients in the low-risk group were admitted because of infectious disease (50.6%), while our largest group were surgical patients (57.9%). This difference can be explained by the fact that more than one third of our patients were surgical, compared to approximately 10% in the study by Huysentruyt et al.[13]

An important finding of our study is the insufficient use of the expertise of the dietician, who was not involved in the notation of the STRONGkids score. For only 9 of 14 high-risk cases were nutritional interventions by dieticians undertaken, and on their own initiative, as it concerned chronic patients. We suggest a more active role by dieticians. Ideally, they should be informed when a high-risk score on the STRONGkids is noted. Preferably, they might also contribute to interception, prevention and treatment of malnutrition during admission.

Evaluation of implementation

The decrease in notation of the STRONGkids scores in month 3 and month 12 is remarkable. What could be noticed, is the fact that the last three days of month 3 covered a public holiday and the last three days of month 12 covered weekend days. Although underlying reasons for not performing the risk score were not specifically asked for, there seems to be not enough attention for screening children at the risk of malnutrition in general. Several reasons could be suggested, but are speculations. Found in literature, the most common noted barriers to nutritional risk screening were lack of training and lack of awareness.[19] We agree with Huysentruyt et al., who pointed out that it only takes 3 minutes to perform such screening.[19]

More importantly, however, is that 32.6% of the risk screening scores were incorrect. Most of the incorrect scores were underestimations and all of them were performed by medical students. These underestimated scores might explain the low percentage of patients classified as high risk (2.6%). With a prevalence of acute malnutrition of 14.8%, in theory many patients with a (high) risk of malnutrition could therefore have been missed out. The STRONGkids score could be a helpful tool to detect children at risk of malnutrition, but it seems too soon to tell. Further, the usage of the tool in the PICU setting can be discussed. Possibly, classifying all patients in the PICU as high risk should be considered because all patients admitted in critical care are at risk of malnutrition and should receive nutritional attention and support anyway.

In conclusion, this study provides additional information about the prevalence of malnutrition in hospitalised children in a tertiary hospital in Belgium. It also evaluates the implementation of the STRONGkids screening tool, a tool for signalling the risk of developing malnutrition. The prevalence found seems roughly comparable to other studies, but appears to be slightly higher. In addition to numbers for acute, chronic and overall malnutrition, we were the first to look at combined malnutrition. Our study also shows that the implementation of a new (screening)tool is not easy. The poor registration of notation of both biometric data and risk scoring was striking. Although no hard conclusions can be made, it suggests that more attention and training is needed on the subject of malnutrition in general. Therefore, it is definitely too soon to state that the implementation of the STRONGkids screening tool is an effective tool for defining risk groups in our patient population.

We conclude that not only malnutrition in hospitalised children still remains a problem, but also the poor registration of biometric data and risk screening is. More and constant awareness of this issue is needed. In Belgium, there is a need for a performance indicator rather than the current quality indicator.

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Current practice of gastro-intestinal endoscopy in children in Belgium.

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Key words

endoscopy, paediatric gastroenterology, oesophagogastroduodenoscopy, RIZIV/INAMI

Abstract

Introduction

In order to develop a paediatric-specific training curriculum, an attempt was made to document the number of gastro-intestinal endoscopic procedures performed in children in Belgium, in the North of the country and Brussels.

Methods

The national registration system, the "Rijksinstituut voor Ziekte- en Invaliditeitsverzekering"(RIZIV)/ "Institut National d'Assurance Maladie-Invalidité" (INAMI) has been contacted to provide data on endoscopic procedures in children and registration numbers of the physicians performing endoscopy. Each technical procedure that is performed is registered by its unique procedural code and registration number of the performing physician. Depending on the physician's specialty training, the registration number is different. This was compared to the numbers from the main paediatric gastroenterology services in the country, which provided their numbers to double check the accuracy of the numbers provided by the RIZIV/INAMI.

Results

The most frequently performed procedures were oesophagogastroduodenoscopy (OGD) (n=4410) and ileocolonoscopy (IC) (n=69). Compared to the information obtained by hospitals, the national registration system seems not to register all paediatric procedures performed by paediatricians. Paediatric endoscopy is performed in many centres in Belgium resulting in a relatively low number of procedures per endoscopist.

Discussion/conclusion

The different reasons for incomplete registration by the national registration system need clarification. According to the recommendations provided by different societies of Paediatric Gastroenterology, Hepatology and Nutrition, centralization of procedures could be beneficial for paediatric care as well was the recognition of the paediatric subspecialty. However, the instauration of an adequate national registration system should be the first goal.

Introduction

Gastro-intestinal endoscopy is increasingly performed in children since the 1960's. Healthcare policy emphasizes the importance of safety, quality and cost-effectiveness of care. A key aspect of paediatric gastroenterology practice is the ability to perform endoscopy in an efficient and safe way[1,2].

In Belgium, every paediatrician is allowed to perform endoscopy in children without any recognized training because paediatric gastroenterology is not recognized as a paediatric subspecialty by the Belgian government. Nevertheless, paediatric gastroenterology is recognized as a paediatric subspecialty in different European countries, the US, Canada and Australia. Similar to endoscopy in adults, performing an endoscopy in a child requires acquisition of technical, cognitive and integrative competencies to effectively diagnose and manage gastrointestinal disorders in children.

The first aim of the authors was to monitor current paediatric endoscopy practice in Belgium. Secondly, our aim was to compare these figures with data from different hospitals in Belgium and to investigate if these data correspond.

Once this information is obtained, recommendations about health care organisation can be formulated[2,3].

Methods

The national registration system, the "Rijksinstituut voor Ziekte- en Invaliditeitsverzekering"(RIZIV)/ "Institut National d'Assurance Maladie-Invalidité" (INAMI) was contacted to obtain information regarding different gastro-intestinal endoscopic procedures in children and the physician who performed the procedure. The RIZIV/INAMI was asked to provide the number of diagnostic endoscopic procedures performed including oesophagoscopy, oesophagogastroduodenoscopy (OGD), rectoscopy, left colonoscopy, total colonoscopy and ileocolonoscopy (IC). Therapeutic procedures were duodenal catheterisation, percutaneous endoscopic gastrostomy tube placement (PEG), oesophageal dilatation, retrieval of foreign bodies, polypectomy, treatment of oesophageal varices (banding/ligation) and treatment of bleeding. Each technical procedure performed is registered by its unique procedural code and the performing physician's registration number. Depending on the physician's specialty training, the registration number is different. Data from the year 2015 were obtained.

We contacted the head of paediatric gastroenterology department of different University Hospitals in Belgium, mainly Flanders and Brussels, and asked to provide complete figures of paediatric endoscopy performed in their hospital in 2015. We received data from 7 Hospitals: UZ Ghent (UZG), UZ Antwerp (UZA), UZ Leuven (UZL), HUDERF, St Luc, and KidZ Health Castle in Brussels (KHC).

Results

The RIZIV/INAMI provided the data from 2015. Endoscopic procedures are categorized in 2 categories depending on the age of the child: patients > 7 years of age or patients < 7 years of age. The former has the same procedural code as

an adult. As a consequence, the figures in older children are estimates. For the procedures performed in patients > 7 years, there is no differentiation possible between children (patients under the age of 16) and adults purely based on the procedural code. We therefore assumed that all procedures carried out by a paediatrician, were performed in children. This evaluation is merely a minimum of paediatric procedures as it remains unclear how many children > 7 years had endoscopic procedures done by adult gastroenterologists.

The investigated endoscopic paediatric procedures are divided in diagnostic and therapeutic procedures. The diagnostic procedures that are most frequently performed are oesophago-gastro-duodeno-scopy (OGD) (n= 4410) and (ileo-) colonoscopy (IC) (n=69).

1552 OGDs, or 0.5% of the total number of OGDs, were performed in children under 7 years old. 1498 (96.5%) OGDs were done by 64 paediatricians, in the other 3.5%, an adult gastroenterologist was the performing doctor. In patients older than 7 years, 2858 OGDs were performed by 62 paediatricians. Consequently, at least 4410 OGD's were registered in children, performed by 64 different paediatricians (Table 1). 3044/4410 (69%) of these procedures were performed in 6 university centres: 720 in the KidZ Health Castle, 643 in UZ Leuven, 380 in UZ Ghent, 190 in UZ Antwerp, 604 in HUDERF Hospital and 507 in St Luc Hospital (Table 3,4).

Table 1

Procedure (code)	N	Paed	KHC	UZG	UZL	UZA	HUDERF	St Luc
Total amount of upper diagnostic endoscopies in children			719	380	643	190	604	507
esophagoscopy (472356)			3					
<7years	4	1						
≥7years	2758	4						
fibroduodenos-copy (473056)			716		643	190	604	507
<7years	1552	1498	402		231	85		
≥7years	322144	2858	314		412	105		

According to the National Registry, rectoscopy in children <7 years old, was performed 95 times. During 2015, the registration code of rectoscopy changed, resulting in less reliable numbers.

The registration counted 35 rectoscopies by a paediatrician, 48 by a surgeon and 12 by an adult gastroenterologist. 92% of the rectoscopies were in children under the age of 7 years old. In older children, most rectoscopies were done by surgeons resulting in unreliable figures in children between 7 and 16 years old. We were not possible to collect separate data from the different endoscopic centres.

Table 2: Data RIZIV/INAMI compared to hospital registration

Procedure (code)	N	Paed	KHC	UZG	UZL	UZA	HUDERF	St Luc
left colonoscopy/ rectosigmoidos-copy (472452)			143		78		40	
<7years	152	135	109		32			
≥7years	51579	117	34		46			
total colonoscopy (473174)			33		26		29	
<7years	17	17	10		7			
≥7years	97731	54	23		19			
ileoscopy (473432)			38		104	55	50	65
<7years	8	5	8		14	18		
≥7years	62371	61	30		90	37		

N= number according to the RIZIV/INAMI data provided
Paediatricians = number of paediatric endoscopists according to the RIZIV/INAMI data

Left colonoscopy/rectosigmoidoscopy was performed 152 times in children under the age of 7 years. In 135 cases (89%), the procedure was carried out by a paediatrician; the others were mainly performed by adult gastro-enterologists. In patients above 7 years old, left colonoscopy was performed 117 times by 30 different paediatricians. 269 left colonoscopies were nationally registered in 2015, performed by at least 23 different paediatricians. The number of total colonoscopies performed in children was 71, by 20 different paediatricians. 23.9% of the colonoscopies were in children under the age of 7 years.

143 left colonoscopies were performed in the KHC. If the data from the RIZIV/ INAMI are correct, 109 (71% of total) left colonoscopies in the younger group were performed in the KHC, and 34/117 in children > 7 years old (Table 2, 3,4).

The total number of ileocolonoscopies registered in children was 69, performed by 10 paediatricians. About 11.6% (n=8) of the ileocolonoscopies in children was performed in children under the age of 7. In our hospital, we counted 38 procedures in all children. In the UZA, 55 ileocolonoscopies were performed (18 < 7) and in the Saint-Luc Hospital 65 paediatric ileocolonoscopies were carried out (Table 2,3,4). In Leuven and in Huderf, respectively 104 and 50 ileocolonoscopies were performed in 2015.

The therapeutic procedures considered are: PEG placement, oesophageal dilatation, retrieval of foreign bodies, polypectomy, treatment of oesophageal varices (banding/ ligation) and treatment of bleeding.

The national registry counted 41 gastrostomies in children <7 years old, performed by 33 different paediatricians, and at least 66 paediatric procedures in older children. In our hospital, KHC, we counted 24 gastrostomy placements, 25% of the total procedures. In the HUDERF Hospital, they registered 2 gastrostomies by paediatricians. In the UZA, 30 gastrostomy placements occurred in 2015, 22 in children under the age of 7 and 8 in older children (Table 3,4). In UZL, another 5 gastrostomy placements were performed.

According to the data from the RIZIV/INAMI, oesophageal dilatation was registered 26 times in children <7 years old, and was performed by only four paediatricians. Of the 827 oesophageal dilatations in patients above 7 years old, only one was registered as performed by a paediatrician, the rest was, according to the national registry, performed by surgeons. No adult gastroenterologists were registered in the RIZIV/INAMI data. However, in our centre, oesophageal dilatation was done 13 times, mainly in young children (n=12). In the UZA and the HUDERF, 4 dilatations were done in each centre. In UZL, 18 dilatations were done, 7 in children under the age of 7, and 11 in older children.

Removal of foreign bodies was registered 104 times in young children, 60 times done by a paediatrician and at least 21 times in children of 7 or older. In KHC, we registered 30 of these procedures, 16 in children <7 years old, 14 times in older children. Also, in the HUDERF hospital, 16 removals of foreign bodies were carried out. We do not have the data of the other hospitals (Table 3,4).

Polypectomy was registered 3 times in children under the age of 7 by the RIZIV/ INAMI. In the KHC we performed in total 7 polypectomies, 5 times in children under the age of 7, 2 times in older children. Also in the UZA and UZL, 3 polypectomies were registered in total; and 6 polypectomies in HUDERF (Table 3,4).

According to the data from the RIZIV/INAMI, endoscopic treatment of oesophageal varices was only performed once in a child <7 years old, and this procedure was done by an adult gastroenterologist.

Above 7 years old 4 ligations were performed by 2 paediatricians (Table 1,2). However, according to the data we collected, one variceal treatment was done in a child under the age of 7, and 3 were done in older children, by a paediatrician in the KHC (Table 3,4). Another two and one were registered respectively in the UZL and HUDERF.

Discussion

Our findings allow two important conclusions. First, the figures from the national registration system seem not in agreement with the data we collected from the different University Hospitals, suggesting an underregistration by the RIZIV/INAMI both for diagnostic and therapeutic procedures. For example, about 70% of OGD were performed in five different hospitals from which we collected data. Regarding ileocolonoscopy, data of three hospitals are almost the double of the registered numbers by the government. Regarding therapeutic endoscopic procedures, most obvious for polypectomy and variceal ligation, an underregistration by the RIZIV/ INAMI is clear. Three polypectomies were registered by the RIZIV/INAMI but five were performed in KHC, one hospital only, which was an unexpected finding. Also considering gastrostomies, are the numbers incorrect or are they unclear, because part has been carried out by surgeons. A reason for this underregistration can be

that the RIZIV/INAMI serves as an insurance organization, and does not act as an official registration database of all medical data. A possibility is that registration by the hospital and/or the endoscopy performers is incorrect.

The main goal is to make health insurance correct and affordable by the government. The RIZIV/INAMI receives data depending on the certificates with the correct registration code on it, that are provided by the doctors and the hospitals. They depend on the mutuality, the health insurance companies and communication to the RIZIV/INAMI of the latter.

Secondly, as the number of performing physicians is high compared to the total number of endoscopies performed, we may argue that the lower patient load may influence endoscopic skills. Good news is that the largest amount of endoscopy is performed in university hospitals following the available data and therapeutic procedures are carried out by only a small group of paediatricians. 68,8% of diagnostic upper endoscopies is carried out in the, in this article mentioned, 6 University Hospitals. Considering lower diagnostic endoscopies, 409 paediatric procedures were registered by the RIZIV/INAMI, were as in the 6 University Hospitals mentioned before: 661 lower endoscopies were counted, 60% more than the RIZIV/INAMI show.

Since paediatric gastroenterology is not a recognized subspecialty, the physician registration number does not allow us to differentiate between a paediatric gastroenterologist and a general paediatrician with a specific interest in gastroenterology.

There is general consensus that experience and thus activity and exposure are mandatory conditions to deliver high quality health care. Especially diagnostic endoscopy is performed in many centres in Belgium resulting in a relatively low number of procedures per paediatrician.

The latter together with our first finding, suspicion of incomplete and incorrect registration, can be questioned when considering quality of care. Recent studies showed that emergency department visits and readmissions after endoscopic procedures vary significantly across different hospitals. There is a decreasing trend of readmission secondary to the performed procedure when this was carried out in a centre with a high frequency [5,6]. The relation between procedural volumes and morbidity is well-documented in the adult population. Paediatric endoscopy is, as important as adult care, a target for quality improvement of medical care [5,6]. The first step towards improvement of the quality of healthcare might be governmental recognition of the subspecialty. This would guarantee that the majority of paediatric endoscopic procedures will be performed by a subspecialist, well-trained paediatricians. It would be preferable to demand a proof of continuous education, training, and activities over the past years.

Centralization of (a part of the) procedures, together with uniform standards of registration across centres will improve and ensure data collection. This improvement of national multicentrea data is extremely helpful for benchmarking purposes when tracking individual institutional data and developing quality programs for paediatric endoscopic procedures. Monitoring the quality of paediatric endoscopy can help identify potential areas for intervention [7].

Over the past decades, the incidence of endoscopy in children has increased. The most frequently performed endoscopic procedures in children are diagnostic OGD and left colonoscopy. The number of paediatricians performing therapeutic endoscopic procedures remains small (Table 3, [8]).

Adult gastroenterologists are allowed to perform endoscopies in children. Some therapeutic procedures are so seldom in children that they are preferably performed by an adult gastroenterologist who have much more technical experience. But endoscopy is more than the technical act: indication and interpretation of findings differ between children and adults. Paediatric endoscopic procedures require an adequate setting in a child-friendly environment with paediatric-sized equipment. Moreover, paediatric gastrointestinal disease origin, course and treatment purposes differ from adult GI disease. Thus, correct indications, disease stratification, appropriate and adapted communication with children of different age and their parents, require an experienced team of dedicated nurses, anaesthesiologists and doctors. Concluding that paediatric healthcare is high-specialized care [9].

Conclusion

Paediatric endoscopy should be part of the national program towards ¬optimisation of paediatric care through quality improvement and patient-oriented medicine. The reasons for incomplete registration by the national registration system need clarification. There is a need to monitor current practice in paediatric endoscopy correctly and to use the results of this monitoring to improve quality of care. Consequently, the instauration of an adequate national registration system should be the first goal. Governmental recognition of the subspecialty would guarantee that endoscopy is performed by well-trained paediatric gastroenterologists.

Consequently, a specific training curriculum in paediatric gastroenterology should be put in place, as it is already today in many other countries.

Acknowledgements:

The authors thank all paediatricians from the different University Hospitals to share their registration of endoscopic procedures.

Table 3: Data according to national registration by RIZIV/INAMI

Procedure (code)	N	Paed	N° paed	surg	Adult GE
esophagoscopy (472356)					
<7years	4	1	1	0	0
>7years	2758	4	4	1	1330
fibroduodenoscopy (473056)					
<7years	1552	1498	64	0	53
>7 years	322144	2858	62	1014	310625
duodenal catheterisation (112254)					
<7 years	4	3	3	0	0
>7 years	212	99	3	20	18
duodenal catheterisation (474272) in child <7 years old	29	33	5	0	0
left colonoscopy/ rectosigmoidoscopy (472452)					
<7 years	152	135	23	0	16
>7years	51579	117	30	586	49342
total colonoscopy (473174)					
<7years	17	17	8	0	0
>7 years	97731	54	20	892	94795
ileoscopy (473432)					
<7 years	8	5	2	0	3
>7 years	62371	61	10	0	60936
esophageal dilatation (472091)					
<7 years	26	26	4	0	1
>7 years	827	1	1	826	0
treatment varices (473270)					
< 7 years	1	0	0	0	1
>7 years	536	4	2	0	532
treatment of bleeding (473771)	793	0	0	0	793
removal foreign body (472393)					
<7 years	104	60	26	0	39
>7 years	3083	21	13	7	2904
gastrostomy (355950)					
<7 years	41	33	10	1	4
>7 years	883	66	14	26	758
polypectomy (473211)					
<7 years	3	2	2	0	1
>7 years	60474	3	3	0	60471
rectoscopy (472511) > 7 years old	46058	8	5	4429	40008
rectoscopy in child <7 years old	95	35	15	48	12

Table 4: Data RIZIV (N) compared to registration in different hospitals

Procedure (code)	N	Paed	KHC	UZG	UZL	UZA	HUDERF	St Luc
Total amount of endos-copies in children			719	380	643	190	604	507
esophagoscopy (472356)			3					
<7years	4	1						
>7years	2758	4						
fibroduodenoscopy (473056)			716		643	190	604	507
<7years	1552	1498	402		231	85		
>7 years	322144	2858	314		412	105		
duodenal catheterisation (112254)								
<7 years	4	3			7			
>7 years	212	99			6			
rectoscopy (472511)								
<7 years	61	2			7			
> 7years	46058	8			5			
left colonoscopy/ rectosigmoidoscopy (472452)			143		78		40	
<7 years	152	135	109		32			
>7years	51579	117	34		46			
total colonoscopy (473174)			33		26		29	
<7years	17	17	10		7			
>7 years	97731	54	23		19			
ileoscopy (473432)			38		104	55	50	65
<7 years	8	5	8		14	18		
>7 years	62371	61	30		90	37		
esophageal dilatation (472091)			13				4	
<7 years	26	26	12		7	4		
>7 years	827	1	1		11	0		
treatment varices (473270)			4				1	
< 7 years	1	0	1		0			
>7 years	536	4	3		2			
treatment of bleeding (473771)	793	0						
removal foreign body (472393)			30				16	
<7 years	104	60	16					
>7 years	3083	21	14					
gastrostomy (355950)			24				2	
<7 years	41	33	12		4	22		
>7 years	883	66	12		1	8		

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From unexplained gastro-intestinal complaints to a nephrologic diagnosis.

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Key words

Gastro-intestinal complaints. Pelvic ureteric-junction stenosis. Renal tubular acidosis. Bartter syndrome.

Abstract

In clinical practice patients present to physicians with various gastro-intestinal symptoms on a daily base. Sometimes the diagnosis is clear-cut, but in many patients further investigations are needed. In some cases, the etiology can be surprisingly outside the gastro-intestinal tract.
We illustrate this with 3 case-reports in which a thorough history eventually offered the clue to the right diagnosis.

Kinderen presenteren zich dagelijks met verschillende gastro-intestinale klachten bij de dokter. Soms is de diagnose meteen duidelijk, maar bij veel patiënten is verder onderzoek noodzakelijk. In sommige casussen vinden we de diagnose verrassend buiten de gastro-intestinale tractus. We illustreren dit aan de hand van 3 casussen waarbij enkele sleutelpunten leiden tot de juiste diagnose.

Introductie

Buikpijn, diarree, constipatie en niet gedijen zijn vaak voorkomende symptomen waarvoor de kinderarts geconsulteerd wordt. Meestal komt men snel tot een diagnose, maar soms is verder onderzoek noodzakelijk. Door ook buiten de gastro-intestinale context te denken, kunnen onverklaarde gastro-intestinale klachten soms toch tot een sluitende diagnose leiden.

We illustreren dit aan de hand van 3 casussen waarbij gastro-intestinale klachten leiden tot een nefrologische diagnose.

Case series

Patiënt A, een jongen van 12 jaar, consulteerde de kindergastro-enteroloog met meer dan een jaar bestaande recidiverende episodes van buikpijn. Hij had last van stekende pijn, afwisselend rechts en links, misselijkheid en een vol gevoel na de maaltijd. Gewicht en lengtegroei waren goed. Bloeddruk was normaal. Klinisch onderzoek toonde geen afwijkingen behoudens drukpijn t.h.v. het epigastrium en het linker hypochonder.

Differentiaal diagnostisch werd gedacht aan: functionele dyspepsie, reflux, constipatie, gastritis, infectie, vertraagde maaglediging, inflammatoire darmziekten en coeliakie.

In het verleden waren een C13-ureumademtest en lactose-ademtest negatief. Een bloedname met o.a. bloedbeeld, lever- en nierfunctie, schildklierfunctie en anti-tissue transglutaminase toonde geen afwijkingen. Feceskweken en echografie van het abdomen waren normaal. Een maagontledigingscan toonde een vertraagde lediging. Een proefbehandeling met Erythromycine had geen invloed op de klachten.

Een jaar na presentatie bleven de klachten persisteren met hierbij dagelijks waterige diarree. De buikpijn ontstond steeds na eten en drinken.

Endoscopie toonde geen bijzonderheden. De zweettest was negatief. Er werd een expectatief beleid gevoerd.

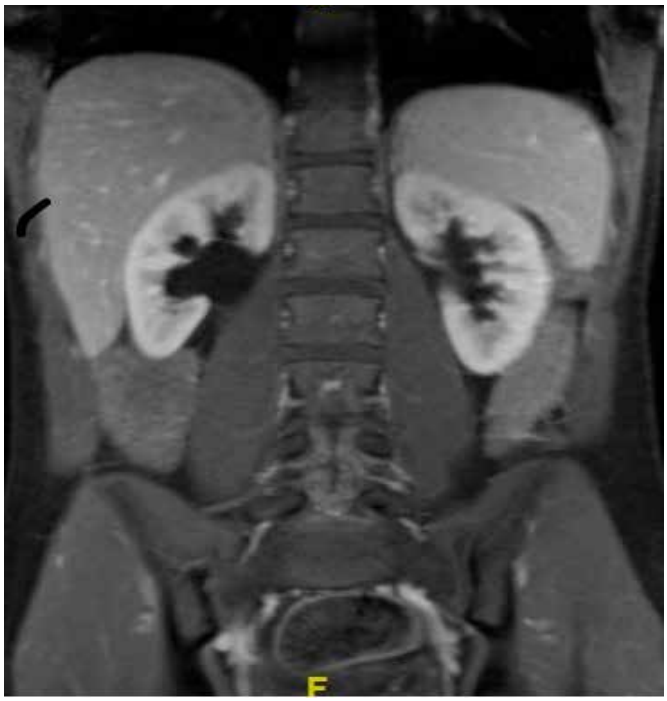
Na bijna 3,5 jaar klachten viel bij een controle raadpleging op dat hij rugklachten vertoonde bij neerliggen. Bij nader onderzoek bleek deze pijn eerder gelokaliseerd ter hoogte van de flanken. Differentiaal diagnostisch werd gedacht aan een nefrologische oorzaak, ondanks een normale echografie van de nieren/urinewegen. Bij sterk vermoeden van onderliggende organische oorzaak en persisteren van de klachten na eten en drinken werd een MRI enterografie uitgevoerd. Dit toonde een bilaterale pyelo-ureterale junctie (PUJ)-obstructie (figuur 1) en de patiënt werd doorverwezen naar de kindernefroloog en kinderuroloog. Een MAG III-scan toonde een bilateraal obstructief renogram met nog symmetrische nierfunctieverdeling met nagenoeg geen respons op furosemide (figuur 2). Tijdens het onderzoek werd de pijn uitgelokt. Er werd bilateraal een laparoscopische pyeloplastie uitgevoerd, waarna deze jongen tot op heden klachtenvrij is. Er bleek bilateraal sprake van een anatomisch milde intrinsieke obstructie.

Patiënt B, een meisje van 9,5 maand oud, ex-prematuur van 31 weken, werd verwezen naar de kindergastro-enteroloog met ernstige therapieresistente constipatie. Zij vertoonde een goede groei en geen andere klachten.

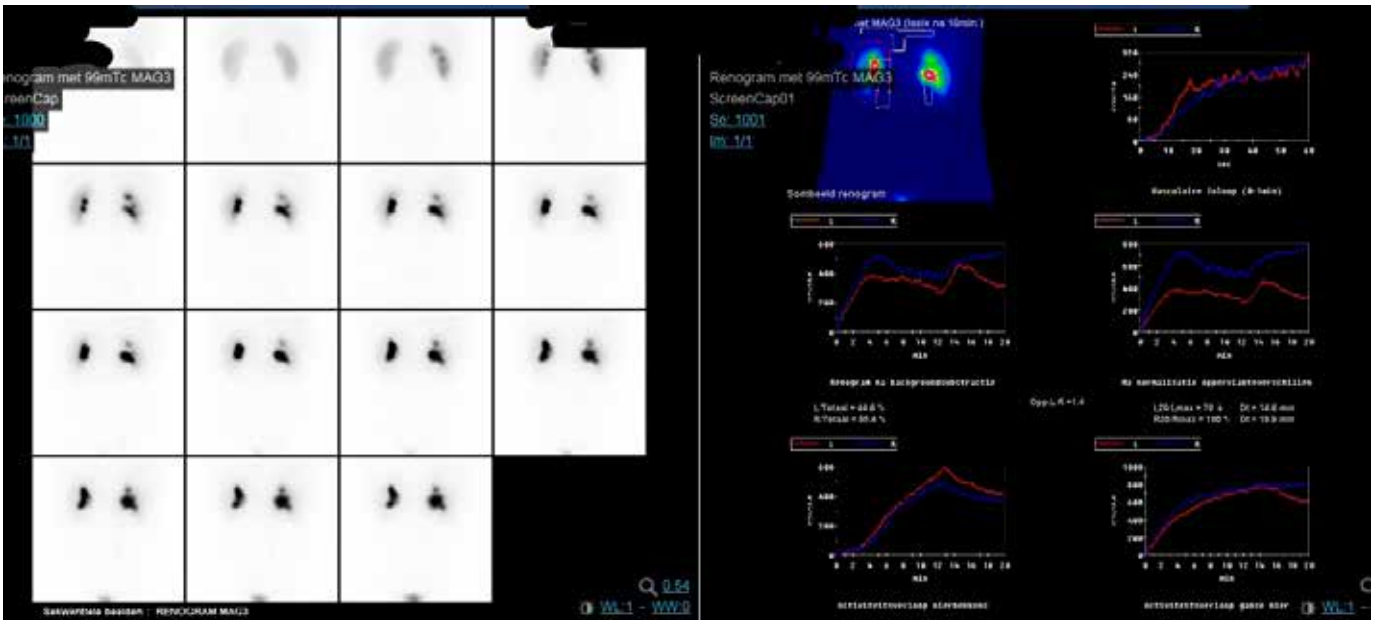
Differentiaal diagnostisch werd gedacht aan allergie, coeliakie, hypothyreoïdie, infectie, ziekte van Hirschsprung, mucoviscidose en metabole aandoeningen.

Er werd uitgebreide diagnostiek ingezet: bloedname, huidpriktesten, rectumbiopten, oesofagogastroduodenoscopie, coloninloop, colon transitstudie en zweettest waren alle normaal.

Figuur 1: MRI bij patiënt A toont een bilateraal gedilateerd pyelocalcieel stelsel, rechts meer dan links, verdacht voor pyelo-ureterale junctie obstructie



Figuur 2: MAG III scan bij patiënt A toont een bilateraal obstructief renogram met nog symmetrische nierfunctieverdeling met nagenoeg geen respons op furosemide



Na enkele maanden bleek er ook sprake van een moeizame voedingsintake, vermoeidheid en een afbuigende groeicurve van Percentiel(P) 25 naar P10.

Urinecollectie met fractionele ionenexcretie toonde een laag normale fractionele natriumexcretie, een lage fractionele kaliumexcretie en laag normale fractionele chloorexcretie (0.05%). Bloedname toonde een milde metabole hyperchloremisch acidose met normale serum anion gap. Een positieve anion gap en een pH van 8 (5.5 - 6.5) in de urine bevestigden de diagnose van renale tubulaire acidose. Bij een aanzuringstest met ammoniumchloride evolueerde de urine pH tot 4, passend bij de diagnose van een proximale renale tubulaire acidose (RTA). (tabel 1)

Een proefbehandeling met kaliumcitraatsuppletie gaf een spectaculair resultaat met binnen een maand normalisering van de stoelgang, toename van de eetlust, het lichaamsgewicht, en activiteit. Genetisch onderzoek toonde een heterozygote mutatie in het ATP6V04 gen (c.2035G>T) passend bij een partiële RTA.

Patiënt C, een meisje van bijna 8 maanden, werd opgenomen in een perifeer ziekenhuis met braken en koorts waarbij de diagnose pyelonefritis werd gesteld. Zij was reeds gekend met recidiverende episodes van braken, chronische constipatie en een afbuigend gewicht (p25 naar p3). Verder was zij een weinig actief meisje met vertraagde grove motoriek.

Bloedname toonde een opvallende metabole alkalose met bicarbonaat 35 mmol/L, hypokaliëmie 2,6 mmol/L, hyponatriëmie 131 mmol/L en hypochloremie van 79 mmol/L, geduid als passende bij het braken. Gezien een snelle klinische verbetering na intraveneuze vochttherapie, werd de bloedname niet meer herhaald. Daags na de hospitalisatie vertoonde zij echter recidief braken waarbij een gelijkaardig gestoord ionogram (tabel 1) werd gezien.

De metabole alkalose met gestoord ionogram in combinatie met de failure to thrive, vertraagde grove motoriek en chronische constipatie, rees het vermoeden op een Barttersyndroom. Zij werd doorverwezen naar ons universitair ziekenhuis alwaar naast de hypokaliëmische en hypochloremische alkalose ook een sterk verhoogd aldosteron van 788 pg/ml (referentie in rust 10-105 en bij activiteit 34-273) werd aangetoond.

Urine toonde een sterk verhoogde fractionele natriumexcretie en verhoogde kaliumexcretie (tabel 1). Fractionele chloorexcretie was normaal. Mucoviscidose werd met een zweettest uitgesloten.

Behandeling met indometacine, kaliumfosfaat en magnesiumoxide toonde een snelle klinische en biochemische respons, snelle inhaalgroei en tevens een vooruitgang van de psychomotoriek. Genetische onderzoek bevestigde een homozygote mutatie in het CLCNKB gen, passend bij Barttersyndroom type III, de klassieke milde vorm.

Discussie

Patiënt A presenteerde zich met chronische buikpijn. De diagnose van bilaterale PUJ stenose werd gesteld.

PUJ stenose is de meest voorkomende obstructieve laesie bij kinderen en wordt meestal veroorzaakt door een intrinsieke stenose van de proximale ureter. De meest voorkomende symptomen van een PUJ stenose zijn buikpijn, intermittente flankpijn, nausea en braken. Soms is er sprake van een urineweginfectie, hematurie of een niersteen, soms zijn er helemaal geen klachten.[1,2]

Een PUJ stenose wordt vermoed bij echografische hydronefrose en bevestigd middels renogram. Pijn uitgelokt door furosemide is nagenoeg pathognomonisch. Bij mildere graad van stenose of bij intermittente obstructie is een hydronefrose echter niet continu aanwezig. Echografie tijdens een acute pijnepisode is dan essentieel en kan soms duidelijkheid brengen. Bij sterke verdenking ondanks normale echografie kan een MRI scan nuttig zijn. [1,2] In deze casus bracht specifiek MRI enterografie de diagnose aan het licht doordat de patiënt veel moest drinken als darmvoorbereiding.

Intermittente flankpijn, nausea en uiteindelijk rug/flankklachten waren de sleutels voor de diagnose in deze casus. Hij vertoonde opvallend meer last na grote hoeveelheden eten en drinken, vermoedelijk door plotse urineflow/hydronefrose. Achteraf was het drinken afzonderlijk niet goed bevraagd, maar dit was waarschijnlijk niet excessief juist omwille van de onderliggende buikklachten. Zijn klachten van diarree en de vertraagde maagontlediging hadden vermoedelijk niets met deze diagnose te maken, maar brachten ons wel op een dwaalspoor.

In kader van de vertraagde maagontlediging zijn er geen evidence based richtlijnen bij kinderen. De ervaring berust voornamelijk op de expertise bij volwassenen. Scintigrafie lijkt bij kinderen een betrouwbaar en sensitief diagnosticum, naast andere methodes zoals bijvoorbeeld motiliteitscapsuletesten. Naast dieetadviezen zijn prokinetica zoals erythromycine een hoeksteen in de behandeling bij volwassenen. Bij kinderen zijn de studies beperkt en geeft erythromycine een wisselend effect. [3,4,5]

Table 1: Laboratoriumwaardes van serum en urine van casus B en C

	Natrium serum (136 -145 mmol/L)	Kalium serum (3.4-4.7 mmol/L)	Chloor serum (98-107 mmol/L)	Bicarbonaat serum (21-32 mmol/L)	Anion gap serum (7-16)	PH serum (7,35-7,45)	PH urine (5.5-6.5)	Fractionele Excretie Natrium	Fractionele Excretie Kalium	Anion gap urine
Tubulaire acidose	143	3.5	119	17	7	/	8	0,03%	1%	8
Bartter	132	2,7	86	34	11	7,57	/	16%	12%	/

Patiënt B en C komen bij de kinderarts met constipatie en braken.

De diagnose van proximale renale tubulaire acidose werd bij patiënt B gesteld.

Een proximale RTA wordt veroorzaakt door een verminderde proximale bicarbonaat reabsorptie, resulterend in een dalend bicarbonaat. Dit kan geïsoleerd voorkomen, zoals in patiënt B, of zich manifesteren als een algemeen tubulair defect (Fanconisyndroom).

Geïsoleerde proximale RTA is een zeldzame aandoening, waarbij kinderen zich meestal in het eerste levensjaar presenteren met groeifalen, herhaaldelijk braken en voedingsproblemen. Andere symptomen zijn polyurie, constipatie en verminderde tonus.[6]

De voedingsproblemen, afbuiging van het gewicht en de milde metabole hyperchloremische acidose deden in deze casus RTA vermoeden. De fractionele excretie van ionen (tabel 1) is een belangrijk hulpmiddel in de diagnose. In deze casus zijn de afwijkingen echter minder typisch.

Bij patiënt C wordt de diagnose van Bartter syndroom gesteld.

Bartter syndroom is een zeldzame autosomaal recessieve stoornis, waarbij het primaire defect een verstoring is in een van de transporters van het NaCl kanaal in de lis van Henle. Dit leidt tot een verstoorde NaCl-reabsorptie wat leidt tot een milde volume depletie en activatie van het renine-angiotensine-aldosteron systeem. Dit leidt vervolgens tot secundair hyperaldosteronisme, hypokaliëmie en metabole alkalose. Urine toont een normale tot hoge urinaire chloorconcentratie. Andere klinische kenmerken zijn vertraagde groei en ontwikkeling, recurrente episodes van dehydratatie, polyurie en polydipsie, braken en constipatie. Constipatie is vermoedelijk een combinatie van verminderde darmmotiliteit door de chronische hypokaliëmie en polyurie. Spierzwakheid is een direct effect van de hypokaliëmie.[7]

De combinatie van failure to thrive, vertraagde motorische ontwikkeling en weinig actief zijn (als uiting van spierzwakte), constipatie en de afwijkende biochemie, waren in deze casus suggestief voor een Barttersyndroom.

Conclusie

Met deze 3 ziektegeschiedenissen presenteren wij u enkele sleutels in de anamnese, het klinisch onderzoek en de aanvullende onderzoeken, om sneller tot de juiste diagnose te komen en overbodige invasieve onderzoeken te voorkomen.

Klachten zoals flankpijn, rugklachten, voedingsgerelateerde klachten, aanhoudend braken, therapieresistente constipatie, klachten sinds de geboorte, polyurie en polydipsie, failure to thrive of niet gedijen zijn allen sleutelpunten om verder te denken.

Bijkomende klachten als diarree in patiënt A kunnen ons op een dwaalspoor brengen waarbij we minder snel geneigd zijn om buiten de gastro-enterologische context te denken.

Er is tevens niet altijd sprake van alarmsymptomen waardoor we minder snel denken aan een organische oorzaak. Zo werd er bij patiënt A initieel gedacht aan functionele dyspepsie en bij patiënt B aan functionele constipatie. Zij voldeden beiden aan de desbetreffende diagnostische criteria (tabel 2)[8,9].

Bij patiënt A en B werden een uitgebreid scala aan aanvullende onderzoeken verricht, meer dan wat de richtlijnen op dat moment zouden aanbevelen. Het niet pluis gevoel van de behandelende artsen speelt hierbij zeker een rol. We raden echter aan vroegtijdig in de oppuntstelling minder invasieve onderzoeken uit te voeren, zoals fractionele urinaire excreties van ionen, serum biochemie en een echo abdomen om zo nefrologische/urologische diagnoses sneller aan het licht te brengen. Hierbij is het belangrijk deze onderzoeken zo veel mogelijk uit te voeren op het moment van de klachten.

Hiernaast raden we aan om selectief te blijven bij het aanvragen van deze onderzoeken en steeds kritisch na te denken bij welke patiënten en dit zinvol kan zijn. RTA en Bartter syndroom zijn zeldzaam en vaak voorkomende oorzaken dienen altijd hoger in de differentieel diagnose te blijven staan. Echter bij niet-pluis gevoel, persisterende klachten of anamnestische aanknopingspunten kunnen bovenstaande onderzoeken hulp bieden. Een multidisciplinaire benadering met het advies van een kindernefroloog is hierbij zeker een meerwaarde.

Tabel 2: Rome IV diagnostische criteria voor functionele dyspepsie en functionele constipatie[8,9]

Diagnostische criteria voor functionele dyspepsie[8] Gedurende 2 maand tenminste 1 van de volgende storende symptomen minimaal 4 dagen per maand:
Postprandiaal vol gevoel
Vroeg verzadigingsgevoel
Epigastrische pijn of brandend gevoel niet geassocieerd met defecatie
Na gepaste evaluatie geen verklaring voor de symptomen door een andere medische aandoening
Diagnostische criteria voor functionele constipatie bij niet zindelijke kinderen tot 4 jaar[9] Gedurende 1 maand tenminste 2 van de volgende:
2 of minder defecaties per week
Verhaal van excessieve stoelgangsretentie
Verhaal van pijnlijke of harde darmbewegingen
Verhaal van grote diameter stoelgang
Aanwezigheid van een grote faecale massa in het rectum

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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.

Pampers® Aqua Pure babydoekjes bestaan voor 99% uit gezuiverd water, bevatten biologisch katoen en een lotion met unieke pH-buffer functie voor een milde en beschermende reiniging van de gevoelige babyhuid.

- Dermatologisch getest
- Geschikt voor de huid van de pasgeborene
- Bevat biologisch katoen
- 99% gezuiverd water
- 0% alcohol, parabenen, phenoxyethanol, kleurstoffen, parfum

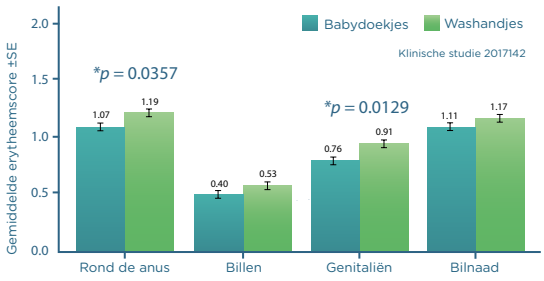
Een nieuwe klinische studie toont aan dat Pampers Aqua Pure-babydoekjes minstens even mild en zacht zijn als een washandje en water

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

- Natriumbenzoaat
- EDTA
- PEG-40 Gehydrogeneerde castorolie
- Citroenzuur
- Natriumcitraat
- Sorbitan Caprylaat

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.

De Pampers® Aqua Pure babydoekjes bevatten:

Geen alcohol
Geen parfum
Geen parabenen
Geen phenoxyethanol
Geen kleurstoffen
Geen chloorbleekmiddel

[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

Antibiotic prophylaxis and immunization in children with a functional or anatomical asplenia.

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Key words

Asplenia, overwhelming postsplenectomy infection, postsplenectomy sepsis, immunization, antibiotic prophylaxis

Abstract

The spleen plays a key role in the immune system, bridging the innate and adaptive immune response and is essential for the protection against encapsulated organisms (e.g. S. pneumoniae, H. influenza and N. meningitidis). Therefore, patients with an anatomical or functional asplenia are at increased risk for OPSI (overwhelming postsplenectomy infection), in literature also called PSS (postsplenectomy sepsis). In case of OPSI the mortality is very high, more than 50%. The risk of developing OPSI decreases with an adequate antibiotic and immunization policy. Besides antibiotic prophylaxis and immunization, education of the patient and health care worker plays an important role in reducing mortality rate. In this article we propose a guideline on vaccination, antibiotic prophylaxis and other preventive measures, appropriate to the Belgian situation.

Casus

Een jongen van acht jaar ondergaat een dringende splenectomie na miltruptuur bij een fietsongeval. Hij was voorheen gezond en werd volledig gevaccineerd volgens het Vlaams basisvaccinatieschema. De kinderarts van wacht wordt gecontacteerd voor het verder beleid. Moeten er extra vaccinaties gegeven worden? Zo ja welke en op welk tijdstip? Moet antibioticaprofylaxe opgestart worden? Zijn er andere belangrijke maatregelen die in acht moeten genomen worden?

Inleiding

De milt is een belangrijk orgaan met zowel een filterfunctie (verwijderen van oude rode bloedcellen en celpartikels) als een immunologische functie en is van essentieel belang bij de immuunrespons ten opzichte van gekapselde bacteriën. Er is een duidelijke associatie aangetoond tussen asplenie en een verhoogde kans op infectieuze complicaties met name OPSI (overwhelming postsplenectomy infection). De mortaliteit bij een OPSI is zeer hoog en bedraagt volgens de literatuur tot meer dan 50%. Het risico op het ontwikkelen van een sepsis neemt af bij een adequaat antibiotica- en vaccinatiebeleid. Ook wordt gezien dat wanneer zowel de patiënt als de zorgverlener voldoende geïnformeerd zijn, de mortaliteit kan teruggebracht worden tot 10% [1-2]. Op heden worden internationaal verschillende protocollen in verband met antibioticaprofylaxe en vaccinatiebeleid gehanteerd. Het doel van dit artikel is om, op basis van een literatuurstudie en een studie van bestaande internationale protocollen, te komen tot een richtlijn, aangepast aan de Belgische situatie.

Methodologie

Om te komen tot een voorstel voor een richtlijn, bruikbaar in België werd een literatuurstudie uitgevoerd. Hiervoor werd gebruik gemaakt van Pubmed en de Cochrane library. De volgende zoektermen werden gebruikt: asplenia, hyposplenia, antibiotics-asplenia, antibiotics-hyposplenia, immunization, vaccination, splenectomy.

Om tot een vergelijking van bestaande richtlijnen in verschillende landen te komen met name Verenigde Staten, Verenigd Koninkrijk, Nederland en België werden de volgende elektronisch beschikbare bronnen gebruikt: Centers for Disease control and Prevention (CDC, Verenigde Staten), The Green Book (Verenigd Koninkrijk), Rijksinstituut voor Volksgezondheid en milieu (RIVM, Nederland) en Hoge Gezondheidsraad (HGR, België). De gevonden richtlijnen worden naar voor gebracht aan de hand van een casus.

Resultaten

De milt is het grootste lymfoïde orgaan in ons lichaam, met zowel een belangrijke filter- (verwijderen van oude rode bloedcellen en cel partikels) als immunologische functie. De immunologische functie van de milt is uitgebreid en omvat de verwijdering van micro-organismen door de macrofagen, de productie van niet antigen- specifieke antilichamen door de IgM positieve memory B cellen - essentieel in de bescherming tegen omkapselde bacteriën-, als de productie van antigen specifieke antilichamen door de interactie tussen antigen presenterende cellen en de B- en T-lymfocyten. Op deze manier vormt de milt een brug tussen de aangeboren en verworven immuniteit. Ze is in staat om zowel geopsoniseerde bacteriën te verwijderen, als om IgM en opsonines te synthetiseren 3. In het geval van asplenie daalt het aantal IgM-producerende B cellen en is er een daling van de filtering van gekapselde bacteriën.

Asplenie komt in 3 vormen voor, met name congenitaal, postchirurgisch en functioneel (bv. bij sikkelcelanemie), waarbij de chirurgische de meest voorkomende oorzaak is [3]. De meest gevreesde complicatie bij patiënten met een asplenie is OPSI (overwhelming postsplenectomy infection), in de literatuur soms ook PSS (postsplenectomie sepsis) genoemd.

Het infectierisico bij patiënten met een asplenie is sterk verhoogd waarbij de incidentie vooral bestudeerd is bij patiënten met een postchirurgische asplenie. Bisharat et al analyseerde de data van 19 680 patiënten na splenectomie, inbegrepen in 78 studies. Over een mediane opvolgtijd van 6,9 jaar, met een spreiding van 11 maanden tot 25 jaar, werd een incidentie van infectie gezien van 3.2% met een globale mortaliteit van 1.4%. Kinderen vertoonden eenzelfde incidentie van infectie als de volwassenen, maar wel met een significant hogere mortaliteit (1.7% versus 1.3% bij volwassenen, $p < 0.001$). Dit betekent dus dat er een zeer hoge mortaliteit is van meer dan 50% in geval van OPSI [4].

De meerderheid van de infecties vindt plaats binnen 2 jaar na splenectomie [5]. OPSI is echter ook beschreven 10 tot 60 jaar postsplenectomie, wat een aanwijzing geeft voor een levenslang risico [6].

De meest voorkomende verwekkers van een OPSI zijn de omkapselde bacteriën S. pneumoniae (50-90%), N. meningitidis en omkapselde H. influenzae types. Asplene patiënten hebben ook een verhoogd risico op infectie met Salmonella sp, E. coli, P. aeruginosa en C. canimorsus (na transmissie bij hondenbeten) en een verhoogd risico op een ernstig verloop van malaria.

Het infectierisico bij asplene patiënten kan sterk gereduceerd worden met een adequaat preventiebeleid, bestaande uit profylactische antibiotica en een adequaat antibioticabeleid bij koorts, optimale vaccinatie en goede educatie van zowel de patiënt als zorgverlener.

Hieronder bespreken we deze drie pijlers van de preventieve maatregelen bij patiënten met een congenitale, chirurgische of functionele asplenie.

1. Antibiotica

a. Profylactisch antibioticum

Het geven van antibioticaprofylaxe maakt deel uit van de standaardzorg bij asplene patiënten. Dit profylactisch antibioticum is gericht tegen S. pneumoniae, de meest frequente verwekker van een OPSI. Dit beleid is ontstaan nadat zowel

gecontroleerde studies, omtrent profylactisch toegediende penicilline bij patiënten met sikkelcelanemie, als retrospectieve studies, bij patiënten onder profylaxe postsplenectomie, een significante reductie van een OPSI en een reductie van de mortaliteit aantoonden [7-8].

In de literatuur is er nog steeds geen eenduidigheid over de optimale duur van de profylaxe. Het hoogste risico op het ontwikkelen van een OPSI wordt gezien bij kinderen jonger dan 5 jaar en tot 2 jaar postsplenectomie. Gezien ook de nadelige gevolgen van langdurige antibioticaprofylaxe met name antibioticaresistentie en een verminderde therapietrouw wordt op heden aanbevolen antibioticaprofylaxe te voorzien tot de leeftijd van 5 jaar of tot 2 jaar postsplenectomie bij kinderen ouder dan 5 jaar. Nadien kan bij patiënten die geen OPSI hebben doorgemaakt en die geen immunosuppressiva nemen veilig gestopt worden [9-11].

Gezien in België geen penicillinesiroop beschikbaar is, stellen we voor amoxicilline (10mg/kg tweemaal daags) te geven aan jonge kinderen. Voor oudere kinderen kunnen penicilline V (fenoxymethylpenicilline) comprimés voorgeschreven worden in een dosering van 125 mg tweemaal daags voor kinderen van 1 tot 5 jaar. Bij kinderen ouder dan 5 jaar wordt 250 mg tweemaal daags aangeraden. Bij het gebruik van alternatieven zoals macroliden of cotrimoxazole moet steeds rekening gehouden worden met mogelijke resistentie, waarbij in België een resistentie van pneumokokken tegen macroliden en cotrimoxazole wordt gezien van respectievelijk ongeveer 20% en 25%.

b. Antibioticabeleid bij koorts

Een OPSI kan een zeer snelle evolutie kennen met een initieel mild klinisch beeld met koorts, malaise, myalgie, hoofdpijn, braken, diarree en abdominale pijn. In een verloop van enkele uren kan dit overgaan naar een septische shock met anurie, diffuse intravasale stolling en hypoglycemie.

Patiënten met een asplenie en de behandelende artsen moeten dan ook op de hoogte zijn dat elke onverklaarde koortsepisode een medische urgentie is waarvoor onmiddellijk een empirische behandeling met antibiotica dient gestart te worden. Deze antibiotica dienen effectief te zijn tegen de meest voorkomende verwekkers van levensbedreigende infecties bij patiënten met een asplenie, ook rekening houdende met eventueel ontstane antibioticaresistentie onder profylactische behandeling. We stellen voor een derde generatie cefalosporine toe te dienen in geval van koorts (bv. IV/IM ceftriaxon of IV cefotaxim)

c. Antibioticabeleid bij dierenbeten

Er is een verhoogd risico op een ernstige sepsis bij patiënten met een asplenie die gekrabd of gebeten worden door dieren. Hondenbeten in het bijzonder zijn geassocieerd met een ernstige sepsis door Capnocythophaga canimorsus. Meteen na een krab of beet moet de zone ontsmet worden en dient een per orale antibioticakuur gestart te worden met amoxiclavulaanzuur gedurende 5 dagen.

d. Malariaprofylaxe

Kinderen met een asplenie hebben tevens een verhoogd risico op een ernstig verloop van malaria door een verminderde klaring van parasieten door de milt. Er wordt dan ook aangeraden steeds deskundig advies in te winnen bij vertrek naar een risicogebied. Aan deze patiënten wordt aangeraden malariaprofylaxe te nemen, adequaat voor de leeftijd en het type malaria dat wordt aangetroffen in het desbetreffende gebied. Hierbij moeten ook alle maatregelen genomen worden om muggenbeten te vermijden. Het is belangrijk dat patiënten die terugkeren uit een risicogebied en die koorts hebben binnen de maand tot een jaar na terugkeer steeds de arts hiervan verwittigen zodat malaria kan uitgesloten worden. Ook bij een vermoeden van malaria dient onmiddellijk een breedspectrum antibioticum gestart en aangehouden te worden tot de hemoculturen negatief zijn.

2. Vaccinatiebeleid

Patiënten met een asplenie dienen naast de routine vaccins, vervat in het basisvaccinatieschema, nog bijkomstige vaccins ten opzichte van pneumokokken en meningokokken te krijgen, alsook het jaarlijks influenzavaccin.

Een belangrijke algemene regel hierbij is dat asplenie geen contra-indicatie vormt voor het toedienen van vaccins, ook niet voor levend verzwakte vaccins. Indien mogelijk wordt aangeraden te vaccineren ten uiterste 2 weken, idealiter minimaal 4 weken voor het uitvoeren van een splenectomie. Bij een niet-electieve ingreep wordt aangeraden te vaccineren vanaf 2 weken postsplenectomie. Dit advies is gestoeld op de studie van Shatz et al bij 59 volwassen patiënten waarbij een betere functionele antilichaam respons werd gezien bij een laattijdige vaccinatie op 2 weken na splenectomie in tegenstelling tot vaccinatie meteen postoperatief of na 7 dagen [12].

a. Pneumokokkenvaccinatie

In België bestaat het basisvaccinatieschema tegen S. pneumoniae uit het geconjugeerd polysacharide vaccin tegen pneumokokken (PCV), momenteel PCV10 (Synflorix®), waarvan 2 dosissen tijdens het eerste jaar en 1 booster tijdens het tweede levensjaar worden toegediend. Bij kinderen met een verhoogd risico op een pneumokokkeninfectie wordt, in plaats van PCV10, vaccinatie met PCV13 (Prevenar 13®) aangeraden, met een 3 + 1 basisschema. Naast het geconjugeerde vaccin wordt bij patiënten met een asplenie vaccinatie met het niet- geconjugeerde polysacharide vaccin PPV23 (Pneumovax 23®) aangeraden na de leeftijd van 2 jaar met een eenmalige booster na 5 jaar. Gezien een fenomeen van immuuntolerantie kan optreden na herhaalde toediening van PPV23 vaccin wordt op heden slechts een eenmalige booster aangeraden na 5 jaar [13]. In tabel 1 wordt een overzicht gegeven van de te voorziene vaccins tegen S. pneumoniae [14].

Tabel 1: Overzicht aanbevelingen Hoge Gezondheidsraad in verband met vaccinatie tegen S. pneumoniae bij patiënten met een asplenie.

Leeftijd van de patiënt	PCV 13	PPV 23
2 tot 12 maanden	3 dosissen met een interval van 6 à 8 weken en een booster na 12 maanden	a volledige vaccinatie met PCV 13, 1 dosis PPV 23 na de leeftijd van 2 jaar met een eenmalige booster na 5 jaar
> 12 maanden tot 5 jaar: reeds gevaccineerd met 2 primovaccinatie dosissen PCV 7 of PCV 10	1 booster dosis PCV 13	1 dosis PPV 23 na de leeftijd van 2 jaar met een eenmalige booster na 5 jaar
> 12 maanden tot 5 jaar: geen of onvolledige vaccinatie	2 dosissen PCV 13 met een interval van 8 weken	
> 5 jaar	1 dosis PCV 13	

b. Meningokokkenvaccinatie

Op heden zijn in België 3 types vaccins tegen meningokokken beschikbaar met name het MenC vaccin (Neisvac C®) tegen serogroep C, het multicomponent 4CMenB vaccin (Bexsero®) tegen serogroep B en het combivalent MenACWY vaccin (het niet-geconjugeerde polysaccharidevaccin Mencevax® en de geconjugeerde vaccins Menveo® en Nimenrix®) gericht tegen zowel serogroep A, C, W als Y. In de bescherming tegen N. meningitidis wordt routinematig in België het MenC vaccin voorzien op de leeftijd van 15 maanden. Het vaccin tegen serogroep B maakt op heden in België nog geen deel uit van de routinevaccinatie. Bij kinderen met een verhoogd risico op een meningokokkeninfectie wordt wel aanbevolen te vaccineren met het 4CMenB vaccin. Tabel 2 geeft een overzicht weer van het aantal dosissen van het 4CMenB vaccin [14].

Tabel 2: Overzicht aanbevelingen Hoge Gezondheidsraad in verband met vaccinatie tegen N. meningitidis serogroep B bij patiënten met een asplenie.

Leeftijd 1ste dosis 4CMenB vaccin	Primovaccinatie: aantal dosissen	Minimaal interval tussen dosissen: aantal maanden	Booster
2 tot 5 maanden	3	1	12-15 maanden
6 tot 11 maanden	2	2	tijdens het 2de levensjaar, 1 dosis minimaal 2 maanden na de laatste dosis van de eerste reeks
12 tot 23 maanden	2	2	1 dosis minimaal 12-23 maanden na primovaccinatie
2 tot 10 jaar	2	2	/
> 11 jaar	2	1	

Naast het 4CMenB vaccin wordt bij asplene patiënten ook vaccinatie met het MenACWY vaccin aangeraden waarbij momenteel een hervaccinatie om de 5 jaar moet voorzien worden. In de keuze van het MenACWY vaccin wordt bij asplene patiënten de voorkeur gegeven aan een geconjugeerd vaccin (Menveo®, Nimenrix®). In tabel 3 wordt een overzicht weergegeven van het aantal dosissen van het geconjugeerde MenACWY vaccin [15].

c. Vaccinatie ten opzichte van H. influenzae type b

In de bescherming tegen H. influenzae moeten bij asplene patiënten, die het routineschema inclusief booster, hebben doorlopen geen bijkomstige vaccins gegeven worden.

d. Griepvaccinatie

Als laatste moet bij patiënten met een asplenie jaarlijks het vaccin tegen seizoensgriep worden voorzien, dit gezien de kans op bacteriële surinfectie met S. pneumoniae bij doormaken van influenza-infectie.

e. Simultaan vaccineren

Voor richtlijnen over simultane vaccinatie kan de website van het Centrum voor Evaluatie Vaccinaties UA geraadpleegd worden [16].

Tabel 3: Overzicht aanbeveling van het Instituut voor Tropische Geneeskunde in verband met vaccinatie tegen N. meningitidis serogroep ACWY.

Leeftijdsgroep 1ste dosis MenACWY	Menveo	Nimenrix
6 weken- 12 weken	niet van toepassing	3 dosissen: 0 maand - 2 maand - 12 maanden
12 weken- 12 maanden	niet van toepassing	3 dosissen: 0 maand - 2 maand- 12 maanden
> 12 maanden	niet van toepassing	Eenmalige toediening met booster elke 3 jaar bij eerste toediening < 7 jaar. Bij eerste toediening > 7 jaar booster elke 5 jaar
> 2 jaar	Eenmalige toediening met booster elke 3 jaar bij eerste toediening <7 jaar. Bij eerste toediening > 7 jaar booster elke 5 jaar	

3. Educatie

Naast medicamenteuze preventiemaatregelen, met name vaccinatie en antibioticaprofylaxe, is educatie van zowel de patiënt als zorgverlener zeer belangrijk om de morbiditeit en mortaliteit bij een asplenie te verminderen. Ook wordt er aanbevolen om bij deze patiënten in het dossier een checklist bij te houden van de reeds toegediende en nog toe te dienen vaccins.

Daarnaast wordt bij patiënten met een asplenie ook aangeraden een alarmkaart bij zich te houden zodat in urgentie steeds een adequaat antibioticabeleid kan worden toegepast.

Naast de alarmkaart dient in het patiëntendossier vermeld te staan dat het een hoog risico patiënt betreft waarbij in geval van koorts urgent moet ingegrepen worden [17].

Discussie

De casus betreft een voorheen gezonde jongen van 8 jaar die een urgente splenectomie ondergaat omwille van een traumatische miltruptuur.

Op deze leeftijd wordt antibioticaprofylaxe met amoxicilline aangeraden tot minimaal 2 jaar postsplenectomie. Wanneer de patiënt in deze periode geen OPSI ontwikkelt, kan besloten worden de antibioticaprofylaxe te staken. Bij koortsepisodes zal steeds zeer snel medische hulp moeten gezocht worden voor het opstarten van een breedspectrum antibioticum met name intraveneus ceftriaxon of ceftazidim.

In deze casus betreft het een urgente ingreep zodat de bijkomstige vaccins voor patiënten met een asplenie voorzien moeten worden vanaf 2 weken postoperatief. De jongen in de casus heeft tot hier toe het volledige basisvaccinatieschema doorlopen. In het kader van bescherming tegen S. pneumoniae dient een bijkomende vaccinatie met het geconjugeerde vaccin PCV13 (Prevenar 13®) voorzien te worden. Minimaal 8 weken na de toediening van het PCV13 vaccin wordt aanbevolen het polysaccharide vaccin PPV23 (Pneumovax 23®) toe te dienen. Een eenmalige booster van PPV23 dient voorzien te worden na 5 jaar. In de bescherming tegen N.meningitidis moeten bijkomstig 2 dosissen van het 4CMenB worden voorzien met een minimaal interval van 1 maand. Hiernaast wordt een bijkomstige vaccinatie aangeraden met het MenACWY vaccin (Nimenrix® of Menveo®). Een booster dient voorzien te worden elke 5 jaar. Gezien in deze casus de patiënt reeds het volledige basisvaccinatieschema heeft doorlopen, moet in de bescherming tegen H. influenzae geen extra vaccin worden voorzien. Naast de bijkomende vaccins tegen S. pneumoniae en N. mengitidis moet jaarlijks het vaccin tegen seizoensgriep worden toegediend.

Om de morbiditeit en mortaliteit van een OPSI te verminderen zullen zowel de patiënt als de naaste familie op de hoogte moeten gebracht worden van het risico dat zijn/haar conditie met zich meebrengt. Het is de taak van de zorgverlener om in het dossier een checklist bij te houden met de reeds toegediende en de nog toe te dienen profylaxe. Ook moet in het medisch dossier duidelijk vermeld staan dat het om een hoog risico patiënt gaat waarbij in geval van koorts zeer urgent maatregelen dienen getroffen te worden. De patiënt dient een alarmkaart bij zich te houden zodat de zorgverlener bij elk contact op de hoogte kan gebracht worden van zijn/haar conditie. Wanneer zowel de patiënt, de naaste omgeving als de zorgverleners op de hoogte zijn van de risico's zal de mortaliteit kunnen teruggebracht worden van 50% naar 10%.

Conclusie

Invasieve infecties bij patiënten met een asplenie zorgen tot op heden nog steeds voor een zeer belangrijke mortaliteit en morbiditeit in deze risicogroep. Bij deze patiënten moet men naast het basisvaccinatieschema bijkomstige vaccins voorzien. Ook wordt in deze groep antibioticaprofylaxe aangeraden tot minimaal 2 jaar na splenectomie en minimaal tot de leeftijd van 5 jaar bij kinderen jonger dan 5 jaar. Naast de preventieve maatregelen is een goede educatie van zowel de patiënt als de gezondheidsmedewerker en de onmiddellijke toegang tot breedspectrum antibiotica in acute situaties van uitermate belang. Wanneer al deze maatregelen in acht genomen worden kan de mortaliteit in geval van een OPSI teruggebracht worden van 50% tot 10%.

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Jong geleerd
is oud gedaan

Het natuurlijke mineraalwater **SPA REINE** wordt jarenlang door de natuur gefilterd **op een plek die strikt wordt beschermd tegen elke vorm van vervuiling, wat een uitzonderlijke zuiverheid oplevert.**
Door zijn zeer lage mineraalgehalte is het bij uitstek geschikt voor de bereiding van babyvoeding.

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SPA STEUNT DE BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE

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NATURAL SINCE 1583
Op het leven

Innovative imaging techniques to predict treatment outcome in paediatric obstructive sleep apnoea

PhD thesis presented on 1th of March 2019 at Antwerp university hospital (UZA) / University of Antwerp, Antwerp, Belgium.

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Introduction

Paediatric obstructive sleep apnoea (OSA) syndrome is a manifestation of sleep-disordered breathing[1,2]. OSA may affect up to 4% of the children in the general population[3]. OSA is often associated with snoring, intermittent hypoxemia, hypercarbia and/or sleep disruption. Additionally, it is associated with a number of significant complications such as daytime neurobehavioral problems, learning deficits, growth retardation and cardiovascular complications[4]. Therefore, OSA needs to be treated correctly.

Adenotonsillar hypertrophy is the most important predisposing factor in children with OSA. However, many other causes of craniofacial narrowing may coexist. Additionally, the pathogenesis of upper airway narrowing is more complex in children with obesity, craniofacial malformations, Down syndrome or neuromuscular disorders. The diagnosis of obstructive sleep apnoea is based on an overnight polysomnography. This investigation is expensive, time consuming, and not widely available[4].

The first line of treatment is adenotonsillectomy (ATE). Further, there are other surgical and non-surgical options for treatment that are used in residual OSA or complex OSA. Treatment outcomes for ATE have been studied extensively and there is a high incidence of residual OSA after ATE (normal-weight children: up to 51%), especially in children with risk factors such as obesity (up to 59%) and Down syndrome (up to 87%)[5-7]. A polysomnography gives the diagnosis of OSA but not the anatomical level of obstruction in the upper airway (UA).

To avoid unnecessary risks and ineffective surgeries, the indication for surgery should be correctly set. Therefore, it seems crucial to couple the exact individual anatomical risk factor with the most appropriate treatment. Imaging could be a non-invasive tool that could assist in the selection of treatment, but more studies are required to validate its utility.

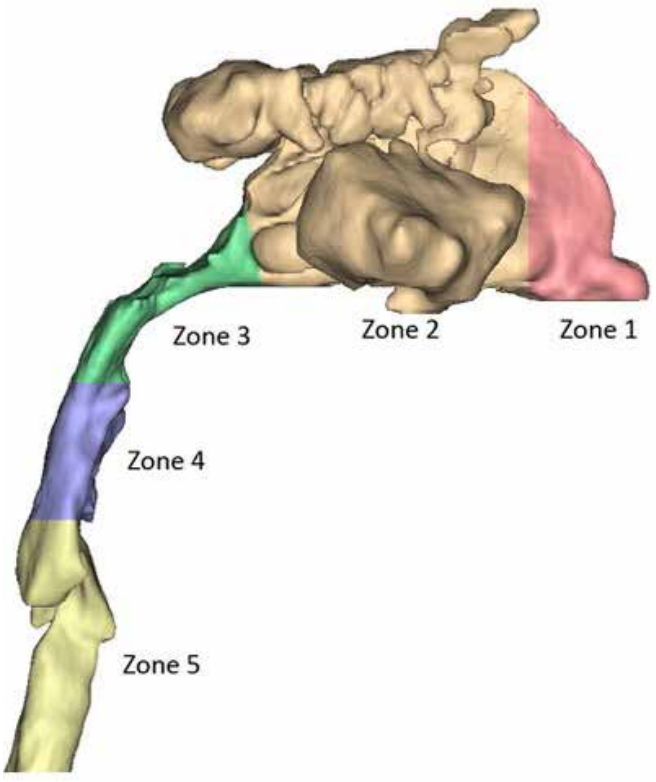
The purpose of this thesis was to investigate whether UA imaging could provide more information about UA characteristics in children with OSA mainly to predict treatment outcome. In this thesis, we investigated the use of (functional) imaging in normal-weight children, obese children, and children with DS.

UA imaging in paediatric OSA

We summarized the different UA imaging methods with regards to their value in the diagnosis of OSA and predicting the effect of ATE. Functional respiratory imaging (FRI) is a relatively new method for further studying UA physical characteristics, including velocity, turbulence, pressure, wall sheer stress and resistances. The UA from nares to trachea can be reconstructed into 3-D models and subdivided into a large number of discrete elements trough images of MRI or CT (figure 1). The model is used for analysis of anatomical parameters, volume meshing (representation of interior volume), and computational fluid dynamics simulation for FRI. This way, effective UA volume and minimal and mean cross-sectional areas are calculated. Preliminary data showed that FRI could identify differences in the UA of children with residual OSA and correlated better with OSA severity than parameters obtained from physical examination. In this thesis, we used CT images by low-dose protocol with FRI[8].

Drug-induced sedation endoscopy (DISE) is another method to evaluate the level and degree of UA obstruction. Only a few studies reported the use of DISE in children with OSA. It is a promising technique in selecting the type of UA surgery because it provides live video of UA obstruction[9].

Figure 1: Computerized 3-D model of the UA. Nostril to bottom of inferior turbinate (zone 1), bottom of inferior turbinate to choanae (zone 2), choanae to tip of uvula (zone 3), uvula to epiglottis (zone 4) and epiglottis to the first thoracic vertebra (zone 5)



Normal-weight children with OSA

We investigated whether FRI could provide more information about UA characteristics in 91 normal-weight children with OSA mainly to predict treatment outcome. We found that imaging parameters correlate with OSA severity at baseline more than the tonsil score obtained by clinical assessment: a smaller overlap region of tonsils/adenoids, a higher resistance and a more concave shape of the UA correlated with more severe OSA. Thereby, a less constricted airway, as characterized by both a higher conductance and a lower tonsil score, was associated with a less favourable response to (adeno)tonsillectomy. In conclusion, both UA conductance and the tonsil score predicted treatment response even in a selected population where treatment was guided by DISE[10].

Children with Down syndrome and OSA

Each year, around 85 children are born with Down syndrome (DS) in Belgium. Since the introduction of the non-invasive prenatal test, the incidence is decreased to 31 children in Flanders in 2016[11]. Prevalence of OSA in children with DS is in up to 79% and as mentioned before, a high incidence of persistent OSA after ATE[7].

We characterized treatment outcome after ATE in 33 young children with DS and OSA by UA imaging (CT of the UA combined with computational fluid dynamics). At baseline, children with more severe OSA had a smaller minimal passage through the upper airway. After treatment, persistent OSA was seen in 79% of the children, however 79% had a decrease of > 50% in oAHI (obstructive apnoea-hypopnoea index) after treatment. Children with less favourable response had a smaller volume of the zones below the tonsils which is probably due to enlargement of the lingual tonsils, glossoptosis or macroglossia which is not treated by ATE. In conclusion, this study suggests that UA imaging could have an influence in treatment selection in children with DS and OSA. Exact cut-off values are need to be confirmed by larger studies[12].

Obese children with OSA

Prevalence and severity of overweight in children is increasing worldwide. Around 20% is overweight and 7% is obese in Belgium of children between 2 and 17 years old[13]. Prevalence of OSA is in up to 59% in obese children with a high incidence of persistent OSA after ATE[6].

In our thesis, we evaluated the UA by imaging (CT) and DISE, and compared the results after ATE in 27 obese children with OSA. There were no differences in baseline characteristics and UA imaging parameters between the different degrees of OSA. Children with more abdominal fat and a more concave shape of the UA had significantly more oxygen desaturations during sleep. All children had DISE to select the type and need for surgery. Weight management was part of the treatment. A more concave shape of the UA and a lower total score during DISE (no multilevel obstruction, no obstruction in other parts than region of adenoids and tonsils) correlated with a better improvement after treatment. In conclusion, a combination of DISE selection for ATE with follow-up of weight management seems to be more successful in treatment response than ATE alone[14].

Ethnicity and OSA

Ethnicity is an important risk factor for OSA, however, there were no studies investigating the influence of ethnicity on UA morphology in European children with OSA. The aim of our study was therefore to investigate whether ethnicity could influence UA morphology, OSA severity or treatment response in European children by functional respiratory imaging (FRI). We hypothesized that black African (bA) children have a different UA morphology, and are more likely to have more severe and more persistent OSA, compared to Caucasian children.

Firstly, bA children had more severe OSA compared to Caucasian children. Furthermore, there was a difference in UA morphology between bA and Caucasian children: the UA volume of the tongue base and hypopharynx was significantly smaller in children from Africa. This difference could be due to lingual tonsillar hypertrophy, glossoptosis or macroglossia. Despite the difference in morphology, we observed no difference in treatment outcome. In conclusion, clinicians should be aware of the possibility of more severe OSA in bA children. An early diagnosis could possibly prevent more OSA-related complications because they suffer from more severe OSA compared to Caucasian children[15].

Conclusions and future perspectives

In the present era of personalized medicine, progress has been made in identifying the exact cause OSA in children. The UA imaging techniques implemented in our thesis are minimally invasive. As mentioned earlier, regardless of the disadvantages of CT images, 3-D construction of the UA by CT provides information on OSA severity. Virtual surgery based on 3-D constructions would then be the next logical research opportunity. Functional imaging is relatively expensive. Due to this cost constraint, children with DS or obese children should be prioritized over children without DS or normal-weight children because the percentage of residual OSA is higher in these populations. Additionally, there is need for more research by imaging or DISE in cases of normal-weight children suffering of persistent OSA. The aforementioned use of virtual surgery modelling could be expanded beyond merely ATE surgery, presumably into the field of orthognathic.

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How to explore children over 3 months old with thrombocytopenia ?
(Enfant de plus de 3 mois thrombotcytopénique : quelle exploration ?)

Nadine Francotte, Christophe Chantrain

CHC-Espérance

Si Plaquettes < 150 000
(âge > 3 mois)

Bilan initial d'une thrombocypénie (après anamnèse détaillée):

- Formule sanguine (+ réticulocytes); schizocytes ?
- Morphologie plaquettaire
- Volume plaquettaire
- IgG, A, M
- Bilan de coagulation de base

Répondre à 10 questions:

Plusieurs pistes numérotées pour arriver au diagnostic …

1) Vraie ou pseudo-thrombopénie ?
2) Atteinte des autres lignées (globules rouges, globules blancs) ?
3) Compte de plaquettes antérieur ?
4) Aiguë ou Chronique ?
5) Stigmates cliniques ?
   - eczéma
   - anomalie avant-bras
   - cardiopathie
6) Contexte infectieux (ou post-infectieux) ou dysimmunitaire ?
7) Congénitale ou acquise ? Quelle est le volume des plaquettes ?
8) Centrale ou périphérique ? Ponction de moelle ?
9) A traiter ou non ?
10) Quand référer à un pédiatre hématologue ?

Answer 10 questions

1) Is it a true or a pseudo-thrombocytopenia ?
2) Are the other lineages of the blood involved ?
3) Do you have a previous platelet count ?
4) Is it an acute or a chronic disease ?
5) Are there any clinical signs involved:
   - eczema,
   - cardiopathy ,
   - anomaly of the forearm,… ?
6) Is it an infectious, postinfectious or dysimmune condition present?
7) Is it a central or a peripheral thrombocytopenia ? Do you need a BMP ?
8) Is it a congenital or an acquired thrombocytopenia ? What Platelet size ?
9) Do you need to treat or not
10) When do you need to refer the patient to an hématologist

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MISE AU POINT THROMBOPENIE – enfants de plus de 3 mois

1

Compatible avec la clinique ?

NON → Agrégats plaquettaires
Pseudo-thrombocytopénie
(Surtout si EDTA)

OUI

2

Atteinte des autres lignées

- **Contexte viral**
  - Evolution favorable
  - Absence de résolution
- Atteinte de l'état général ?
- Atteinte des 3 lignées
- **Anémie hémolytique avec consommation plaquettaire**

Autres lignées sanguines normales

- Aigu → 4
- Chronique → Compte de plaquettes antérieur ? 3
  - Non → **Probable PTI ***
  - Oui
    - Signes dysmorphiques
      Anomalies congénitales
    - Altération fonction plaquettes
    - Antécédents Familiaux
    - Dysrégulations immunitaires
      Maladies auto-immunes
      - Déficit Immunitaire Commun Variable (CVID)
      - Lupus Erythémateux Disséminé (LED)
      - Syndrome Lymphoprolifératif avec Auto-immunité (ALPS) ,,,

* 1 à 10 ans
* aigu
* diagnostic d'exclusion
* auto-anticorps contre les glycoprotéines plaquettaires
* souvent secondaire à une virose ou à une vaccination par virus vivant
* Helicobacter Pylori :
lien moins clair que chez l'adulte

*** PTI** : Purpura Thrombocytopénique Immun

Ponction de moelle osseuse (PMO)

- Envahissement moelle osseuse
  Blastes
  Métastases
- Aplasie / hypoplasie médullaire
  - Congénitales
    Ex : Fanconi
    (+ S. dysmophique)
  - Infectieux AIGU
    Post-infectieux
    CMV
    EBV
    HIV
  - Toxiques
    Médicaments
    Carences :ac folique
    vit B 12

5

Autre porte d'entrée pour arriver au diagnostic

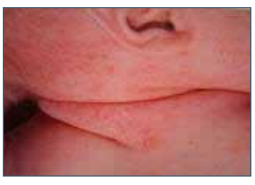
Autres signes cliniques

Thrombopenia with Absent Radius (TAR)
Malform. Cardiaques
Kasabach Meritt
Syndromes dysmorphiqs
ue…

Masse abdominale
Adénopathies

Maladies chroniques
- auto-immunité (FAN)
- Infection (ex. HIV)
…

Déficit immunitaire
Wiskott Aldrich
Eczéma
Garçon
infections à répétition
Plaquettes de petite taille



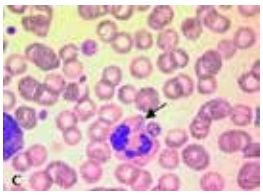
- Hypersplénisme
- Consommation plaquettaire
  Syndrome Hémolytique Urémique (SHU)
  Coagulation Intravasculaire Disséminée (CIVD)
  Sepsis
  Purpura thrombotique Thrombocytopénique (PTT)
  …

Congénitale ou acquise ? Volume des plaquettes ? 7

PS < 150 000

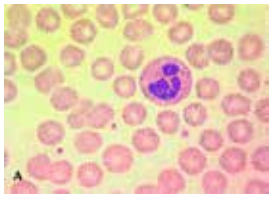
Autre porte d'entrée pour arriver au diagnostic

Vol plaquettaire
N = 7 à 11 fL



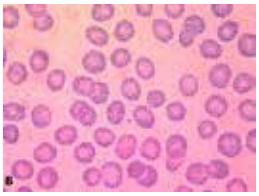
Grandes
> 11 fL

Thrombopénies héréditaires
- Bernard Soulier
- Gène MYH-9
- Syndrome des plaquettes grises
- Autres étiologies ...



Normales
7-11 fL

- Certaines thrombopénies héréditaires
- Autres étiologies ....



Petites
< 7 fL

- Wiskott Aldrich X linked thrombocytopénie
- Autres étiologies ...

Diagnostic : gene panel for thrombosis and hemostasis (genome sequencing)
Contact : Dr Kathleen FRESON (KUL)

8

Autre porte d'entrée pour arriver au diagnostic

Centrale ?

Acquise — **Constitutionnelle**

- Leucémie
- Aplasie médullaire
- Syndrome myélodysplasique
- Infiltration médullaire métastatique (lymphome, neuroblastome, sarcome d'Ewing)

Périphérique ?

Par séquestration splénique
- Hypertension portale
  * Cavernome portal
  * Atrésie des voies biliaires
- Maladie de Gaucher
- Autres

Par destruction périphérique

Non immunologique
Par consommation
CIVD
Infections
Microangiopathies thrombotiques
Kasabach-Meritt
SHU

Immunologique
PTI
Origine médicamenteuse
Postvaccinal (virus vivant)
Postinfectieux

Prix public Belgique	86,52€
Prix public Luxembourg	84,07€

Bexsero : premier vaccin contre le méningocoque de sérogroupe B.

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

BEXSERO

Vaccin méningococcique groupe B (ADNr, composant, adsorbé)

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

Tableau 1. Résumé de la posologie

Age lors de la première dose	Primovaccination	Intervalles entre les doses de primovaccination	Rappel
Nourrissons de 2 à 5 mois	Trois doses de 0,5 ml chacune,	1 mois minimum	Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel [b,c]
Nourrissons de 3 à 5 mois	Deux doses de 0,5 ml chacune	2 mois minimum	
Nourrissons de 6 à 11 mois	Deux doses de 0,5 ml chacune	2 mois minimum	Oui, une dose au cours de la deuxième année avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel [c]
Enfants de 12 à 23 mois	Deux doses de 0,5 ml chacune	2 mois minimum	Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel [c]
Enfants de 2 à 10 ans	Deux doses de 0,5 ml chacune	1 mois minimum	Besoin non établi [d]
Adolescents (à partir de 11 ans)et adultes*	Deux doses de 0,5 ml chacune	1 mois minimum	Besoin non établi [d]

[a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne doit pas être administrée au-delà de l'âge de 24 mois. [c] Voir rubrique 5.1 du RCP complet. La nécessité et le moment d'administration d'une dose de rappel n'ont pas encore été déterminés. [d] Voir rubrique 5.1 du RCP complet. * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, sous-cutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **CONTRE-INDICATIONS** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **MISES EN GARDE SPÉCIALES ET PRÉCAUTIONS D'EMPLOI** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entraîner le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vaso-vagales (syncope), de l'hyperventilation ou des réactions en rapport avec le stress peuvent survenir lors de la vaccination comme réaction psychogène à l'injection avec une aiguille (voir rubrique « Effets indésirables »). Il est important que des mesures soient mises en place afin d'éviter toute blessure en cas d'évanouissement. Ce vaccin ne doit pas être administré aux patients ayant une thrombocytopénie ou tout autre trouble de la coagulation qui serait une contre-indication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination avec Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation. Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles post-vaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. **EFFETS INDÉSIRABLES** Résumé du profil de sécurité La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6837 étaient des nourrissons et des enfants (de moins de 2 ans), 1051 étaient des enfants (entre 2 et 10 ans) et 2677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3285 ont reçu une dose de rappel au cours de leur deuxième année de vie.. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69% à 79 % des sujets lorsque Bexsero était co-administré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et ***Haemophilus influenzae*** de type b), contre 44% à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés avec Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) Fréquent : (≥ 1/100 à < 1/10) Peu fréquent : (≥ 1/1 000 à < 1/100) Rare : (≥ 1/10 000 à < 1/1 000) Très rare : (< 1/10 000) Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles) Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans)** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Troubles du métabolisme et de la nutrition Très fréquent : troubles alimentaires Affections du système nerveux Très fréquent : somnolence, pleurs inhabituels, céphalée Peu fréquent : convulsions (y compris convulsions fébriles) Fréquence indéterminée : épisode d'hypotonie-hyporéactivité Affections vasculaires Peu fréquent : pâleur (rare après le rappel) Rare : syndrome de Kawasaki Affections gastro-intestinales Très fréquent : diarrhée, vomissements (peu fréquents après le rappel) Affections de la peau et du tissu sous-cutané Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel) Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans) Peu fréquent : eczéma Rare : urticaire Affections musculo-squelettiques et systémiques Très fréquent : arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité Peu fréquent : fièvre (≥ 40 °C) Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois) **Adolescents (à partir de 11 ans) et adultes** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Affections du système nerveux Très fréquent : céphalée Fréquence indéterminée : syncope ou réaction vaso-vagale à l'injection Affections gastro-intestinales Très fréquent : nausées Affections musculo-squelettiques et systémiques Très fréquent : myalgies, arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois) **Déclaration des effets indésirables suspectés** La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique** Agence fédérale des médicaments et des produits de santé Division Vigilance EUROSTATION II Place Victor Horta, 40/40 B-1060 Bruxelles Site internet: www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be **Luxembourg** 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 **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie **DATE D'APPROBATION DU TEXTE** 06/2018(v05) **MODE DE DELIVRANCE** Sur prescription médicale.

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

BE/BEX/0011/16a(1) – July 2018 - E.R.: GlaxoSmithKline Pharmaceuticals s.a., av Pascal 2-4-6, 1300 Wavre

In collaboration with Cebam, Cochrane Belgium
(http://belgium.cochrane.org)

C-reactive protein unlikely to be accurate for early diagnosis of late-onset infection in newborn infants

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Clinical question

Is serum C-reactive protein (CRP) measurement at initial evaluation useful to diagnose late-onset infection in newborn infants?

Context

Newborn infants, especially those who are unwell or preterm, are at risk of developing severe infections (such as bloodstream infections) during their stay on neonatal units. Late-onset infections occur at least 72 hours after birth and are difficult to diagnose early. The current standard test to confirm this diagnosis, positive microbiological culture, takes about 24 to 48 hours. A delayed treatment increases the morbidity and mortality of late-onset infections. Therefore, clinicians are using additional tests in the hope of identifying infants with infection earlier and being able to optimally target early treatment. An example is measuring the blood level of CRP, which takes about 1 hour and has become common practice in neonatal units. It remains unknown, however, if this test at initial evaluation in infants with signs of possible late-onset infection is actually accurate to make the diagnosis.

To correctly assess the usefulness (accuracy) of the CRP test, studies should recruit newborn infants that are suspected to have a late-onset infection. These infants should be tested twice: first using the new test (CRP) followed by the standard test (blood culture). Results can then be compared: how many infants with an infection have a positive CRP test (true positive), and how many infants without an infection indeed have a normal CRP (true negative). Alternatively, it would be important to know how many infants would be falsely diagnosed, i.e. infants with infection having a negative CRP (false negatives) as well as infants without infection having an elevated CRP (false positives). The analysis determines the optimal value between sensitivity of the test (the ability of the test to correctly diagnose infants with an infection) and the specificity (the ability of the test to correctly identify infants who do not have an infection).

The review describes 20 studies including a total number of 1615 newborn infants, which stayed in the hospital for at least 72 hours after birth. Most were small, single-centre, prospective cohort studies conducted in neonatal units in high- or middle-income countries since the late 1990s. The authors used the threshold for the CRP test as defined by individual studies (expected typically to be in the range of 5 mg/L to 10 mg/L). The prevalence of late-onset infection in the included studies

ranged from 20% to 82% (median of 40%). The authors applied the results of the meta-analyses to a hypothetical cohort of 1000 neonates with a prevalence of infection of 20%, 40%, or 60%.

Summary of the results

Sensitivity and specificity are related: At median reported specificity (0.74), sensitivity was 0.62 (95% CI 0.50 to 0.73); at the lower quartile reported specificity (0.61), sensitivity was 0.76 (95% CI 0.65 to 0.84); at the upper quartile reported specificity (0.85), sensitivity was 0.44 (95% CI 0.32 to 0.57).

The results varied between studies, but it was not possible to assess whether results depended on gestational age, types of infection, or types of infecting micro-organism mostly because no subgroup data were available. Whether the studies used a predefined threshold or not, and whether studies used a standard threshold of between 5 mg/L and 10 mg/L or not, did not explain the variation between the studies.

What happens when we apply these results to a hypothetical group of 1000 newborn infants that are about to be evaluated for possible late-onset infection?

Results vary based on the prevalence of infection, therefore the authors estimated results in three situations. If the prevalence of true infection is 40% (which was the median prevalence in the included studies), then, on average, 152 cases of infection would be missed (false negative) and 156 non-infected infants would be wrongly diagnosed with an infection (false positive).

Table: Results of the meta-analysis applied to a hypothetical cohort of 1000 newborns in three situations: infection prevalence 20%, 40% and 60%.

Infection	Prevalence 20%		Prevalence 40%		Prevalence 60%	
	Positive culture	Negative culture	Positive culture	Negative culture	Positive culture	Negative culture
Positive CRP	124	208	248	156	372	104
Negative CRP	76	592	152	444	228	396
	200	800	400	600	600	400

Remarks

Certainty of evidence was moderate. Risk of bias in the included studies was generally low. Studies avoided inappropriate exclusion of infants. The serum CRP level was measured in infants presenting with clinical features of late-onset infection before the results of the reference standard were known. Most (13/20) studies prespecified a threshold of CRP level consistent with current clinical practice (5 mg/L to 12 mg/L). All studies used blood samples taken at the initial investigation of each infant to determine the serum CRP level and for the blood culture. Due to the nature of the reference standard, the blood culture results followed 24 to 48 hours after the index test, depending on laboratory procedure. Across all studies, there was a low risk that the patient flow might have introduced bias.

Conclusion:

Measuring the blood level of CRP as an additional triage test for late-onset infection in newborn infants is not sufficiently accurate to determine which infant should receive treatment with antimicrobial agents or further testing.

Implications for practice:

CRP measurement at initial evaluation of an infant with suspected late-onset infection does not aid early diagnosis and is not likely to be considered a sufficiently accurate test to select infants who would undergo further investigation or who should be treated with antimicrobial therapy or other interventions.

REFERENCE:

Brown JVE, Meader N, Cleminson J, McGuire W. C-reactive protein for diagnosing late-onset infection in newborn infants. Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD012126. DOI: 10.1002/14651858.CD012126.pub2.

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

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Data Analysis: Description of data analysis should provide the specific methods used, their rationale, the underlying assumptions, whether data met those assumptions, and how any missing data were handled

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Eponyms and acronyms: eponyms should be used in their non-possessive form (e.g. Down syndrome and not Down's syndrome). Acronyms should be avoided; if this is not possible they should be fully explained when first used.

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- Gonzalez-Aguero A, Vicente-Rodriguez G, Gomez-Cabello A, Ara I, Moreno LA, Casajus JA. A combined training intervention programme increases lean mass in youths with Down syndrome. Res Dev Disabil. 2011;32(6):2383-8.
- 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.

For a chapter in a book: list Authors. Title (of chapter). In: Editors. Title (of book). Place of publication: Publisher, year. Start and end page. Example:

- Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

More examples of other published and unpublished material can be found on the website of the U.S. National Library of Medicine: https://www.nlm.nih.gov/bsd/uniform_requirements.html.

Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/archive/20130415/tsd/serials/lji.html.

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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

- Testées dermatologiquement
- Conviennent à la peau des nouveau-nés
- A base de coton bio
- 99% d'eau purifiée
- 0% alcool, parabène, phénoxyéthanol, colorant, parfum

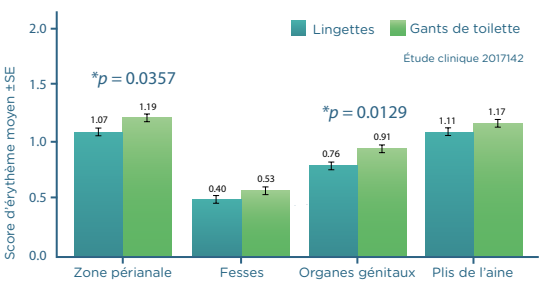
Une nouvelle étude clinique démontre que les lingettes Pampers® Aqua Pure sont au moins aussi douces qu'un gant de toilette imbibé d'eau

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 :

sans alcool
sans parfum
sans parabène
sans phénoxyéthanol
sans colorant
sans blanchiment au chlore

[1] Données internes de P&G

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