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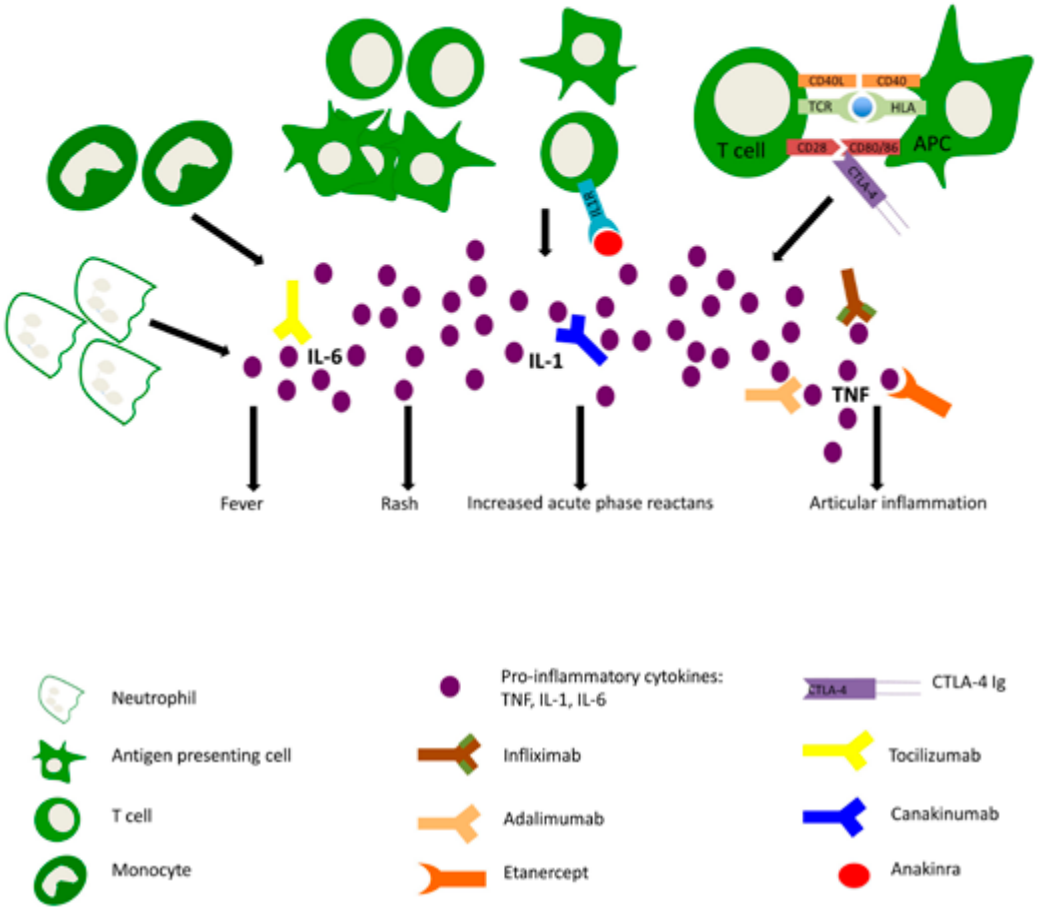

Theme: Pediatric rheumatology

Article

Review Article

Case Report

Short Communication

Paediatric Cochrane Corner

Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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NAAM VAN HET GENEESMIDDEL Enterol 250 mg poeder voor orale suspensie Enterol 250 mg harde capsules. *Saccharomyces boulardii CNCM I-745.* KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Enterol 250 mg poeder voor orale suspensie: Elk zakje poeder voor orale suspensie bevat 250 mg gelyofiliseerde *Saccharomyces boulardii CNCM I-745* (hetzij minstens 6 x 10^9 levensvatbare cellen op het ogenblik van de fabricage en 1 x 10^9 gelyofiliseerde levensvatbare cellen op de vervaldatum). Enterol 250 mg harde capsules: Elke harde capsule bevat 250 mg gelyofiliseerde *Saccharomyces boulardii CNCM I-745* (hetzij minstens 6 x 10^9 levensvatbare cellen op het ogenblik van de fabricage en 1 x 10^9 gelyofiliseerde levensvatbare cellen op de vervaldatum). Hulpstof(fen) met bekend effect: Enterol 250 mg poeder voor orale suspensie: fructose, lactose. Enterol 250 mg harde capsules: lactose. Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de SKP. FARMACEUTISCHE VORM: Enterol 250 mg poeder voor orale suspensie: Poeder voor orale suspensie. Enterol 250 mg harde capsules: Harde capsule. KLINISCHE GEGEVENS: Therapeutische indicaties: Preventie van diarree bij behandeling met breedspectrumantibiotica van patiënten voorbeschikt tot het ontwikkelen van diarree door *Clostridium difficile* of hervallen in een diarree veroorzaakt door *Clostridium difficile*. Adjuverende behandeling naast orale rehydratie van acute diarree bij kinderen tot 12 jaar. Dosering en wijze van toediening: Dosering: Volwassenen: 2 tot 4 harde capsules of 2 tot 4 zakjes per dag, in 2 innames. Pediatrische patiënten: Kinderen: 2 harde capsules of 2 zakjes per dag, in 2 innames. Wijze van toediening: Harde capsules: de harde capsules met wat water inslikken. Zakjes: het poeder mengen in een glas water. Te nemen voorzorgen voorafgaand aan gebruik of toediening van het geneesmiddel. Vanwege een risico op besmetting via de lucht, mogen zakjes of capsules nooit worden opengemaakt in patiëntenkamers. Beroepsbeoefenaren in de gezondheidszorg moeten tijdens het hanteren en het toedienen van probiotica handschoenen dragen, waarna de handschoenen onmiddellijk moeten worden weggegooid en de handen moeten worden gewassen. Duur van de behandeling: Preventie van een nieuwe episode of recidief van diarree door *Clostridium difficile*: 4 weken. Behandeling van diarree als aanvulling op orale rehydratie bij het kind: 1 week. Contra-indicaties: Overgevoeligheid voor de werkzame stof of voor één van de in rubriek 6.1 van de SKP vermelde hulpstoffen. Patiënten met een centrale veneuze katheter, patiënten in kritieke toestand of immuungecompromitteerde patiënten, vanwege een risico op fungemie. Allergie voor gisten, vooral *Saccharomyces boulardii CNCM I-745.* Bijwerkingen: De bijwerkingen worden hieronder geklasseerd per orgaansysteem en volgens de frequentie. Die laatste wordt als volgt gedefinieerd: 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).Infecties en parasitaire aandoeningen: Zeer zelden: fungemie in patiënten met een centraal veneuze katheter

10	9,16 €	10	9,16 €	10	9,25 €
20	16,96 €	20	16,96 €	20	17,50 €
50	36,95 €				

katheter en in patiënten in kritieke toestand of immuungecompromitteerde patiënten, mycose door *Saccharomyces boulardii CNCM I-745.* Immuunsysteemaandoeningen: Zeer zelden: anafylactische shock. Bloedvataandoeningen: Zeer zelden: anafylactische shock. Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen: Zeer zelden: dyspneu. Maagdarmstelselaandoeningen: Zeer zelden: verstopping, epigastralgie, abdominaal meteorisme (epigastralgie en abdominaal meteorisme werden waargenomen in klinische studies) Huid- en onderhuidaandoeningen: Zeer zelden: jeuk, exantheem, Quincke-oedeem. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer zelden: dorst. Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijk 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: www.fagg.be, adversedrugreactions@fagg-afmps.be; Luxembourg: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html). HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN BIOCODEX Benelux NV/SA - Marie Curiesquare 20 - 1070 Brussel - België - Tel: 0032(0)23704790. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN: Enterol 250 mg poeder voor orale suspensie: BE 269026. Enterol 250 mg harde capsules in glazen flesje: BE 269035. Enterol 250 mg harde capsules in blisterverpakking: BE 397896. AFLEVERINGSWIJZE: Vrije aflevering. DATUM VAN HERZIENING VAN DE TEKST: Herziening: 01/2018. Goedkeuring: 03/2018.

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Contents

Les bons choix
commencent tôt

L'eau minérale naturelle **SPA REINE** a été filtrée par la nature pendant plusieurs années dans un endroit rigoureusement **protégé de toute pollution, donnant à cette eau unique une pureté extrême.**
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A la vie

Editorial

In this autumn issue of the BJP (2018 vol 20 nr 3) you can explore, under the general theme "Arthropaties", a disease entity poorly recognized in paediatrics. Our team of guest editors, Carine Wouters and Pierre Philippet, have gathered a series of articles that invite the reader to discover these diseases through their diverse clinical aspects and enjoy the scientific journey devoted to the "Problem solving approach in pediatric rheumatology". It addresses several common symptoms such as *back pain* ("When to refer to a pediatric rheumatologist?"), *fever* ("Beyond recurrent fever: inflammasome-related auto-inflammatory diseases") *skin* ("Dermatological presentations of pediatric rheumatic diseases"), *eye* ("Paediatric non-infectious uveitis"), *emergency* ("Recognition of rheumatic condition at the emergency unit") to end up with an update on recent *treatments* ("New therapies for children with rheumatic conditions").

You will also find an original update article "Adjusted Bristol Stool Scale for non-toilet-trained children " of a useful tool to assess the common symptom of constipation, a review article on "Congenital pulmonary malformations", several interesting unusual case reports "A child with mercurial results of the lactose breath test", "Pacemaker implantation as a successful treatment of complicated breath holding spells" and "two cases of pyelonephritis" . Of special interest a short warning communication about the imminent outburst of the seasonal respiratory syncytial virus.

In our section Paediatric Cochrane Corner an interesting provocative point of view is developed "Antibiotics may be effective to treat prolonged wet cough in children".

Do not be surprised by the absence of PhD theses summaries in our regular section on MIB (made in Belgium) probably due to summer holidays but be reassured, our next winter issue is ready to publish several MIB manuscripts that illustrate the work of our scientific researchers in Belgium.

Notice that two young colleagues, Christophe Barrea and Anne Rochtus, have joined the editorial board together with Natacha Meignen, our efficient edition secretary.

Last, but not least, as planned two years ago, we will soon submit the BJP to international recognition by Medline. We expect a successful issue of this important step for the future of the BJP and wish to thank our colleague Marek Wojciechowski for his remarkable efforts to harmonize the edition of our journal.

Samy Cadranel and Marc Raes

Uw vragen of commentaar
Vos questions ou commentaires

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

Comité de rédaction - Redactieraad
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NAAM VAN HET GENEESMIDDEL: HEMANGIOL 3,75 mg/ml, drank **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING:** 1 ml oplossing bevat 4,28 mg propranolol hydrochloride equivalent aan 3,75 mg propranololbase. **FARMACEUTISCHE VORM:** Drank. Heldere, kleurloze tot lichtgele drank met een fruitgeur. **THERAPEUTISCHE INDICATIES:** HEMANGIOL is geïndiceerd voor de behandeling van prolifererend infantiel hemangioom waarvoor systemische therapie vereist is: levens- of functiebedreigend hemangioom, geülcereerd hemangioom met pijn en/of gebrek aan respons op eenvoudige maatregelen voor wondverzorging, hemangioom met een risico op blijvende littekens of ontsiering. De behandeling moet gestart worden bij kinderen in de leeftijd van 5 weken tot 5 maanden. **DOSERING EN WIJ-ZE VAN TOEDIENING:** Een behandeling met HEMANGIOL moet worden gestart door artsen met ervaring in de diagnose, behandeling en aanpak van infantiel hemangioom en in een gecontroleerde ziekenhuisomgeving waar geschikte apparatuur aanwezig is voor het behandelen van bijwerkingen, met inbegrip van bijwerkingen die een spoedprocedure vereisen. Dosering: De dosering wordt uitgedrukt in propranololbase.De aanbevolen startdosis is 1 mg/kg/dag die over twee afzonderlijke doses van 0,5 mg/kg wordt verdeeld. Het wordt aanbevolen om de dosis onder medisch toezicht tot de therapeutische dosis als volgt te verhogen: 1 mg/kg/dag gedurende 1 week, dan 2 mg/kg/dag gedurende 1 week en dan 3 mg/kg/dag als onderhoudsdosis. De therapeutische dosis bedraagt 3 mg/kg/dag, die ook in 2 afzonderlijke doses van elk 1,5 mg/kg moet worden toegediend, één 's morgens en één in de late namiddag, met een tijdsinterval van minstens 9 uur tussen twee innamen. Het geneesmiddel moet tijdens of onmiddellijk na een voeding worden ingenomen.Het wordt aanbevolen om de dosis over te slaan als het kind niet eet of als hij/zij braakt. Als het kind een dosis teruggeeft of niet al het geneesmiddel ingenomen heeft, mag geen andere dosis gegeven worden tot de volgende geplande dosis.Tijdens de titratiefase moet elke dosisstijging door een arts gecontroleerd en gemonitord worden volgens dezelfde voorwaarden als het toedienen van de startdosis. Na de titratiefase zal de dosis door de arts opnieuw aangepast worden volgens de gewichtsveranderingen van het kind. Klinische monitoring van de toestand van het kind en dosisaanpassing moeten minstens elke maand uitgevoerd worden. Duur van de behandeling: HEMANGIOL moet toegediend worden gedurende een periode van 6 maanden. Het stoppen van de behandeling vereist geen geleidelijke dosisverlaging. Bij een minderheid van de patiënten bij wie de symptomen opnieuw optreden na het stopzetten van de behandeling, mag de behandeling opnieuw gestart worden onder dezelfde omstandigheden met een bevredigende respons. Speciale populaties: Door de afwezigheid van klinische werkzaamheids en veiligheidsgegevens mag HEMANGIOL niet gebruikt worden bij kinderen jonger dan 5 weken oud. Er zijn geen klinische werkzaamheids- en veiligheidsgegevens beschikbaar uit de klinische studies die zijn uitgevoerd met HEMANGIOL om het starten van deze behandeling bij kinderen ouder dan 5 maanden aan te bevelen. Kinderen jonger dan 1 jaar met een lever- of nierfunctiestoornis: Er zijn geen gegevens beschikbaar. Daarom wordt toediening van het middel aan kinderen jonger dan 1 jaar met een lever- of nierfunctiestoornis niet aanbevolen. Wijze van toediening. Voor oraal gebruik. HEMANGIOL moet tijdens of onmiddellijk na een voeding gegeven worden om het risico op hypoglykemie te vermijden. Het moet rechtstreeks in de mond van het kind toegediend worden met behulp van een gegradueerde doseerspuit voor orale toediening, gekalibreerd in mg propranololbase, die bij de fles met drank is meegeleverd (zie instructies voor gebruik in rubriek 3 van de bijsluiter). De fles niet schudden vóór gebruik. Indien nodig, mag het geneesmiddel verdund worden met een kleine hoeveelheid babymelk en/of appel- of sinaasappelsap dat aangepast is aan de leeftijd van het kind. Het geneesmiddel mag niet in de volle fles gedaan worden. Voor kinderen tot 5 kg mag het geneesmiddel gemengd worden met één theelepel (ongeveer 5 ml) melk. Voor kinderen die meer dan 5 kg wegen, mag het gemengd worden met een eetlepel (ongeveer 15 ml) melk of vruchtensap. Dit mengsel wordt dan in de zuigfles aan het kind gegeven. Het mengsel moet binnen 2 uur gebruikt worden. HEMANGIOL en de voeding moeten door dezelfde persoon worden gegeven om het risico op hypoglykemie te vermijden. Als verschillende personen betrokken zijn, is een goede communicatie noodzakelijk voor de veiligheid van het kind. **CONTRA-INDICATIES:** Premature kinderen jonger dan 1 jaar bij wie de gecorrigeerde leeftijd van 5 weken niet bereikt is (de gecorrigeerde leeftijd wordt berekend door het aantal weken prematuriteit af te trekken van de reële leeftijd) • Kinderen jonger dan 1 jaar die borstvoeding krijgen, als de moeder behandeld wordt met geneesmiddelen die gecontra-indiceerd zijn met propranolol • Overgevoeligheid voor de werkzame stof of voor één van de hulpstoffen • Astma of een voorgeschiedenis van bronchospasme • Tweede- of derdegraads atrioventriculair blok • Sicksinussyndroom (inclusief sinoatriaal blok) • Bradycardie onder de volgende grenzen: Leeftijd: 0-3 maanden/ 3-6 maanden/ 6-12 maanden - Hartslag (slagen/min.): 100/90/80. Lage bloeddruk onder de volgende grenzen: Leeftijd: 0-3 maanden/ 3-6 maanden/ 6-12 maanden - Bloeddruk (mmHg): 65/45 / 70/50 / 80/55. Cardiogene shock • Hartfalen dat niet onder controle is met medicatie • Prinzmetal-angina • Ernstige verstoringen van de perifere arteriële bloedsomloop (fenomeen van Raynaud) • Kinderen die vatbaar zijn voor hypoglykemie • Feochromocytoom. **BIJWERKINGEN:** Samenvatting van het veiligheidsprofiel: In klinische studies voor prolifererend infantiel hemangioom waren de meest gemelde bijwerkingen bij kinderen jonger dan 1 jaar behandeld met HEMANGIOL slaapstoornissen, verergerde luchtweginfecties zoals bronchitis en bronchiolitis in combinatie met hoesten en koorts, diarree en braken. Globaal hadden de bijwerkingen gemeld bij het gebruiksprogramma in schrijnende gevallen en in de literatuur betrekking op hypoglykemie (en gerelateerd voorval zoals hypoglykemisch insult) en verergerde luchtweginfecties met ademnood. Tabel van bijwerkingen: De volgende tabel geeft de bijwerkingen, ongeacht de dosis en de duur van de behandeling, die gemeld werden in drie klinische studies waaraan 435 patiënten deelnamen die behandeld werden met HEMANGIOL 1 mg/kg/dag of 3 mg/kg/dag gedurende een maximale behandelperiode van 6 maanden. De frequentie wordt gedefinieerd aan de hand van de volgende afspraak: 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). Omwille van de omvang van de database van de klinische studie worden de categorieën zelden en zeer zelden niet gegeven. Binnen elke systeem/orgaanklasse worden de bijwerkingen gerangschikt naar afnemende ernst. Infecties en parasitaire aandoeningen: Zeer vaak (Bronchitis) - Vaak (Bronchiolitis). Voedings- en stofwisslingsstoornissen: Vaak (Verminderde eetlust). Psychische stoornissen: Zeer vaak (Slaapstoornis-sen) - Vaak ((Agitatie, Nachtmerries, Prikkelbaarheid). Zenuwstelselaandoeningen: Vaak (Somnolentie) - Niet gekend (Hypoglykemisch insult). Hartaandoeningen: Soms (AV-blok) - Niet gekend (Bradycardie). Bloedvataandoeningen; Vaak (Perifere koude) - Niet gekend (Hypotensie, Vasoconstrictie, Fenomeen van Raynaud). Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen: Vaak (Bronchospasme). Maagdarmstelselaandoeningen: Zeer vaak (Diarree, Braken) - Vaak (Obstipatie, Abdominale pijn). Huid- en onderhuidaandoeningen: Vaak (Erytheem) - Soms (Urticaria, Alopecia). Onderzoeken: Vaak (Bloeddruk verlaagd) - Soms (Bloedglucose verlaagd - Hartfrequentie verlaagd - Neutropenie) - Niet gekend (Agranulocytose - Hyperkaliëmie). Beschrijving van de geselecteerde bijwerkingen. Wat betreft de onderste luchtweginfecties, zoals bronchitis of bronchiolitis, werd er een verergering van de symptomen (met inbegrip van bronchospasme) gezien bij patiënten die behandeld werden met HEMANGIOL vanwege het bronchoconstrictieve effect van propranolol. Deze effecten leidden zelden tot definitieve stopzetting van de behandeling. Slaapstoornissen komen overeen met insomnia, een slaap van slechte kwaliteit en hypersomnie. Andere aandoeningen van het centraal zenuwstelsel werden hoofdzakelijk waargenomen in de vroege perioden van de behandeling. Diarree werd frequent gemeld en was niet altijd geassocieerd met een gastro-intestinale infectieziekte. Het optreden van diarree lijkt dosisafhankelijk te zijn tussen 1 en 3 mg/kg/dag. Bij geen van de gevallen was de intensiteit ernstig of leidde tot stopzetting van de behandeling. Cardiovasculaire gebeurtenissen die tijdens klinische studies werden gemeld waren asymptomatisch. In de context van de cardiovasculaire monitoring gedurende 4 uur tijdens de titratiedagen werd na de toediening van het geneesmiddel een daling van de hartslag (ongeveer 7 bpm) en van de systolische bloeddruk (minder dan 3 mmHg) gezien. Één geval van tweedegraads atrioventriculair blok bij een patiënt met een onderliggende geleidingsstoornis leidde tot definitieve stopzetting van de behandeling. In de literatuur werden geïsoleerde gevallen van symptomatische bradycardie en hypotensie gemeld. De dalingen van het bloedglucosegehalte die tijdens klinische studies werden waargenomen, waren asymptomatisch. Niettemin werden tijdens het gebruiksprogramma in schrijnende gevallen en in de literatuur verschillende gevallen van hypoglykemie met een gerelateerd hypoglykemisch insult gemeld, vooral tijdens een vastenperiode bij een intercurrente ziekte. Gelijktijdige behandeling met systemische corticosteroïden kan het risico op hypoglykemie verhogen. In de literatuur werd bij enkele patiënten met groot geülcereerd hemangioom hyperkaliëmie gemeld. 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 België : Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie EUROSTATION II Victor Hortaplein, 40/ 40 B-1060 Brussel Site internet: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN:** PIERRE FABRE DERMATOLOGIE - 45 place Abel Gance - F- 92100 Boulogne. **NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN.** EU/1/14/919/001. **DATUM EERSTE VERGUNNING-VERLENING/VERLENGING VAN DE VERGUNNING.** Datum van eerste verlening van de vergunning: 23 april 2014. **DATUM VAN HERZIENING VAN DE TEKST.** 09/2014. Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau (http://www.ema.europa.eu). **AFLEVERWIJZE.** Op medisch voorschrift.

04/2017

20170205

Pierre Fabre
DERMATOLOGIE

* Waarvoor systemische behandeling vereist is

President's address

Dear colleagues,

We experienced an exceptional dry and hot summer, even those scattered across the world for summer travels and even going on at the release of this September issue of our Journal. June 2018 seems – as time often does to us – like a long time ago.

At the publication of this issue, I'll start my last 6 months as your president.

Part of the role of the BVK/SBP president is to promote and to facilitate its mission goals, from which we chart progress. Our mission is a scientific one, representing caregivers involved with children, to obtain in our profession a continuous improvement in care of excellence, both preventive and curative, and this in our rapidly changing society. And today we can cite significant progress: the 2018 annual congress was again of outstanding scientific quality. The number of participants is growing annually since the last 3-4 years. More diversity in participants is observed, with growing participation of all paediatricians, including those in training and coming from all universities and hospitals and not only from the organizing institution, as was often the case before. The number of members has also increased since the last 2 years, and this is of course essential for the existence of the BVK/SBP. We also record an increasing number of visits to our website, which confirms the growth of our society. And last but not least, our Journal will soon be submitted to obtain recognition by Medline, as explained in the editorial by Samy Cadranel and Marc Raes. I thank all colleagues who contributed to this progress.

But part of the role of a president, at least as I understand it, is to provide perspective on work that remains undone and on areas that require our attention for the future. In this issue you will find an invitation to renew you membership for 2019: in the invitation the advantages of this membership are described and cannot be denied. Membership costs remain unchanged for the coming year. We thank all members for their fidelity and hope they will renew their 2019 membership; we also invite warmly new young colleagues in training, and also hope to welcome established paediatricians as new members. By becoming a member, you will contribute to the future and the optimization of our profession. We especially think of the young settled colleagues, in private or working in an institution to join us and rejuvenate our society. We Belgian paediatricians need each other and there is still room for doubling the number of BVK/SBP members and increase the number of active members in our board. Please don't hesitate to contact us if you have suggestions to improve our society.

In this issue, you will find more information about the 2019 Congress, organized by our colleagues of the University of Leuven, which will take place in Brussels, Conference Center The Egg, on March, 21-22, 2019. I am happy to announce you that also during this Congress, scientific prizes to support research in the field of paediatrics will be again awarded. In this issue you will find all information and call for application to these prizes. More details will also be available on the website www.bvk-sbp.be

For most of us summer and holidays ended, and in a few weeks fall and winter viral diseases need to run their course. This will become the main occupation for most of us. I wish you all a lot of job satisfaction in the coming season.

Anne Malfroot

President BVK-SBP

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- The grant is awarded to a paediatrician, either in training or certified.
- Applications need to be written in English.
- Applications must be submitted to the Belgian Society of Paediatrics, by e-mail to Natacha Meignen, BVK/SBP secretary, **secr_bvksbp@hotmail.com**. The deadline for application is January 16th, 2019 (before midnight). All information is also available on **www.bvk-sbp.be**
- Applications will be judged by a jury appointed by the president and the board of the Belgian Society of Paediatrics.
- Documents to be submitted include:
    - A detailed fellowship program and research project approved and signed by the responsible supervisors.
    - Recent curriculum vitae.
    - Motivation for application.
- The candidates must present their project in the paediatric dermatology session at the congress.
- The jury will make a ranking and transfer it to the president of the Belgian Society of Paediatrics.
- The award ceremony takes places at the annual congress of the Belgian Society of Paediatrics (2019, March 21 -22, Brussels).
  The laureate agrees to present the results after completion of the project at a next congress.
- The grant can be awarded only once to the same candidate.

Research PRIZES of the Belgian Society of Paediatrics BVK/SBP 2019
Guidelines 2018-2019

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

1- This prize of an amount of **7.500€** will be awarded during the next edition of the BVK/SBP Congress taking place on March 21-22, 2019. The prize rewards authors of a research project in the field of paediatrics.
The research project must be related to one of the Belgian Universities or University hospitals and contribute to the development of paediatrics in Belgium. The applicant can have the Belgian or foreign nationality on the condition that he/she is or has been doing research activities in Belgium in a paediatric context.

2- Candidates need to be
   a. graduated physicians for less than 15 years on the date of submission deadline
   b. paediatricians or paediatricians in training
   c. members of the BVK/SBP

3- The award will be granted on the basis of the recommendations of a jury, composed by members of the Steering Committee of the BVK/SBP and experts from European Societies of Paediatrics. Evaluation of the projects will be based on the scientific strength of the project as well as on its feasibility and its relevance. The results of the evaluation will be given during the coming 2019 BVK/SBP Congress.

4- Guidelines will be available from October 2018 on the website of the Belgian Society of Paediatrics www.bvk-sbp.be.

5- The application form can be downloaded from www.bvk-sbp.be. Completed forms must be completed in English and should be sent to the scientific secretariat of the Society, Natacha Meignen secr_bvksbp@hotmail.com by November 30th, 2018 at the latest. A curriculum vitae of the candidate written in English needs to be attached to the application.

6- Funding can be cumulated with other sources of finance.

7- The project can be submitted twice to the BVK/SBP

8- BVK/SBP is empowered to decide not to award the prizes depending on the quality and number of submissions.

9- It will be requested to the candidates to attend the 2019 annual congress and to present their submitted projects in English during the dedicated session "Young Investigators" . The winner of the prize will be announced during the award ceremony at the end of the annual congress on March 21-22, 2018 in Brussels

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 préremplieVaccin 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

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GSKPRO.COM

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE

SOCIETE BELGE DE PEDIATRIE

Hernieuwing lidmaatschap 2018

Beste Collega,

De leden van de Raad van bestuur wensen u te bedanken voor het vertrouwen dat u stelde in de BVK. Door uw bijdrage als lid van onze vereniging kunnen we samen werken aan de toekomst van de pediatrie. Wij, Belgische kinderartsen, hebben elkaar nodig. De BVK heeft in de eerste plaats een wetenschappelijke rol en steunt en handhaaft de wetenschappelijk gezondheidszorg voor kinderen. De vereniging werkt ook samen met de Academie en het College pediatrie in de beleidsvisies en de organisatie van de pediatrie op maatschappelijk vlak.

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

De voordelen van een BVK lidmaatschap zijn talrijk: via de site van de BVK, krijgen de leden toegang tot de numerieke bibliotheek van de CEBAM (Belgian Center for Evidence Based Medicine). Die toegang maakt het mogelijk de artikels van de belangrijkste pediatrische tijdschriften te lezen en te downloaden (Pediatrics, Journal of Pediatrics, Pediatric Infectious Disease Journal, etc.). De site geeft ook toegang tot de “big five” (New England Journal of Medicine, Lancet, BMJ, JAMA en Annals of Internal Medicine) alsook tot talrijke databases van Evidence-Based Medicine (Cochrane Library, etc) en elektronische boeken. Verder krijgen de leden ook gratis het tijdschrift “Belgian Journal of Paediatrics”.

Door uw bijdrage als lid van onze vereniging kan u zich ook aan een voordelig tarief inschrijven voor het komende Jaarlijks Congres van de BVK op 21 en 22 maart 2019. Mede door uw lidmaatschap kunnen wij een beurs voor onderzoek uiteiken aan de beste inzending. Help ons onze onderzoekers aan te moedigen en ze in België te houden!

Het lidmaatschap tot de BVK loopt van 1 oktober 2018 tot september 2019.

De jaarlijkse bijdragen blijven ongewijzigd:

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

Uw lidmaatschap verlengen kan via de website www.bvk-sbp.be

Wij rekenen opnieuw op uw bijdrage en werken samen aan de realisatie van onze toekomst.

Van harte,

Prof Dr Anne MALFROOT
Voorzitter BVK/SBP

Renouvellement cotisation 2018

Cher collègue,

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

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

Les avantages d'une adhésion à la Société sont nombreux : notamment, les membres bénéficient, via le site de la SBP, d’un accès à la bibliothèque virtuelle CEBAM (Belgian Center for Evidence Based Medecine). Je vous rappelle que l’accès au volet pédiatrique du site de la CEBAM permet la lecture et le téléchargement d’articles des principaux journaux pédiatriques (entre autres Pediatrics, Journal of Pediatrics, Pediatric Infectious Disease, etc.). Le site donne également accès aux “big five” (New England Journal of Medicine, Lancet, BMJ, JAMA et Annals of Internal Medicine) ainsi qu’à de nombreuses bases de données d’Evidence Based Medecine (Cochrane Library, etc) ainsi qu’à des livres électroniques. Les membres reçoivent aussi gratuitement le BJP (Belgian Journal of Paediatrics).

Votre adhésion en tant que membre de notre société vous permettra de vous inscrire à un tarif réduit au futur Congrès Annuel de la SBP qui aura lieu le 21 et 22 Mars 2019. Grâce à votre adhésion, nous pouvons, en autres, décerner un prix pour la recherche à la meilleure contribution. Aidez-nous à encourager nos chercheurs et à les garder en Belgique!

L’adhésion à la société est valable du 1er octobre 2018 jusqu'au 30 septembre 2019.

Les cotisations annuelles restent inchangées :

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

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

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

Cordialement,

Prof Dr Anne MALFROOT
Président SBP/BVK

We care for children

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE

SOCIETE BELGE DE PEDIATRIE

SAVE THE DATE

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Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

DYNAMICS IN PEDIATRICS

21 & 22.03.2019

THE EGG, Brussels

www.bvksbp2019.be

BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

Registrations opening
15 October 2018

Abstracts submission deadline
21 December 2018

Organizing Committee (UZ Leuven):

K Arts, G Buyse, A Devroey, R Heying, I Hoffman, N Knops, I Meyts, G Naulaers, E Ortibus, M Raes, T Salaets, A Smits; J Toelen, A Uyttebroeck, C Wouters

Gunnar Buyse, MD PhD
Congress President, UZ Leuven

Anne Malfroot, MD PhD
President BVK/SBP

DE BVK BEDANKT ZIJN PARTNERS VOOR HUN STEUN

LA SBP REMERCIE SES PARTENAIRES POUR LEUR SOUTIEN

LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

gsk

Pierre Fabre
DERMATOLOGIE

NUTRICIA
early life nutrition

abbvie

SPA

What's up doc

EXPANSCIENCE
LABORATOIRES

BIOCODEX
Benelux

bioprojet

Pampers

We care for children

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE

SOCIETE BELGE DE PEDIATRIE

Dear colleagues,

It is our great pleasure to invite you to the autumn meeting of the Belgian Society of Pediatric Neurology which will take place in Flanders Meeting & Convention Center Antwerp - part of Elisabeth Center Antwerp, November 9th 2018.

"New Treatments and Ethical Considerations"

New treatments are becoming more and more available for neurometabolic, neuromuscular as well as epileptic disorders in children. However the cost of these treatments raises social questions and the discussion for whom these treatments must be available becomes a real ethical challenge for us pediatric neurologists.

With kind regards,

The team of Pediatric Neurology, University Hospital Antwerp and the BSPN board.
Info: kinderneurologie@uza.be

Participation fee all included

Trainee	25 €
BSPN member	Free
Non-BSPN member	50 €
On-Site registration	70 €

Please use the registration tool in the calendar section of our website www.bspn.be.
Registration will only be valid after payment of the participation fee, on a first paid first accepted basis.
By bank transfer to the account number
IBAN : BE38 2100 0475 5072
BIC : GEBABEBB
using the account name "ASBL SOCIETE BELGE DE NEUROLOGIE PEDIATRIQUE", and mentioning "BSPN Autumn Meeting 09/11/2018" and name of the participant

Free communications

Colleagues (especially trainees) are encouraged to submit a scientific abstract, preferably related to the theme of the day. Abstracts should be sent before October 15th , only by email to diane.beysen@uza.be
Clearly indicate title, authors, address, and e-mail address. The abstract should be typed in MS-Word and not exceed 2000 characters.

BIOCODEX
MICROBIOTA
FOUNDATION

BELUX 2018

NATIONAL CALL FOR RESEARCH PROJECTS

GUT MICROBIOTA IN HUMAN HEALTH AND DISEASES

Submission deadline:
October 31, 2018

Amount of the grant:
€25.000

Decision of the National Scientific Committee:
January 2019

Please send the application form by email to:
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Perspectives : Problem solving approach in pediatric rheumatology

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Pediatric rheumatology is a relatively young specialty. It emerged as a distinct entity during the seventies, under the impulse of a few pioneers in Europe, USA and Canada (Barbara Ansell, Anne-Marie Prieur, James Cassidy, Ross Petty, …) who defined the major rheumatic conditions affecting children, naming their essential features and recognizing their diversity. In over nearly 50 years, pediatric rheumatology has evolved to a distinct and well-recognized specialty, concerned with the understanding and care of a wide spectrum of autoimmune and auto-inflammatory diseases affecting children and young people, characterized by systemic inflammation as well as inflammation of joints, muscles, bone, skin, blood vessels and diverse organs such as eye, brain and visceral organs. The scope of Pediatric Rheumatology also includes non-inflammatory musculoskeletal pain and dysfunction syndromes.

Close links have always existed between rheumatology and other pediatric disciplines. This is especially true for the interactions with immune deficiency, both specialties being characterized by a dysregulation of the immune response.

Thanks to an acceleration of scientific research into the etiology and mechanisms of pediatric rheumatic and systemic inflammatory conditions, there has been a major advance in identification of genetic causes of several auto-inflammatory and some autoimmune diseases as well as in the development of effective targeted biological therapies especially for juvenile idiopathic arthritis.

The pediatric rheumatology community today is well organized, with a training program recognized at the European level, an organized platform for European and international clinical research (Paediatric Rheumatology International Trials Organization - PRINTO), an active European society (Paediatric Rheumatology European Society – PreS), and multiple collaborations all around the world.

In the beginning of the eighties, a small group of pediatric rheumatologists, pediatricians and rheumatologists with a special interest in pediatric rheumatology, founded a discussion group, and formally created an association in 2009, named the Belgian working group of Pediatric Rheumatology (BPR). The BPR aims to share experience and knowledge, create a network in Belgium, support the child's and their families, and sensitize the medical world and the authorities to the cause of children suffering from auto-inflammatory, autoimmune and other rheumatic diseases. This is an open group, eager to welcome all participants interested in.

Nine years ago, in the 2009-Vol.11-Nr.2 edition of the « Tijdschrift van de Belgische Kinderarts /Journal du Pédiatre Belge », nowadays the « Belgian Journal of Paediatrics », a special issue has been dedicated to Pediatric Rheumatology. The issue presented a differential diagnosis for the child presenting with persistent joint pain or fever, an overview of the major pediatric rheumatic conditions and of new treatments for JIA.

In the present issue, we have chosen to focus on a problem solving approach in children presenting with cutaneous manifestations, ocular manifestations, fevers, back pain or an emergency which all may masquerade a spectrum of autoimmune/ auto-inflammatory conditions. The recent advances in therapies will also be addressed.

We wish you an enjoyable reading.

Recognition of rheumatic condition at the emergency unit

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Key words

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Abstract

Addressing some usual symptoms and signs such as pain, arthritis, fever or cutaneous rash, we give to the physician facing clinical problems in an emergency ward, some clues to think about a "rheumatic" condition and some tools to guide his diagnosis.

Introduction

Pediatric emergency wards have to face several conditions with objective urgent goals, but have also often to manage with child, parental or treating physician stress.

The mission of the resident, the urgentist or the pediatrician will be to recognize some clue signs enjoining a rapid medical care, allowing to reassure the patient or his parents, or requiring to address for complementary exploration and advice. From this point of view, the wide spectrum of diseases and clinical presentations covered by pediatric rheumatology is a particular challenge. A way to address the reasoning is to start from the symptoms and the history/anamnesis. Without any objective to be complete, we present a selection of some of these most frequent and evocative symptoms, with some clues to identify an inflammatory or autoimmune condition.

A/ Main symptoms

1) The child with pain and/or arthritis

- **Acute pain** focused on a joint or a bone area should generally be taken into account in association with complementary context and signs :
  - Traumatic history will naturally orient towards a fracture or another traumatic lesion. However, some inflammatory conditions could have an apparent traumatic point of origin. It is obvious to exclude a bone fracture or a soft tissue injury by appropriate imaging (X-ray or ultrasound in first intention), but we have not to forget the possibility of an alternative etiology.
  - Fever push to exclude acute infection. If classical septic arthritis due to Staphylococcus aureus has often a noisy presentation, the prevalence of subacute arthritis due to Kingella Kingae (KK) is growing. Symptoms of KK arthritis are more attenuated, with less fever, swelling, redness, heat, and inflammatory parameters.
- **Subacute pain** has to make us think to a wide spectrum of origins, from benign situations as transient synovitis of the hip or growing pain, to more problematic pathologies.

  A warning sign is the diffuse localization of bone pain which could be the first and only sign of a leukemia. More focused subacute pain has always to alert the clinician for a tumoral problem (osteosarcoma, Ewing sarcoma, histiocytosis, metastasis, …). Any pain which wakes up the child during the night has to be considered as a serious condition. Infectious diseases has also to be considered : late phase arthritis due to Borrelia (Lyme disease) has a more subacute evolution.
- **Recurrent/chronic pain** is less frequent in childhood. In these cases, characteristics of the pain are often clues for diagnosis :
  - "Mechanical pain" caused, arisen, or worsened by movement in mostly due to an underlying traumatic lesion.
  - On a contrary, "inflammatory pain" will occur after a period of immobilization, and be associated with a degree of impotency and stiffness. The cardinal signs of inflammation are : heat, redness (less frequently observed in these chronic situations), swelling, pain and loss of function. Morning stiffness and derusting is a clue sign suggesting inflammatory origin of the arthritis.

    Muscular inflammatory diseases, such as juvenile dermatomyositis, could begin with such diffuse subacute and recurrent muscular pain.
  - The two pain presentations ("mechanical" and "inflammatory") are often mixed. The anamnesis has to be conducted by precise and oriented questions to the child and the parents to guide the clinical reasoning.
  - These signs could be combined at different levels and fluctuating on a timeline. In these conditions different chronic diseases has to be address : juvenile idiopathic arthritis (JIA) is clearly the leading one, but also other diseases such as chronic recurrent multifocal osteomyelitis, complex regional pain syndrome or metabolic diseases (Gaucher or Fabry disease, …), Ehlers-Danlos disease, …

2) The child with fever

- Inflammatory origin of fever is generally considered after exclusion of other causes such as infection or malignant disease. However, association with some clinical symptoms could suggest an inflammatory or auto-immune disease :
  - Macular cutaneous eruption will orient for the systemic form of JIA (sJIA or Still's disease).
  - Purpura will suggest Henoch-Schönlein or another vasculitis.
  - Mucous or conjunctival lesions could suggest Kawasaki disease.
  - Abdominal pain or diarrhea point out for an inflammatory bowel disease. The schedule of the fever, the general condition of the child and the associated symptoms will guide the diagnosis.
- A special attention has to be paid to fever associated with lymphadenopathies and hepatosplenomegaly. Beside tumoral situations, macrophage activation syndrome is a severe and potentially fatal condition we cannot miss.
- The question of recurrent fever is a classical reason for consultation. After excluding infectious causes of fever, some clues could point to an auto-inflammatory disease. (cfr article on "The Child with recurrent fever"). Characterization of the fever on a daily, weekly and monthly calendar and objectification of associated signs are essential to guide the diagnosis.

3) The child with cutaneous lesions

Beside typical cutaneous or mucosal lesions suggesting directly a diagnosis (butterfly of systemic lupus (SLE), aphtous ulcers of Behçet disease, palpable purpura of Henoch-Schönlein, …), a lot of inflammatory diseases could be associated with a wide range of cutaneous rash : sJIA, juvenile dermatomyositis (cfr article on "Dermatological presentations of pediatric rheumatic diseases ").

4) Other presentations

A wide range of symptoms could be a sign of an autoinflammatory or autoimmune disease :

- Abdominal pain in Familial Mediterranean Fever, or sometimes as the first sign of Henoch-Schönlein purpura, more rarely of polyarteritis nodosa (PAN).
- Pancreatitis in SLE.
- Stroke or central nervous system hemorrhagic event in vasculitis, SLE, or antiphospholipid syndrome.
- Cardiovascular problems : acute pericarditis in systemic JIA, recurrent pericarditis in periodic fever syndromes, congenital heart block in neonatal lupus, coronary lesions in Kawasaki disease, …
- Pulmonary hemorrhage in granulomatous with polyangiitis (formerly known as Wegener granulomatosis), Goodpasture syndrome, …
- Glomerulonephritis in SLE.
- Uveitis (cfr article on "Paediatric non-infectious uveitis").

B/ Tools for the diagnosis

If the presentation suggests a traumatic origin, appropriate **imaging** is the first complementary to the clinical examination. For bone structures, X-ray remains the first step, sometimes completed by ultrasounds, CT-scan, MRI or Tc-scintigraphy. Soft tissues lesions are well addressed by ultrasounds, completed by MRI if necessary.

- If an inflammatory origin is suspected, some **biologic markers** are useful :
- A complete blood cell count, with a white blood cell formula, is essential to evaluate the inflammatory level, and exclude a malignant disease such as a leukemia.
- The most useful inflammatory markers for acute phase inflammation are C-reactive protein **(CRP)** and erythrocyte sedimentation rate **(ESR)**. In pure inflammatory conditions, it is usual to note a discordance between a relatively low level of CRP and a high level of ESR. **Ferritin** is also an acute phase reactant. A high level of ferritin is relevant with Macrophage Activation Syndrome (MAS).
- Chronic markers of inflammation are also adequately evaluated by **ferritin** level, **immunoglobulins** dosage, or microcytic anemia.
- The most useful "rheumatic" marker in pediatric rheumatology, is the **antinuclear antibodies** (ANA), which can be found positive in a wide range of infectious situations, but is a clue sign in the mono/oligo-arthritis form of JIA. The level of positivity could give a good orientation between a reactional positivity and a signature for JIA. A specific identification of these ANA will point to an autoimmune disease.
- **Rheumatoid factor**, anti-CCP antibody or Waaler-Rose testing are less useful in first intention in pediatric as they are only found in some rarer polyarticular forms of JIA.
- **Complement C3** and **C4** factor are interesting to evaluate, increased in inflammatory conditions, and decreased in autoimmune pathologies (SLE).
- HLA typing, looking for identification of **HLA-B27** could be useful when we suspect a juvenile spondylarthropathy. This analysis is not a first-intention diagnostic tool, but more adequate for subsequent classification.

Every time an infectious origin is suspected, **blood cultures** has to be performed, even if the efficiency of these cultures remains low.

A **joint puncture** should always be performed, with cell count and details, cultures on appropriate substrate, and PCR if KK or Lyme is suspected. A good collaboration with the orthopedist or the radiologist is mandatory to obtain this sample before beginning antibiotics.

To be complete, a **urine sample** needs to be analyzed, looking for proteinuria.

Conclusion

With a good knowledge of the potential presenting situations of (auto-)inflammatory and auto-immune diseases, adequate questions during the anamnesis, fine clinical observation, and the help of a few oriented analysis, will relatively easily guide the clinical reasoning.

Back pain: when to refer to a paediatric rheumatologist? A concise review on juvenile spondyloarthritis.

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Key words

JIA, enthesitis, sacroiliitis, arthritis, HLA-B27

Abstract

Juvenile spondyloarthritis can cause (chronic) back pain in children. In this review, we will discuss the different presentations of juvenile spondyloarthritis going from symptoms, lab work and imaging to treatment and prognosis.

Introduction

David is a ten-year-old boy who is referred by his pediatrician to further investigate his back pain. His back pain started spontaneously four months ago and is typically located at his lower back just above his buttocks. The parents also note that David wakes up during the night in the early morning, complaining of back pain and seems to experience morning stiffness at his back during the first hour of the day. After walking to school everything seems to be much better. Moreover, sitting down for half an hour also aggravates his back pain. David says that there was no prior injury or infection before the back pain onset. The parents add however, that David has had several long lasting episodes of Achilles heel tendinitis for which non-steroidal anti-inflammatory drugs (NSAIDs) were needed.

David's father has Crohn's disease and the sister of his father has recurrent painful red eyes.

The case of David is quite suggestive for inflammatory back pain and most likely for sacroiliitis. This type of pain is different from mechanical pain for example caused by lumbar muscle spasms, discopathy or spondylolysis where movement (and not resting) seems to aggravate the pain. In patients with mechanical low back pain morning stiffness is absent (or very short in duration) and there is no pain during the night.

One of the possible causes of inflammatory low back pain can be infection. Anyhow a non-infectious pathology (such as a juvenile spondyloarthritis) is more frequent, certainly in a protracted course of disease.

In this review, we will discuss the spectrum of juvenile spondyloarthritis (jSpA).

What is a juvenile spondyloarthritis?

Juvenile spondyloarthritis is a group of diseases with common characteristics. They affect as well peripheral joints as tendons and in a number of patients the vertebral column and the sacroiliac joints. These diseases can be accompanied by non-articular manifestations affecting the eye, the skin, the intestine, the urogenital system.[1,2]

It is important to understand that terms such as enthesitis related arthritis, juvenile ankylosing spondylitis, to a certain extent some forms of psoriatic arthritis, reactive arthritis, etc … are part of the spectrum called juvenile spondyloarthritis.[1,2]

Different presentations of juvenile spondyloarthritis

Juvenile Idiopathic Arthritis – Enthesitis Related Arthritis (JIA-ERA)

JIA-ERA is a subcategory of JIA. The (current) criteria for the diagnosis of JIA are:[3]

- Arthritis persisting for longer than 6 weeks.
- Arthritis beginning before 16 years of age.
- exclusion of other conditions associated with or mimicking arthritis.

The specific criteria for JIA-ERA are:[3]

- Arthritis and enthesitis.

OR

- Arthritis or enthesitis.

AND minimal 2 of the following

- Presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain.
- Onset of arthritis in a male over 6 years of age.
- Acute (symptomatic) anterior uveitis.
- HLA-B27 positivity.
- History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative.

Several additional exclusion criteria exist including the history of psoriasis in the patient of first-degree relative, or the presence of a systemic onset of the arthritis.

These criteria emphasize that this is typically a disease of boys older than 6 years old. They typically present with enthesitis of the Achilles tendon, fascia plantaris or infra - patellar tendons and/or asymmetric oligo-arthritis of the lower limbs (although polyarticular presentations might exist as well). Furthermore, involvement of the joints of feet (tarsitis) and hip are quite frequent and specific complaints in these patients.

Although sacroiliitis is a paramount symptom it rather occurs in a minority of patients with JIA-ERA. A familial predisposition mediated through HLA-B27 is frequently present. We note that in contrast to the chronic uveitis in other subcategories of JIA, the acute anterior uveitis is a typical symptomatic uveitis presenting with a red, photophobic and/or painful eye.

Juvenile Idiopathic Arthritis - Psoriatic Arthritis (JIA-PsA or JPsA)

Similarly as JIA-ERA, JIA-PsA is a subcategory of JIA.

Specific criteria for JIA-PsA are:[3]

- Arthritis and psoriasis.

Or Arthritis AND minimal 2 of the following:

- Dactylitis (sausage-like swelling of a digit beyond the joints).
- Nail pitting or onycholysis.
- Psoriasis in a first-degree relative.

Again, several additional exclusion criteria exist including presence of HLA-B27 in a boy older than 6 years or HLA-B27-associated pathology in a first-degree family member.

Depending on whether the above exclusion criteria are applied or not, we can distinguish two different types of JIA-PsA:[4]

- Type 1: young (2-4y) antinuclear antibody (ANA)-positive children (mainly girls) with asymmetric oligoarthritis and increased risk of chronic uveitis.
- Type 2 : adolescent children with asymmetric oligoarthritis and higher risk of enthesitis and sacroiliitis, thereby being very similar to JIA-ERA. This group could be considered as a juvenile version of adult-onset psoriatic arthritis.

Inflammatory Bowel Disease (IBD) associated arthropathy

Crohn's disease, ulcerative colitis and indeterminate colitis are IBDs with potentially juvenile onset and which are associated with an increased risk of arthropathy. In general we distinguish two subtypes:[5]

- Type 1: presenting with peripheral arthralgia/arthritis that is correlated with intestinal activity (and thus transient and self-limiting).
- Type 2: presenting with axial arthritis (sacroiliitis) and enthesitis in older children and little correlation with intestinal activity. The HLA-B27 association further underscores the similarity with JIA-ERA. This type has a higher risk for evolution towards adult spondyloarthritis

Reactive arthritis (ReA)

An acute oligoarthritis (including sacroiliitis), enthesitis and/or tenosynovitis can occur between 1-4 weeks after enteric or genitourinary infection. Best-known infections causing reactive arthritis are Chlamydia, Salmonella, Campylobacter, Shigella and Yersinia. Arthritis can be associated with overlying erythema of the joint. Typical for ReA are the associated symptoms such as aphtosis, erythema nodosum, conjunctivitis and/or uveitis. ReA occurs more frequently in HLA-B27 positive children (especially boys) and although it usually is self-limiting within 6 weeks, longer episodes can occur (thereby disturbing the differential diagnosis with other forms of juvenile spondyloarthritis).

Chronic non-infectious osteomyelitis

Some children suffer from chronic non-infectious osteomyelitis, which is often recurrent and multifocal (in those cases it is also called chronic recurrent multifocal osteomyelitis (CRMO)). Almost every bone in the body can be affected, but most frequent sites of inflammation are the metaphyseal regions of the long bones, the clavicles and the vertebral bodies. In the context of this review it is important to realize that this disease can also affect the sacrum. Chronic non-infectious osteomyelitis (or CRMO) is also associated with arthritis and skin eruptions such as pustulosis. Treatment includes the use of NSAIDs and if not sufficient disease modifying antirheumatic drugs (DMARDs), anti-TNFa or biphosphonates can be used.

Diagnosis of juvenile spondylarthropathies

An in-depth clinical assessment including detailed anamnesis (both patient and family) and clinical examination is a key starting point for the diagnosis of jSpA.

When clinical suspicion has risen several technical assessments can be performed.

Imaging

- Ultrasound (including power doppler) is one of the basic tools to assess the presence of arthritis and enthesitis. One should note however that ultrasound is operator sensitive and that the use of power Doppler (to assess pathological versus physiological hypervascularisation) should be specifically asked for.
- Magnetic Resonance Imaging is the best instrument to document sacroiliitis in patients with sacroiliacal tenderness. In some cases MRI can also be used when ultrasonic findings are ambiguous.
- In some cases a standard radiograph might show new bone development (e.g. calcaneal bony spur formation or ankylosing joints elsewhere), or erosions. When in doubt and in particular when only one joint has been affected with persistent arthralgia/arthritis a radiograph should be made to rule out malignancy (certainly when symptoms at night are present).
- Plain radiographs of sacroiliac joints in children are however not suitable for evaluation of presence of sacroiliitis, because of the immaturity of the skeleton.

Laboratory examinations

- All forms of jSpA can be associated with an inflammatory blood examination (including increased sedimentation, increased white blood cell count, increased c-reactive protein (CRP), increased thrombocytes), but can also present without any signs of inflammation in the blood.
- For all formal classifications, HLA-B27, ANA and rheumatoid factor (RF) should be requested, although presence or absence of these is not diagnostic, but can be helpful.
- If anamnesis suggests the presence of abdominal pain and/or diarrhea fecal calprotectine should be performed to rule out IBD. Fecal bacterial culture should be performed as well. We note however that subclinical enteric inflammation has been noted in jSpA patients.[6]

Treatment of jSpA

In general for all categories of jSpA NSAIDs can be used in a first step. Although all NSAIDs can theoretically be used, our preferred molecules are ibuprofen (10 mg/kg q8h), naproxen (7.5 mg/kg q12h), piroxicam (0.3 mg/kg q24h) or diclofenac (1mg/kg q12h). Side-effects of NSAIDs are rarely seen in children, but in case of gastric intolerance a proton-pump inhibitor such as omeprazole can be associated.

In case of persistent mono-arthritis an intra-articular injection of corticosteroids (IAC) should be performed. Triamcinolone hexacetonide seems to be one of the most effective preparations with prolonged efficacy. The use of systemic steroids is nowadays only used as a bridging option between therapies or to alleviate severe pain in a child on a short term.

If NSAIDs and IAC do not resolve the inflammatory manifestations in jSpA or if too frequent relapses occur, DMARDs should be used. Methotrexate (MTX) and sulfasalazine (SSZ) are the two most used DMARDs for JIA-ERA and JIA-PsA with MTX being more frequently used in the latter form. MTX efficacy can be evaluated after three months and SSZ only after six months.

Side effects do occur. The use of both DMARDs requires regular blood examinations to monitor potential disturbances of blood cell lines (in particular neutropenia) and liver tests (AST/ALT elevation). MTX can also cause nausea and SSZ is notoriously known for allergic skin reactions.

During the last two decades novel biological therapies have been introduced in paediatric rheumatology and have revolutionized the field. Briefly, these therapies consist of antibodies directed against inflammatory cytokines such as the in jSpA frequently used anti-tumor necrosis factor alpha (anti-TNFa) antibodies. These biological therapies are in most instances capable in controlling disease activity without many significant side effects (although regular blood examinations are needed here as well). For an in-depth discussion we refer to another review in this journal's edition.

Finally, physical therapy in order to maximize joint mobility, increase muscle strength and avoid contractures is an extremely important aspect of the holistic approach to children with jSpA.

Prognosis and transition into adulthood

Although in most cases the prognosis of a juvenile spondyloarthritis is favorable, in some patients the disease might evolve as a chronic, aggressive, destructive or ankylosing arthropathy. So, if the disease course seems to be resistant to NSAIDs a referral to a paediatric rheumatology center is necessary in order to decide upon long-term treatment.

Some forms of JIA (such as the oligoarticular forms or the systemic form) are typical for childhood and are only rarely seen to start in adulthood (i.e. adult Still's disease). However, the group of juvenile spondyloarthritides, seems to be the early onset of the same spectrum of diseases seen in the spondyloarthritis of adulthood. Yet, juvenile onset spondyloarthritis presents with different characteristics such as more frequent peripheral arthritis, less axial involvement, more hip involvement.[2]

It is thus important that both paediatricians and rheumatologists are aware of these diseases with their differences of presentation in children and adults. New initiatives to make classification of and communication about juvenile spondyloarthritis more clear are underway.

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Beyond recurrent fever, inflammasome-related auto-inflammatory diseases.

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Key words

Periodic fever, Auto-inflammation, Inflammasome, Biotherapy blocking Il-1

Abstract

Periodic fever syndromes are autoinflammatory diseases characterized by recurrent episodes of fever associated with various systemic clinical symptoms during inflammatory attacks, alternating with normal clinical periods and often related to a positive family history and/or genetics mutations. Differential diagnosis with other causes of fever must be done eliminating infections, malignancies, and other chronic inflammatory disorders such as autoimmune or connective disorders. These diseases are rare and start mainly in childhood. Autoinflammatory disorders are caused by a deregulation of the innate immune system involving different pathways, resulting in overproduction of cytokines, mainly interleukin-1 specifically in inflammasomopathies. We describe in this review some of them namely Familial Mediterranean fever, Cryopyrin-associated periodic syndrome, Tumour necrosis factor receptor-associated periodic syndrome, Mevalonate kinase deficiency Periodic fever, aphtous stomatitis, pharyngitis, and cervical adenitis. For each disorder, we discuss clinical presentation, duration of the attack, genetic mutation, and response to therapy or complication such as amyloidosis. Prognosis of autoinflammatory disorders has improved since the development of new-targeted therapies such as IL-1 blocking agents.

Introduction

Fever is one of the most classical reasons of consultation in the pediatric field, and it is an unspecific sign for a lot of illnesses in children. In children, recurrent fever is caused by a broad spectrum of infections of viral or bacterial origin. However, the pediatrician should think of the possibility of an underlying auto-inflammatory condition, especially if the fever is periodic, unrelated to infection and associated with distinct systemic manifestations (cutaneous, pulmonary, ocular, cardiac, ..) in the absence of autoantibody production or malignancy. In the following text, we will address a number of auto-inflammatory diseases in which recurrent or periodic fever is the major symptom. The best recognized disorders include Familial Mediterranean fever (FMF), Cryopyrin-associated periodic syndrome (CAPS), Tumor Necrosis Factor α (TNF α)-receptor associated periodic syndrome (TRAPS), Mevalonate kinase deficiency (MKD) and Periodic fever, aphtous stomatitis, pharyngitis, and cervical adenitis syndrome (PFAPA). Several of these conditions are also called inflammasomopathies since they are caused by increased inflammasome activation and release of the inflammatory cytokine interleukin-1[1]. Since the description of inflammasomopathies, the spectrum of auto-inflammatory conditions has enlarged importantly to include diseases in which type I Interferon, Nuclear Factor Kappa Beta (NF-kB) signaling or as yet unidentified inflammatory pathways play a major role. In more recent years, additional conditions displaying an overlap between autoinflammatory, immunodeficiency and auto-immunity diseases have been defined as well[2]. Many autoinflammatory diseases are caused by a single gene mutation and inherited in autosomal dominant or recessive ways, but also polygenic autoinflammatory conditions are becoming recognized. Mechanisms involved in the pathophysiology of autoinflammation include the hyperactivity of an intracellular sensor causing activation of intracellular protein complexes (eg inflammasome), generation of an intracellular stress resulting in production of reactive oxygen species and defective regulatory mechanisms affecting cytokine signaling, or loss of function of cytokine inhibitors. Importantly, the increasing knowledge of the pathogenesis of autoinflammatory diseases in combination with the improvement of functional assays and the potential for therapeutic trials of cytokine inhibitors and biological therapies continue to change the perspectives of affected patients[3,4].

In the present review, we will address only those diseases that present with recurrent fever.

Definition

Hereditary recurrent fevers are a group of diseases initially described on clinical findings and more recently identified on a genetic base.

Auto inflammatory diseases are caused by a dysfunction of the innate immune system that leads to an over active immune system. This over activation causes severe systemic inflammation throughout the body. The episodes are characterized by fever attacks of varying duration, associated with a variety of symptoms including most often, abdominal pain, polyserositis, adenopathies, …[5,6]

Diagnosis

Clinical history/anamnesis

Fever can be predictable, cyclic, but also can come and go erratically in some cases.

The anamnesis can highlight the recurrence of fever but also give information about duration of attacks, the maximal fever, the spontaneous resolution, and associated signs. Therefore, it is essential to follow the patient for a sufficient period of time and to propose to complete a diary with attacks and their pattern of presentation before the reliable diagnosis of auto inflammatory diseases is confirmed and the treatment is started.

Fever is often accompanied by other clinical signs caused by autoinflammation: abdominal pain, possibly accompanied by nausea, vomiting, diarrhea or constipation, polyserositis (pericarditis, pleuritis), arthralgia, myalgia and arthritis, lymphadenopathies, mouth ulcers and cutaneous involvements mimicking cellulitis.

During attacks, abnormal blood tests such as hyperleukocytosis and inflammatory markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are always seen during disease's flares.

During the intervening symptomless period, children are usually very well and have no inflammation markers in blood. The growth curves are normal; signs of failure to thrive are seen only in rare cases.[1]

Age of onset

Many patients start the illness in childhood, sometimes during the first year of life. Precipitating factors such as vaccination or infection can trigger attacks, generally during nursery school or in the first decade of life. However, it could start even in adolescence or adulthood.[1-3]

Positive family history

In many cases of auto-inflammatory diseases, there is a positive family history of a similar illness. The physician needs to be aware for a history of signs related to auto-inflammatory disease like deafness, neuro-sensitive impairment, articular problems, inflammatory bowel disease, …

Furthermore, renal disease in a family could highlight a history of complications underlying an untreated disease, e.g. renal failure caused by Amyloide A (AA) amyloidosis[7].

Familial anamnesis and ethnic origin are also helping to prove the genetic patent. This can lead to specific genetic tests and confirm the so-called monogenic or hereditary auto inflammatory diseases, especially for FMF which has a high incidence in the Mediterranean basin, and Middle East[8].

Clinical examination, complementary tests and differential diagnosis

During childhood, there are a lot of challenges. In most cases, fever is due to infections, linked to nursery or school frequentation and the immaturity of the immune system.

The first step of the clinical approach is to eliminate other pathologies contributing to recurrent fever such as:

- Recurring infections of the upper airways (most often ear-nose-throat) resulting from nursery/school frequentation
- Deep abscess
- Endocarditis
- Urinary tract malformation
- Immunodeficiencies - Cyclic neutropenia
- Tumor - malignant hemopathies

It is important to examine the patient during the crisis but also during the interval-free disease. That contributes to the best knowledge and understanding of the autoinflammatory disease. Furthermore, it is helping to recognize the differential diagnosis. In the same way, some additional tests could be done during the flare or the intervening period (table 1). They are not exhaustive and they have to be adapted according to the clinical examination[7].

The normalization of symptoms and laboratory tests between attacks is characteristic and differentiates autoinflammatory diseases from other chronic diseases such as autoimmune diseases, neoplasm, inflammatory bowel disease.[1]

Recent progress in genetic assays (next generation sequencing techniques) has led to an increasing ability to identify new genes and new syndromes, expanding the spectrum of autoinflammatory disorders. To identify some of these rare diseases, analysis of a panel of genes can help to make diagnosis in combination of clinical symptoms and family history[3]. If hereditary periodic or recurrent fever is suspected, analysis of a gene panel implicated in autoinflammatory diseases (set of 15 genes) can be performed and contribute to confirm diagnosis. Recently, consensus proposal for taxonomy and definition of the autoinflammatory diseases has been published allowing inclusion of clinical disorders mainly associated with defects in the innate immune system related or not with identified specific genetic mutation[9].

Table 1: Useful tests during flare and symptomless period

During flare	During the symptomless period
Hemoglobin, White blood Count, platelets	Hemoglobin, White Blood Count, platelets
C-Reactive Protein, Erythrocyte Sedimentation Rate	C-Reactive Protein
Ionogram, LDH	Ionogram, urea, creatinine
+/-Ferritin	Immunoglobulin G, A, M, complement
Blood culture	+/- immune tests (cytometry, vaccine response, ..)
Urinary sediment and culture	
Chest radiography +/-Abdominal ultrasound +/- Heart ultrasound	

Autoinflammatory diseases

Studying patients with auto inflammatory diseases has contributed in this past 20 years to discover some keys of the innate immune pathway. FMF was the first so called monogenic auto-inflammatory disease leading to the over production of interleukine-1(Il-1). As mentioned above, we also know about another group, interferonopathies, in which vasculitis may be the predominant presenting manifestations such as STING-associated vasculopathy with onset in infancy (SAVI) but may also attack the central nervous system such as Aicardi-Goutières syndrome. Another group of auto-inflammatory diseases is caused by increased the NFκB signaling. This pathway can promote inflammation not only by inducing multiple inflammatory cytokine production but also by promoting cell death. This group includes Blau Syndrome also known as early onset sarcoïdosis. Not forgetting the other autoinflammatory conditions that are a mixture of inflammation and immunodeficiencies, for example, the DADA2 (deficiency of the Adenosine Deaminase 2) or APLAID (auto-inflammation with PLCγ2-associated antibody deficiency and immune dysregulation)[2,5,10].

Inflammasome related diseases

The inflammasomopathies are diseases induced by a dysregulation of the innate immune system. These complex processes lead to the overproduction of IL-1 as observed in FMF and CAPS; or to intracellular stress that result in the production of reactive oxygen species, aberrant autophagy and activation of kinases as seen in TRAPS and MKD. Table 2 gives an overview of the principal auto-inflammatory diseases.

1. Familial Mediterranean Fever

Familial Mediterranean fever is the most common inherited autoinflammatory disease, with predominance in people originating from eastern Mediterranean regions (Sephardi and Ashkenazi Jewish, Arab, Armenian, Turkish and Italian)[3]. Although its familial dimension was well established since many years, the genetic basis of FMF was elucidated in 1997 by the discovery of mutations in the MEFV gene encoding for the Pyrin, a protein involved in the inflammasome[11,12]. Among pathogenic variants, the M694V is the most frequent and is associated with a more severe clinical course. Known to be inherited as an autosomal recessive disease, the majority of patients have two mutations but as much as 20% are reported to be heterozygous[17].

Most of patients have disease onset before 5 years. Clinically, patients present with recurring attacks of fever, lasting from 12 to 72 hours, and that are typically associated with signs of acute serosal inflammation. Abdominal pain is frequent, mimicking sometimes appendicitis. Pleuritic chest pain, usually unilateral, or acute oligoarthritis can also be seen. Other serositis like pericarditis and testicular involvement are rare. The cutaneous manifestations include an erysipelas-like erythema, usually at the dorsum of the foot. Attacks resolve spontaneously and there is no regular periodicity of recurrences. Although this disease is quite invalidating by the recurrence of severe multisystemic attacks, patients do not develop serious long-term complications in the majority of cases. Thanks to an appropriate control of FMF achieved by long-term colchicine administration, most patients will be free of symptoms and the risk of AA amyloidosis and end-stage renal failure as a consequence of persistent inflammation, has almost completely disappeared[8].

2. Cryopyrin Associated Periodic Syndromes

Cryopyrin-associated periodic syndromes (CAPS) include three clinical entities, historically described as distinct diseases with an autosomal dominant inheritance pattern: the familial cold autoinflammatory syndrome (FCAS), the Muckle-Wells syndrome (MWS) and the chronic infantile neurological cutaneous and articular syndrome /neonatal-onset multisystem inflammatory disorder (CINCA/NOMID).

Although clinically distinct, those three syndromes are all related to NLRP3 mutations, the gene encoding for the Cryopyrin and which is a key component of the IL-1-related inflammasome. Mutations in NLRP3 result in constitutive overactivation of the inflammasome and overproduction of IL-1beta. There is no gender or ethnic predisposition for CAPS[14].

Clinically, the excess of IL-1 production can start from birth, leading to chronic inflammation.

FCAS is characterized by urticarial rash and fever spikes of short duration induced by cold exposure. Arthralgia and conjunctivitis are commonly observed, as headaches and sweating. Daily symptoms have a typical diurnal pattern, worsening as the day progresses, with a major impact on quality of life[15].

In MWS, recurrent episodes of urticaria and fever can start in the early infancy. They are less strictly triggered by cold exposure. During the course of the disease, neurosensorial deafness and polyarthritis may develop.

Table 2: Overview of the principal auto-inflammatory diseases

	FMF	MKD	TRAPS	FCAS/MWS	CINCA	PFAPA
Age of onset	< 20 years	< 1 year	< 20 years	< 1 year	< 1 month	< 2-3 years
Fever	12-72h	3-7 days	Often > 7 days	Variable	Continuous with exacerbations	3-6 days
Dominant symptoms	Abdominal pain Arthritis	Lymphadenopathy, Severe abdominal pain	Migratory rash with underlying myalgias	Cold-induced urticaria	Urticarial	Tonsillitis Aphtous ulcers
Associated symptoms	Serositis, Erysipeloid rash	Arthralgia, Rash, Splenomegaly	Periorbital edema, Conjunctivitis, Pleuritis Abdominal pain, Scrotal pain, Arthralgia	Conjunctivitis, Hearing loss, Arthralgia	CNS symptoms, Aseptic meningitis, Cartilage hypertrophy, Eye, Hearing loss, Dysmorphism	Lymphadenopathy
Ethnic origin	Oriental Mediterranean	Netherlands, France	Ireland, Scotland	European	European	Any ethnic group
AR/AD	AR	AR	AD	AD	AD	
Gene	MEFV	MVK	TNFRSF1A	CIAS1	CIAS1	
Protein	Pyrin/marenostrin	Mevalonate kinase	TNFRSF1A	Cryopyrin	Cryopyrin	
Treatment	Colchicine	NSAIDs Corticoids Anti IL-1 Etanercept	Corticoids Etanercept	Corticoids Anti-IL 1	Corticoids Anti-IL 1	Corticoids (single dose) Adenoido-tonsillectomy

Legend: AR: autosomic recessif/AD: autosomic dominant/NSAIDs : non steroid anti-inflammatory drugs

CINCA/NOMID represents the more severe phenotype associated with Cryopyrin mutations. Symptoms may develop during the first weeks of life. Urticarial rash is associated with chronic inflammatory polyarthritis (sometimes with epiphyseal overgrowth of the lower limbs), dysmorphism, central nervous system manifestations (including chronic aseptic meningitis, increased intracranial pressure, cerebral atrophy with mental retardation and seizures), sensorineural hearing loss and papillary edema. Eye inflammation can lead to vision loss. Patients often exhibit persistence of acute phase reactants.

Amyloidosis is a complication of the late stage of the disease.

3. TNF receptor-associated periodic syndrome

TNFα receptor-associated periodic syndrome is a clinical entity initially described in Caucasians as the Familial Hibernian Fever. It was renamed in 1999 after the discovery of causative mutations in the gene for the TNF-receptor superfamily member 1A (TNFRSF1A). The inheritance pattern is mostly autosomal dominant.

The median age at presentation is 7 years. TRAPS attacks last generally more than 5 days and up to 3 weeks. A minority of patients can present with chronic low active disease with acute exacerbations. The most distinctive sign is the development of swollen, warm and tender plaques of varying size, observing a migratory course from the root to the extremity of the upper or lower limbs, and accompanied by painful myalgias. A variety of other features are observed during the attacks, including fever, abdominal pain, eye manifestations (orbital edema and conjunctivitis), pleuritic pain, headache and lymphadenopathy. Emotional stress, menstrual cycle, fatigue, infections, exercise and vaccinations can trigger attack. Being related to TNF, symptoms are typically accompanied biologically by a marked acute-phase response and leucocytosis. Long-term consequences include a significant risk for AA amyloidosis [16].

4. Mevalonate kinase deficiency

Mevalonate kinase deficiency is a very rare autosomal recessive disease caused by mutations in MVK, the gene encoding for mevalonate kinase [17]. This autoinflammatory disease is due to a partial deficiency of this enzyme, with a residual activity of about 10%. Complete deficiency causes the severe phenotype of mevalonic aciduria, an inherited metabolic disorder. MVK is involved in sterol and isoprenoid biosynthetic pathways. The pathologic mechanisms of autoinflammation in MKD are uncompletely understood, but reduced synthesis of isoprenoid lipids downstream of MVK, are thought to play a central role, resulting in over-activation of the pyrin inflammasome and, consequently, in the dysregulated production of IL-1β [18].

This disease was initially called hyperimmunoglobulinemia D syndrome (HIDS), but high Immunoglobulin D plasma level is no longer considered as a diagnostic hallmark, because neither specific nor sensitive [19]. Patients present increased urinary mevalonic acid during attacks, and reduced MVK enzyme activity in leucocytes or fibroblasts.

MKD was initially reported in families originating from the Netherlands, but its distribution is not limited to the northern European populations. Patients have also been observed in the Mediterranean basin and Asia [20, 21].

Onset is usually observed very early in life, in the first 6 months. Almost all patients develop the disease during the first decade of life. Fever attacks have an abrupt onset, lasting from 3 to 7 days . They are associated with gastrointestinal symptoms (severe abdominal pain, diarrhea and vomiting), headache, lymphadenopathy, arthralgia, myalgia, skin rash and mucosal ulcers. Attacks can be triggered by vaccination, stress or infection. MKD attacks persist for years, but tend to become less pronounced with time [22].

5. Periodic fever, aphtous stomatitis, pharyngitis, and cervical adenitis

Periodic fever, aphtous stomatitis, pharyngitis, and cervical adenitis is a recurrent fever syndrome described by Marshall in 1987. It is probably the most common cause of periodic fever in childhood. Unlike the other hereditary periodic fever syndromes described above, there are no specific confirmatory laboratory or genetic tests to confirm this diagnosis. However, a strong familial clustering is often observed, suggesting a potential genetic origin of the syndrome.

Episodes of fever last for 3 to 6 days, with a regular recurrence every 3 to 8 weeks; associated with at least one of the three main symptoms: aphtous stomatitis, cervical adenitis or pharyngitis. Disease onset is usually before the age of 5. Patients are asymptomatic between episodes and show normal growth. PFAPA has favorable natural history; it generally resolves by adolescence. Diagnosis relies on clinical criteria.

Medical treatment with single doses of glucocorticoids induces a rapid remission of episodes, without modifying the outcome. Adeno-tonsillectomy may also be proposed. No long-term consequences have been described [23].

Treatment

Primary treatment goal of autoinflammatory syndromes is reduction of acute inflammatory symptoms affecting quality of life as well as chronic inflammation potentially resulting in significant long-term morbidity such as systemic amyloid A amyloidosis [24]. Autoinflammatory disorders are often characterized by episodic flares

that are either unpredictable or elicited by specific triggers such as vaccination, infection or cold exposure in patients with FCAS for example[3]. Therefore, optimal treatment should be effective at both decreasing chronic inflammation and preventing acute flares, but safe enough to be used for long period of time. Until recently, controlled trials in patients with autoinflammatory syndromes were missing because of disease rarity and lack of interest from pharmaceutical industries. Efforts of orphan disease program, industry recognition, and medical societies (such as American, European or Belgian rheumatology or pediatric rheumatology societies) are made to better approach and treat these diseases. In parallel, development of new therapies (biological therapy or small molecules) and better understanding of auto inflammatory disease such as signaling pathway or dysregulation of cytokine production implicated in their physiopathology has an effect to improve the care of patients with autoinflammatory disorders[24,25].

Traditional drugs such as corticosteroids or colchicine are the standard of care for some autoinflammatory diseases. Colchicine, known to be efficient in various rheumatologic diseases, such as gout, is a safe drug with minor effect. Most frequent side effects are diarrhea, nausea, vomiting, and abdominal cramps. In rare cases, it may cause muscle weakness, decreased of blood count or neurotoxicity. It can be used safely in most patients if dosed appropriately. Usual doses are 0,5 to 1 mg once or twice per day. Colchicine is administrated as long-term prophylaxis in order to prevent acute manifestations, but during attacks, additional analgesia (with paracetamol or nonsteroidal anti-inflammatory drugs) is needed. It is permitted during pregnancy. Although colchicine is the standard care for FMF, it is not effective in some patients with FMF or other patients with autoinflammatory diseases.

Recent advances in targeting specific cytokines, such as TNF-α, have improved the prognosis and the care of patients with chronic inflammatory diseases. Etanercept or infliximab were described to be efficient in patients with TRAPS but most of them discontinue the drug because of its declining effect[3].

Interleukin-1 (IL1) blockade is effective in many autoinflammatory disorders specifically in inflammasomopathies where deregulation of innate system is a consequence of overproduction of IL-1. Two biological agents targeting IL-1 are described to be effective in many autoinflammatory disorders such as TRAPS, CAPS, FMF and MKD. Anakinra is an IL-1 receptor antagonist requiring daily subcutaneous injections. It was the first therapy used but its short half-life and common painful injection-site reaction has limited its use. Canakinumab is a fully human monoclonal antibody with high specificity to IL-1β and is a longer-acting IL-1 targeted drug with a half-life of more than 3 weeks. It is administrated subcutaneously every 8 weeks. In Belgium, canakinumab is reimbursed for CAPS since a few years and recently (2018) for FMF, TRAPS and MKD/HIDS. This therapy has showed efficacy in term of clinical response, acute-phase response and dramatic improvements in quality of life. Safety data to date have been encouraging, although treatment is associated with an increased risk of infections and modest neutropenia[26].

JAK-STAT signaling (Janus-kinase/signal transduction) is a pathway recently described to be implicated in some autoinflammatory disorders and inhibition of these kinases could be efficient in rare autoinflammatory diseases with a type I interferon signature such as STING–associated vasculitis with onset in infancy (SAVI)[27].

Conclusion

Although periodic fever syndromes are rare, it is important to recognize them because treatment improves the patient's quality of life and can reduce morbidity, prevent long-term complications and decrease mortality.

The differential diagnosis of childhood fever could be hard when recurrent fever persists despite the exclusion of acute and chronic infections, immune deficiencies, inflammatory bowel disease and malignancies. The growing spectrum of autoinflammatory diseases including the most common periodic fever syndromes, such as FMF, CAPS, TRAPS, MKD or PFAPA needs to be considered in these patients. Despite our better knowledge of these diseases thanks to the genetics, we should not forget that the genetic tests are not always the cornerstone for diagnosis. A detailed history including genealogy, ethnicity, age of onset, associated symptoms, physical examination, and thoughtful investigations often lead to diagnosis.

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Dermatological presentations of paediatric rheumatic diseases

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Key words

Child, Autoimmune Disease, Hereditary Autoinflammatory Diseases, Skin Rash

Abstract

Rheumatologic diseases can present with various cutaneous manifestations. It can be sometimes tricky to identify a skin rash and to associate it with an auto-immune or auto-inflammatory disease. The help of a dermatologist is sometimes very precious to correctly identify a skin rash but paediatricians facing it first should be able to distinguish when a rash is potentially induced by a rheumatologic disease or not.
We reviewed different cutaneous manifestations that could happen in rheumatologic diseases. We described each of them macroscopically and also microscopically when appropriate, to help to the diagnosis.
Most of the cutaneous manifestations described can happen both in rheumatologic and non-rheumatologic diseases. Once the skin rash identified, it's important to look for other clinical, biological and/or radiological signs to find the correct diagnosis.

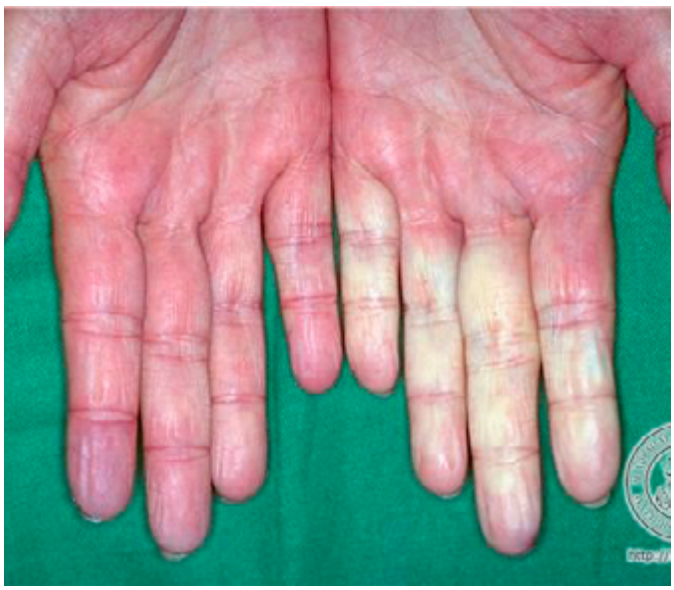
Introduction

Skin and rheumatologic conditions in children are often intricated. Skin diseases can lead to rheumatologic involvement, and dermatological signs can be pathognomonic or herald rheumatologic diagnosis. Skin involvement can also interfere with the quality of life of the child with rheumatism, and sometimes need specific work-up and treatment. We try in this review to consider these different aspects. We have artificially separated the different dermatological conditions but it must be kept in mind that in most cases, skin involvement is part of a larger clinical picture, or that several cutaneous signs can coexist in a rheumatologic condition. It's the case for example in lupus skin disease or juvenile dermatomyositis.

Raynaud phenomenon

Raynaud phenomenon (RP) is the clinical description of acroparoxystic attack of skin changes. It mostly affects fingers and toes, but can also target ears, nose, lips, cheeks or nipples. Most RP are triphasic with succession of pallor, cyanosis and redness, but biphasic attacks can occur (white to blue). Attacks are often associated with pain, tingling, numbness, hyperhidrosis of affected zones. Typically only some fingers or toes are affected (fig.1).

Figure 1: Raynaud Syndrome



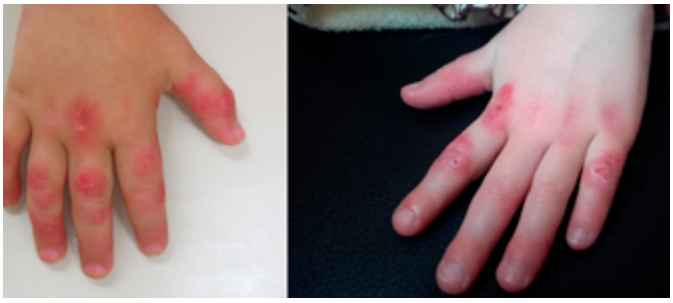
RP are classified in primary (formerly known as "Raynaud disease") and secondary forms. In general, 69% of children are affected by primary RP, and in both forms, female predominance is classical (sex ratio 1:8), with a mean age of symptoms onset of 12.3 ± 4.3 years [1,2]. Differential diagnosis could include acrocyanosis (no paroxysms, no influence of cold exposure, symmetrical and painless), primary erythromelalgia (rare, paroxysmal redness, pain and swelling relieved by cold) and chilblains. The next items can help to distinguish primary RP from secondary: isolated without tegument (skin ulcerations, oral ulcers, alopecia, easy bruising) or others systems abnormalities (sicca syndrome, headaches, dyspnea, weight loss, fever,…), positive familial history, preferential winter occurrence, no signs of peripheral vascular disease, absence of antinuclear antibodies (ANA) and normal erythrocyte sedimentation rate (ESR), and nailfold capillaroscopy . In case of strictly unilateral involvement, macrovascular evaluation could be useful [3].

A lot of paediatric rheumatologic conditions can be associated with secondary RP, the most frequent being juvenile systemic scleroderma (JSSc), mixed connective tissue disorder (MCTD), juvenile dermatomyositis (JDM) and juvenile systemic lupus erythematosus (JSLE). Rarely, autoinflammatory conditions can include RP, the most classical being familial mediterranean fever (FMF) which is known to be associated with some forms of vasculitis like Henoch-Schönlein purpura (HSP) and periarteritis nodosa (PAN) [4].

Chilblains - Pernio

Chilblains, also called perniosis, are cold-induced lesions of the extremities. Toes, fingers, ears and/or nose are cyanotic, swollen, cold with increased capillary refill time. They can be associated with pruritic and painful purpuric papules, nodules or even ulcers. It should be distinguished from RP by the lack of blanching and by the lack of a clear delimitation (fig.2, reproduced with the kind permission of Dr Lien De Somer). Acrocyanosis should also be ruled out by the absence of pain or swelling during cyanotic episodes.

Figure 2: Chilblains – Perniones



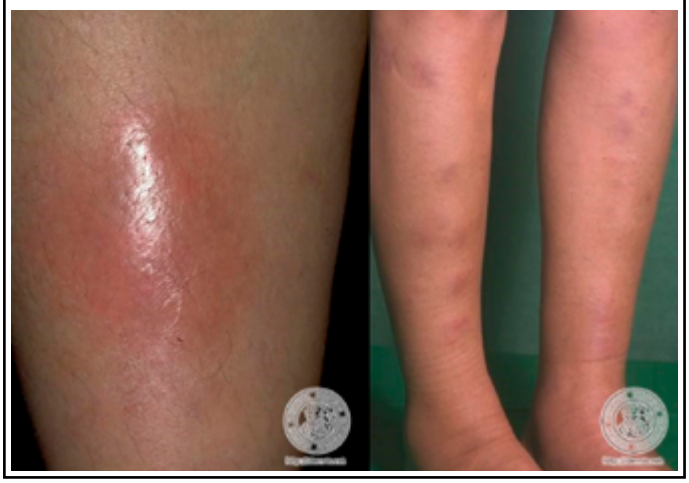
The main cause in cold-injury with no other underlying disease but in some rare cases, it can be a sign of systemic disease. In the absence of other manifestation and with no other clinical or biological abnormalities, chilblains can be considered as idiopathic. ANA positivity in the absence of other abnormalities is not a criterion to go further as it can happen in idiopathic chronic pernio. Nailfold capillaroscopy can help to the differential diagnosis and is normal in idiopathic cases.

The presence of ulcers or signs of ischemia, the extension to other location than fingers and toes (as the end of the nose or the ear), high acute phase reactants (ESR, CRP) and the association with other clinical manifestations should lead to additional workup. Systemic lupus erythematosus (SLE) should be excluded as some rarer genetic diseases (type I interferonopathies, Adenosine deaminase 2 (ADA2) deficiency, STING Associated Vasculopathy with onset in Infancy (SAVI), ...).[5]

Erythema nodosum

Erythema nodosum (EN) is a panniculitis due to hypersensitivity reaction occurring more often in the adolescents, with a female predominance except in children in which sex ratio is nearly equal. It is classically localized on the pretibial area, but also on thighs, face, arms and trunk, and rarely on palms and soles, which is less the case in adults[6]. It presents as tender symmetrical red nodules, with an evolution to a typical brownish red or purplish bruise-like appearance, and disappears in 3 to 6 weeks (fig.3). It is associated in more than 90% of cases with arthralgias. 50% of EN in children are idiopathic. 25% of EN are caused by streptococcal infections, followed by Mycoplasma pneumoniae, Herpesviridae (EBV, CMV), mycobacteria (tuberculosis and atypical) and coccidioidomycosis. This predominance of infections can explain the seasonal pattern of EN, with predominance in spring and fall. Others infectious causes are rare, as well as the classical association with sarcoidosis, Behçet disease and inflammatory bowel diseases, malignancies and drug reactions. Treatment is causal and symptomatic (rest, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), …).

Figure 3: Erythema nodosum



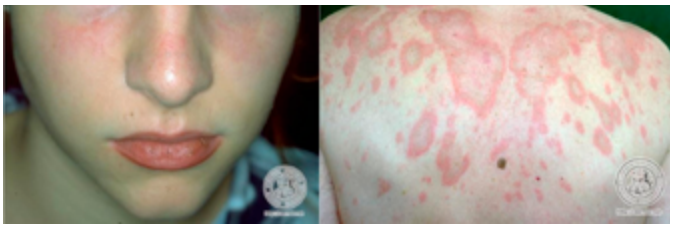
Photosensitive rash

Photosensitive rashes are hallmark of some rheumatologic diseases: systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM) and mixed connective tissue disease (MCTD). Photosensitivity describe all exacerbated cutaneous reaction to sun light (or in some cases even to artificial light). Photosensitivity can be immunological, genetical or environnementally induced (drugs, phytophotosensitivity, …)

Rash of SLE and JDM differs by its presentation, with SLE vespertilio being a maculopapular rash touching malar zones and nasal bridge with relative preservation of nasolabial folds and periorbital skin. The SLE rash can be thick with a follicular or scaled pattern. JDM rash on the other hand involves preferentially periocular regions ("heliotropic rash"), being less thick but more telangiectatic. A differential diagnosis can be made with parvoviral infection, but this latter generally spares nasal bridge and is a simple erythema.

Another skin distinction can be made on the extremities, with SLE rash involving dorsum of the phalanx and present sometimes with a vasculitic rash of palms and soles, whereas Gottron papules of JDM appears on flexion aspect of metacarpophalangeal and proximal interphalangeal, and less frequently distal interphalangeal articulations. Perionyxis (inflammation of nail bed) can be seen in the two conditions, whereas hard palate ulcerations or vasculitis are more frequent in SLE.

Figure 4: A. Malar rash of SLE. B. Subacute lupus lesions.



Lupus skin lesions

Malar rash: erythematous rash on the cheeks and the nasal bridge. The nasolabial folds are usually not affected (fig.4).

Photosensitivity: skin rash can appear on areas exposed to sun, macular or diffuse (see above).

Subacute lesions: papular lesions that can enlarge and become confluent (fig.4). They can be sometimes difficult to distinguish from polymorphous erythema. If papulosquamous, differential diagnosis needs to be made with psoriasis or lichen planus. Subacute cutaneous lupus lesions are photosensitive, nonscarring lesion.

Discoid rash: erythematous lesions, disc-shaped with areas of follicular hyperkeratosis, usually around head and neck. It can be sometimes lightly painful or pruriginous. It can lead to changes in pigmentation, atrophy, alopecia, ... It can be localized (above the neck) or generalized (above and below the neck).

Lupus panniculitis (also known as (lupus profundus): indurations or subcutaneous nodules usually under normal skin. The skin can be erythematous, atrophic, ulcerated and after healing, leave a depressed scar. It is especially located to the proximal extremities (arms, shoulders, thighs, buttocks) but also on trunk, breasts, face and on the scalp.

Lichen planus: pruritic papular lesions generally found in the flexion surface of upper limbs, on genitalia and on mucous membranes.

RP: see above. Nailfold capillaroscopy can show dilated capillary nailfold loops, giant capillaries and microhaemorrhages.

Cutaneous small vessels vasculitis: it can present with various forms: punctuate lesions, palpable purpura, urticaria, ulcers, erythematosus macules or erythema with necrosis.[7]

Urticaria and urticaria-like lesions

Urticarial-like lesions involved in systemic diseases last in general more than 24 hours, are non-migrating and non-prurigenic, and leave sometimes a localized hyperpigmentation as in Urticarial vasculitis (UV).

UV is a leukocytoclastic vasculitis presenting as an urticarial eruption. Most cases are idiopathic and normocomplementemic. In some cases, called hypocomplementemic urticarial vasculitis syndrome (HUVS), C1q levels are low due to antibodies against C1q and systemic involvement is more severe with obstructive pulmonary disease and ocular inflammation, associated with arthritis and glomerulonephritis[8]. HUVS is primary, or secondary associated with SLE and Sjögren syndrome (SS). A differential diagnostic of UV can be a serum sickness-like reaction to drugs.

Henoch-Schönlein purpura (HSP) is the most frequent vasculitis in children and may sometimes present with a rather urticarial pattern[9], besides the classical vascular purpura presentation (fig.5). Systemic juvenile idiopathic arthritis (sJIA) presents in 25 to 50% of cases with an evanescent urticarial-like eruption but without pruritus. This eruption presents as salmon-pink to red flat or slightly elevated macules, with an irregular border, and are classically small (2-6mm) but sometimes coalescent and localized preferentially on trunk and roots of limbs, and sometimes on face. It can be the first manifestation of sJIA, preceding other systemic manifestations from several months. When sJIA is full-blown, eruption classically follows pattern of fever, with a rather vesperal exacerbation (fig.6, reproduced with the kind permission of Dr Lien De Somer)

Cryopyrin-associated periodic syndromes (CAPS) have in common the presence of urticarial-like eruption without pruritus, triggered by cold exposure or spontaneously, associated with more or less severe systemic symptoms and occurring earlier or later in life depending of the type of cryopyrinopathy (fig.7, reproduced with the kind permission of Dr Lien De Somer). [10]

Finally, hyper IgD syndrome with periodic fever (HIDS), belonging to the spectrum of mevalonate kinase deficiency (MKD), presents in more than 90% of cases with skin eruption, sometimes urticarial-like.

Figure 5: Henoch-Schönlein Purpura

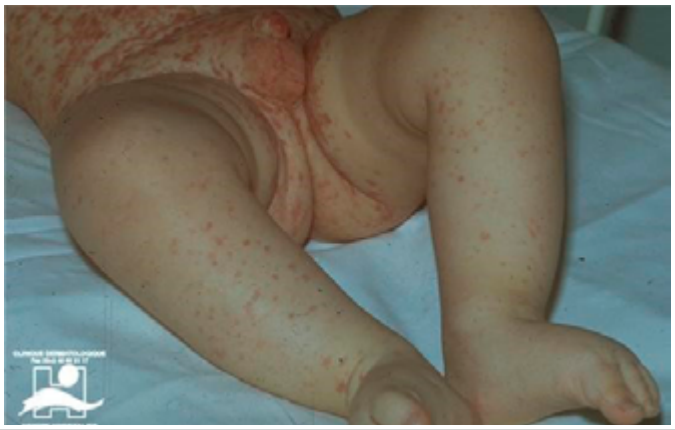


Figure 6: Systemic juvenile idiopathic arthritis

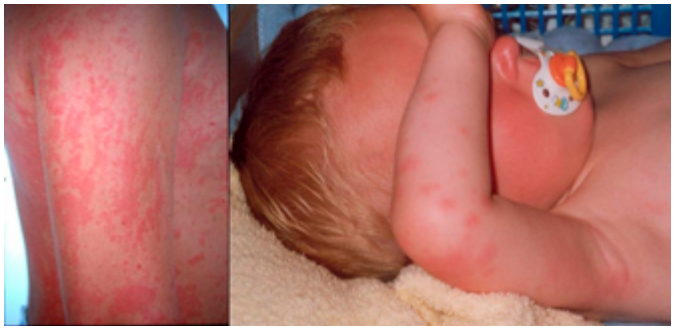


Figure 7: Cryopyrinopathy

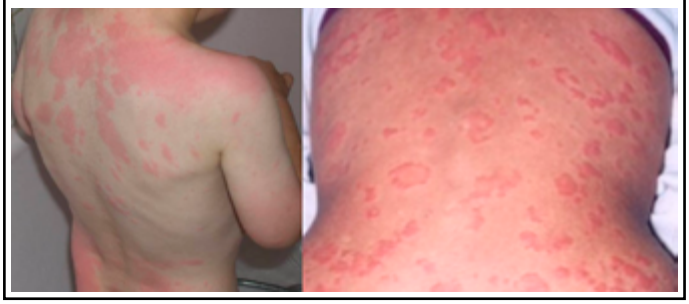
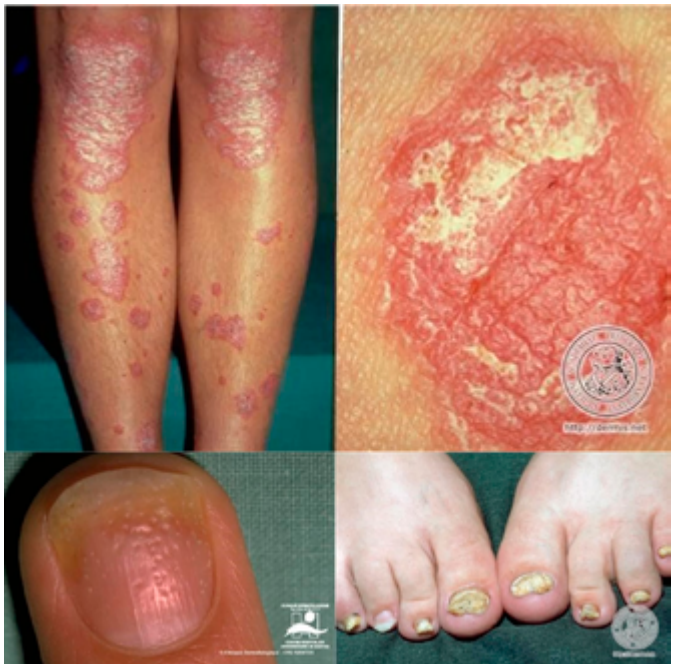


Figure 8: Cutaneous psoriasis lesions and psoriatic nail involvement



Pseudo-erysipelas

Erysipelas relates to dermis inflammation and present clinically by a relatively sharply limited and elevated plaque, often painful, differentiating from panniculitis involving hypodermis, and frequently more diffuse. The most classical case is infection by pyogenic bacteria. Sometimes, autoinflammatory disorders can present with erysipelas-like eruptions. It is mostly the case for familial mediterranean fever (FMF) and TNF receptor-associated periodic syndrome (TRAPS), the latter giving frequently cellulitis-like lesions with a more profound component of muscle tissue and fascial inflammation, producing severe myalgias. Another characteristic of TRAPS is the centrifugal migratory pattern of lesions.

Sclerodermatous changes

Cutaneous sclerodermatous changes refer to progressive thickening of skin, with an appearance of non-pitting edema, followed by sclerotic evolution and retraction, with frequent secondary RP. It traduces an excessive deposit of extracellular matrix (mostly hyaluronic acid and collagen) in the sclerodermatous zone. Two large types of diseases can be individualized: juvenile systemic sclerosis (jSSc, with severe systemic involvement) and morpheas (limited to skin and sometimes underlying structures)[11]. On a clinical basis, diffuse scleroderma with symmetrical extremities involvement and secondary RP points toward jSSc. Other scleroderma-like disorders include chronic graft-versus-host disease, eosinophilic fasciitis, scleroderma from toxins (as in toxic oil syndrome), nephrogenic systemic fibrosis (NSF), and sclerodermatous plaques in genetic diseases as progeria, Werner syndrome and phenylketonuria. In the neonate, stiff skin syndrome can be confused with SSc.

Calcinosis cutis

Calcinosis cutis consists in the deposition of calcium under the skin and subcutaneous. It can be of different subtypes: dystrophic, metastatic, iatrogenic or idiopathic. In the paediatric population, calcinosis cutis was mainly described in juvenile dermatomyositis. It happens more frequently than in adult-onset dermatomyositis. In adults, systemic sclerosis, systemic lupus erythematosus, lupus panniculitis and mixed or undifferentiated connective tissue disease are linked to calcinosis cutis. In juvenile dermatomyositis, calcinosis cutis is preferentially located to extremities.

Psoriasis

Diagnosis of psoriasis as a clue to juvenile psoriatic arthritis (JPsA) in children is sometimes difficult. There is no clear association between the type of psoriasis and the risk of developing JPsA, even if in adults, the presence of scalp, intergluteal and perianal psoriasis, an increased psoriatic body surface area and familial history of PsA are considered as risk factors, as could be a psoriasis with Blashko-linear distribution[12,13]. Psoriasis can present with different clinical pictures, mimicking more usual conditions as seborrheic dermatitis, atopic dermatitis or infectious processes like tinea capitis. The two most frequent forms in paediatrics are psoriasis "en plaque" and scalp psoriasis.

The primary lesion of psoriasis consists of round, brightly erythematous, well-marginated plaques covered by a characteristic grayish or silvery-white (mica-like, or "micaceous") scale (fig.8a and b).[14] This scale is rather centrally attached to the plaque, and when removed with a gentle scratching, gives place to punctuate bleedings (Auspitz sign). Lesions are classically bilateral, symmetric, with a predominantly extensor surfaces (elbows, knees), facial, scalp or anogenital distribution, but sometimes diffuse. Sometimes flexor surfaces (inversed psoriasis) or palms and soles only are involved. Plaque can spontaneously disappear with frequent pallor around the plaque or just inside of the outer border, called Woronoff ring. A Koebner phenomenon is classical, with appearance of psoriatic lesions in zones of skin microtrauma (explaining probably that scalp psoriasis is more frequent in girls due to combing).

Nail involvement is frequent in psoriasis, and its recognition is important in paediatric rheumatology, being part of the criterion of ILAR classification for JPsA. The classical lesion is pitting, presenting as regular pinpoint depressions in the nail table, probably due to psoriatic lesions of the nail matrix (fig.8c). Onycholysis and hyperkeratosis are two other frequent nail lesions in psoriasis (fig.8d).

Livedo reticularis

Livedo reticularis a mottled or reticulated, blue-red discoloration of the skin that occurs predominantly on the lower extremities and less commonly on the trunk or upper extremities. Its recognition is important due to its possible association with several diseases (SLE, JDM, JSSc, antiphospholipid syndrome (APLS), systemic vasculitides as polyarteritis nodosa, granulomatosis with polyangiitis (GPA, former

Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, former Churg-Strauss syndrome). In APLS, lesions can be coarser, called livedo racemosa, strongly associated with cerebral and ocular arterial stroke events. Others skin manifestations are chronic leg ulcers, subungueal splinter-like haemorrhages, digital necrosis and secondary RP.

Purpura and vasculitic processes

Purpura describes cutaneous sign of haemorrhagic diathesis. Clinical confirmation is non-blanching character at pressure or diascopy. It can be produced by disorder of haemostasis (more frequently of primary haemostasis, as in thrombocytopenia and thrombopathies, or sometimes von Willebrandt disease, and in disseminated intravascular coagulation, for example in meningococcemia or pneumococcemia) and presents then as a haemorrhagic flat macule, with progressive extension. Vascular purpura denotes rather an inflammation of vascular wall of skin small vessels with secondary diathesis, presenting as erythematous palpable maculopapules. They are frequently more pronounced in dependent areas due to hydrostatic pressure, as in thrombocytopenic purpura. Vascular purpura traduces the presence of leukocytoclastic vasculitis, isolated to skin or as a part of a systemic vasculitis.

Systemic vasculitides in children are a large group of diseases, classified following the main type of vessel involved, in large, medium and small-vessels vasculitis. Most cases of vascular purpura concern small-vessels vasculitides, large-vessels vasculitis as Takayasu disease presenting rather with systemic symptoms. The two most frequent vasculitides in children are Kawasaki disease (KD) (medium-size vessels) and Henoch-Schönlein purpura (HSP) (small-size vessels). Polyarteritis nodosa (PAN) can also have a marked cutaneous picture. The frequent hypersensitivity vasculitis (HV) (small-size vessels), leukocytoclastic vasculitis limited to skin, and secondary to infection or drug exposure is a differential diagnosis but would not be detailed because of absence of rheumatologic component.

Kawasaki Disease (KD) is well known by paediatricians even if the diagnosis remains challenging in cases of incomplete of atypical forms. Only the tegumental aspect of the disease will be discussed. As already discussed, KD can be isolated or rarely arises in a context of FMF. Conjunctivitis has some characteristics: absence of exsudate, involvement of bulbar conjunctiva more often than palpebral conjunctiva, relative perilimbal sparing (in opposition of infectious or allergic conjunctivitis)[15]. Oro-pharyngeal changes include dry, red, fissured and crusted lips, and diffuse erythema of mouth mucosa with sometimes strawberry tongue. On the cutaneous point of view, different lesions are suggestive (fig.9, reproduced with the kind permission of Dr CM Hedrich).

HSP cutaneous lesions present classically with vascular purpura predominating on lower limbs and buttocks, sometimes preceded by an urticarial phase heralding the purpuric lesions (fig 4). Involvement of upper extremities, face and trunk is possible, as well as reinforcement at pressure sites (i.e. compression for blood sampling). Sometimes bruises and petechiae predominate on vascular purpuric lesions. Lesions can be more severe with vesiculae or bullae, ulcerations, gangrene, erythema multiforme. A characteristic is the presence of synchronous lesions with flares of lesions of the same age evoluting in 5 days to residual bruising or hyperpigmentation, giving a polymorphous appearance. Edema of extremities, face and scalp can be seen, as well as acute scrotal swelling in males. Isolated skin disease is rather rare, as more than 80% of HSP cases exhibits systemic symptoms (articular, digestive or nephrologic). As a rule, the older the age at HSP presentation, the higher the possibility of being in presence of a secondary vasculitis (for example SLE). Except if the classical tetrad is at least partially present in an adolescent, a complete work up is necessary to ascertain the diagnosis.

PAN is rather uncommon in paediatrics, but cutaneous PAN (cPAN) is more frequent and represent probably an isolated cutaneous involvement of PAN (middle size arteries) without visceral disease. Lesions present as firm tender red nodules localized on lower extremities and malleoli, with livedo reticularis, purpura, ulcers and necrosis. Healing produces atrophic, ivory colored stellate scars. Constitutional symptoms as well as mononeuritis multiplex is rare.

Pyoderma gangrenosum

Pyoderma gangrenosum is a sterile neutrophilic dermatosis and can be a sign of inflammatory disorder. It can be pustules, bullae or nodules. The latter shows pathergy and typically enlarge concentrically. The lesions are painful and erythematous. It can evolve into necrotic macules with raised margins (fig.10). Another possible evolution is into deep ulcers. In this case, the lesion is more violaceaous with bluish borders. When healing, it leaves an atrophic scar. It can be classified as ulcerative, pustular, bullous or vegetative depending on the clinical aspect.

Figure 9: Kawasaki Disease. Other possible cutaneous lesions in KD include:

- Non-pitting edema of the dorsum of hands and feet, with sometimes red-violaceous coloration and fusiform swelling of fingers
- Diffuse maculopapular erythematous or urticarial eruption involving also palms and soles
- Scarlet fever-like rash with micropapules on a red skin, with reinforcement in fold areas (i.e. groin and perineum, with desquamation, highly suggestive)
- Erythema multiforme-like eruption with target lesions
- Reaction to BCG site
- Rarely more severe vasculitic process with peripheral gangrene
- Later in evolution, in general after at least one week: desquamation beginning at the tips of the fingers and toes with progressive involvement of palms and soles, sometimes recurrent in the next years after an infection, and Beau lines of the nails (transversal linear grooves)
- No vesicula, bulla or purpura
- Other very evocative clinical features are fever not responding to conventional antipyretics and irritability.

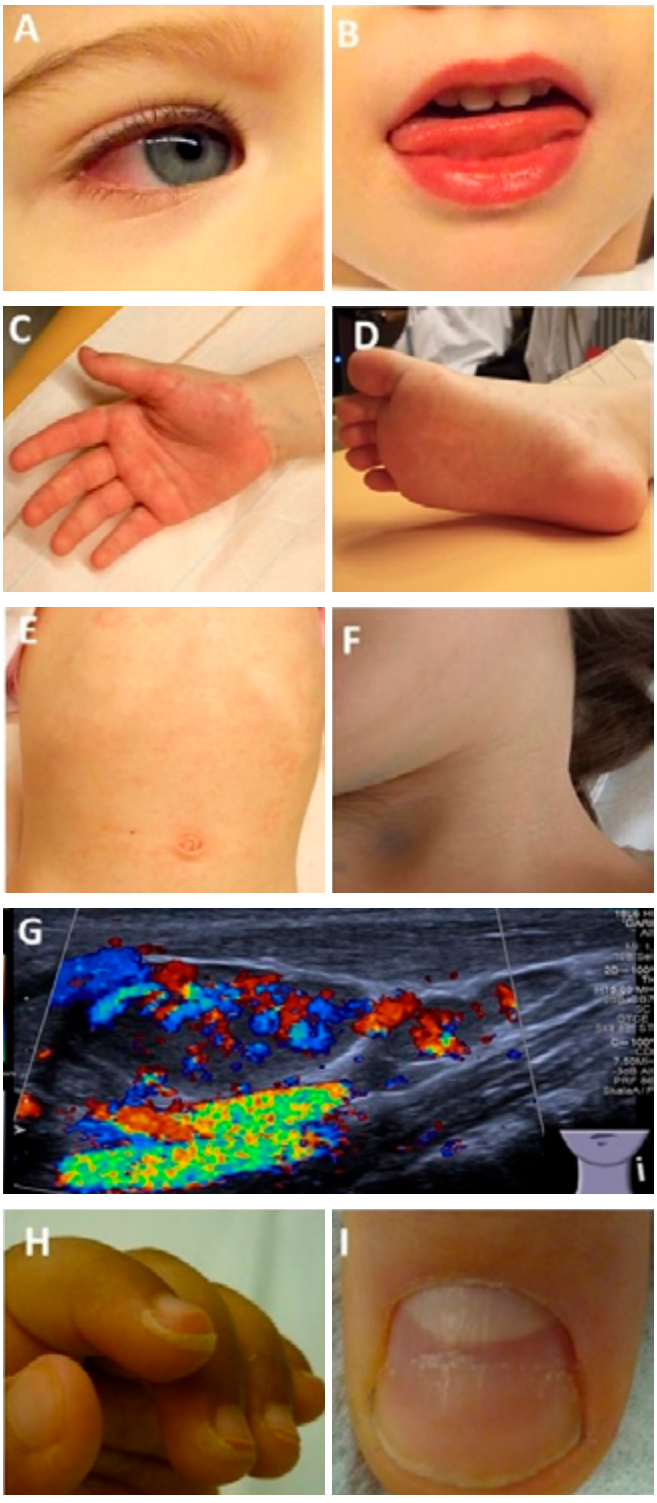
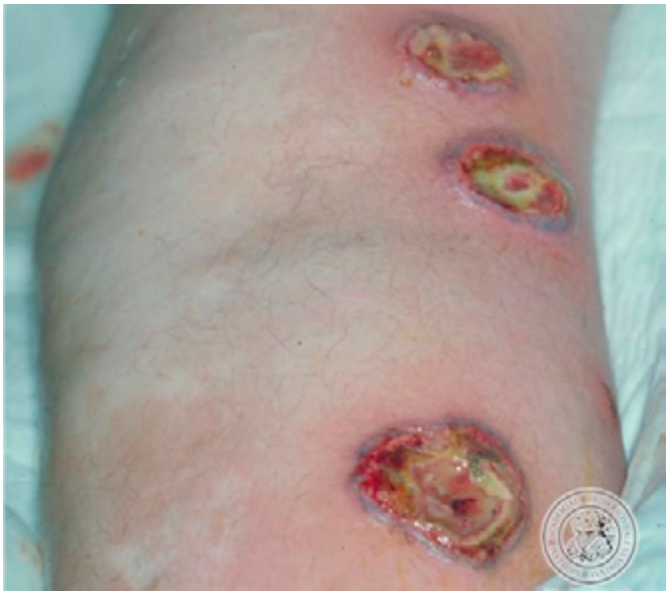


Figure 10: Pyoderma Gangrenosum



PG is mainly an adult disease. Only 4% happens in children[16]. Extracutaneous lesions can be found in lungs, eyes and musculoskeletal system. Diagnosis can be made by the clinical aspect of the lesions. If a skin biopsy is made, it will show some unspecific features such as neutrophilic aggregates, mononuclear cells, fibrosis, haemorrhage, necrosis, giant cells.

In a recent systematic review of PG in the paediatric population, more than half of the patients have underlying disease (55%). Among those patients, inflammatory bowel diseases were the most frequent (20%) with an equivalent distribution between Crohn Disease and Ulcerative Colitis. Less frequently, patients were diagnosed with hemopathy, vasculitis, primary immune deficiencies or Pyogenic Arthritis Pyoderma gangrenosum and Acne (PAPA)/ Pyogenic Arthritis Pyoderma gangrenosum and Acne and Suppurative Hidradenitis (PAPASH)/ Pyoderma gangrenosum and Acne and Suppurative Hidradenitis (PASH) syndrome.

Pustulosis

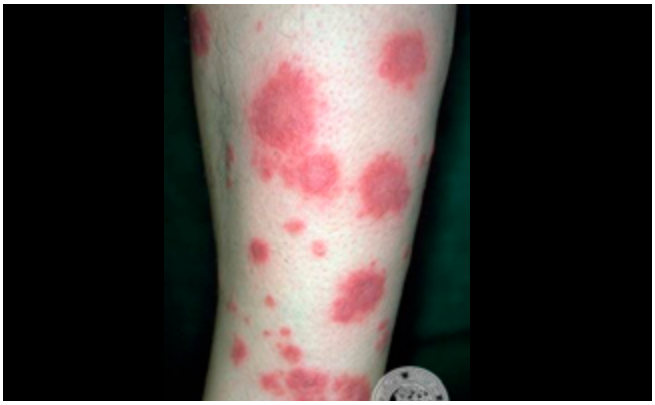
Pustules are skin lesions containing purulent fluids. Depending of the age of the patient and of the localisation, the spectrum of diagnosis can vary a lot. Before thinking to rare causes of pustular dermatoses, common conditions need to be ruled out. In neonates or infancy, infantile acne, infantile acropustulosis, transient infantile dermatoses, candidiasis and scabies should be excluded. In older children and adolescents, folliculitis, perioral dermatitis acne and again scabies need to be ruled out. Rarer conditions can also present as pustular dermatoses in children. Further workup is required if any clinical sign is suggestive of one or another of the diseases below. Some of those rare diagnosis present during the neonatal period or infancy as autosomal dominant hyperimmunoglobulin E syndrome, congenital cutaneous candidiasis, congenital syphilis, DIRA (Deficiency of Interleukin-1 Receptor Antagonist) and Eosinophilic pustular folliculitis. In children and adolescents, acute generalized exanthematous pustulosis should be ruled out as a severe drug-induced (or sometimes infection-induced) reaction. Rare inflammatory disorders can also be at the origin of pustulosis at this age: Behçet disease, CARD14-mediated pustular psoriasis, Chronic Recurrent Multifocal Osteomyelitis (CRMO), Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO), Majeed syndrome (autosomal recessive due to mutation of LPIN2, associated with dyserythropoietic anemia), Deficiency of IL-1 Receptor Antagonist (DIRA) and Deficiency of IL-36 Receptor Antagonist (DITRA), PASH syndrome (Pyoderma gangrenosum, acne and suppurative hidradenitis), PAPA syndrome (Pyogenic sterile arthritis, pyoderma gangrenosum, and acne), Sweet syndrome (see below). The pustular subtype of pyoderma gangrenosum and generalized pustular psoriasis can also be involved in pustular dermatoses.

Sweet syndrome

Sweet syndrome is part of the neutrophilic dermatosis. Lesions of Sweet consist in a well-defined erythematous and edematous papules and plaques. It can also present as arcuate lesions, pseudovesiculous lesions, hemorrhage or with violaceous coloration (fig.11). Pathergy can be demonstrated. They usually don't scar. Fever, elevated acute phase reactants, neutrophilic leukocytosis can be associated as arthritis, myalgias and some extracutaneous lesions (eyes, lungs, bones, ...) where sterile neutrophilic abscess can be found.

About 42% of children with Sweet syndrome won't have any associated disease or had a transient disease prior the development of the dermatosis (especially respiratory tract infections). 25% of the children with Sweet syndrome were diagnosed with malignancies. The rest of the patients had inflammatory disorder (central nervous system vasculitis, aortitis, arthritis, systemic lupus erythematosus, sarcoïdosis, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome and chronic recurrent multifocal osteomyelitis (CRMO), sometimes associated with dyserythropoietic anaemia in the context of Majeed syndrome) or immune deficiency (chronic granulomatous disease, lymphopenia associated with trisomy 21, human immunodeficiency virus (HIV) infection, and humoral immune deficiencies)[17].

Figure 11: Sweet Syndrome



Conclusion

Cutaneous manifestations of rheumatologic diseases are various and most of them are unspecific. Furthermore, many of those rashes can be isolated or be associated to non-rheumatologic diseases. We emphasize the need to combine the information given by the recognition of the skin lesions of a patient to the complete picture, including complaints, personal and familial history, clinical signs, biological and radiological results to obtain the more accurate possible diagnosis.

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Paediatric non-infectious Uveitis

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Key words

pediatric, non-infectious uveitis, treatment

Abstract

Paediatric uveitis is a rare, but aggressive disease which can, when left untreated, lead to childhood blindness. The 'International Uveitis Study Group' published different classifications and descriptors of uveitis. Assessing the onset (sudden, insidious), course (acute, chronic, recurrent), duration (≤ 3 months, > 3 months) and site of inflammation (anterior, posterior, intermediate, panuveitis) can be useful tools in the differentiation of the underlying etiology. Distinguishing infectious from non-infectious uveitis is key to start the proper treatment and prevent complication. In Western countries non-infectious causes are most prevalent, where uveitis can be strictly confined to the eyes or associated with a systemic disease, including Juvenile Idiopathic Arthritis (JIA), Behçet Disease, Tubulo-interstitial nephritis and uveitis syndrome (TINU), Sarcoidosis and Vogt-Koyanagi-Harada syndrome (VKH). JIA-associated uveitis accounts for approximately 20% to 40% of all childhood uveitis. JIA gives both musculoskeletal and extra-articular manifestations, with uveitis as most common one, where screening schemes have been developed for the early detection. Treating non-infectious uveitis follows a step-by-step approach, usually starting with local corticosteroids. In children with severe and/or refractory uveitis, timely management with disease-modifying antirheumatic drugs (DMARDs) and biologic agents is important. This article will provide an overview of uveitis etiology, classifications, current standards in treatment and follow-up.

1. Introduction

Uveitis, an inflammation of the middle layers of the eye, must be adequately recognized and treated in view of the serious complications that may develop over time, including permanent vision loss. Yet recognition and diagnosis in a paediatric setting is often more difficult compared to an adult population. Children cannot always indicate when they experience symptoms, and often parents will only recognize symptoms when they become externally visible, at an already advanced stage.

Additionally, uveitis at an early age is often asymptomatic and examination of the young child is not always sufficiently feasible, where early stages of uveitis are more easily missed[1]. As uveitis can be associated with underlying autoimmune diseases, also non-ophthalmologists need to be able to provide adequate diagnosis and follow-up. Moreover, when confronted with a child with a systemic inflammatory disease, the potential presence of uveitis should be considered and excluded. This article will provide an overview of uveitis etiology, classifications, current standards in treatment and follow-up.

2. Epidemiology

Although its low incidence in a paediatric population, uveitis is an important cause of blindness in children. Of all patients with uveitis, 2 to 16% are children[2, 3]. In a Finnish study, the incidence was between 4.2 and 4.9/100,000 children/year, which was significantly lower than the incidence in adults (27.2 per 100,000)2. A retrospective Dutch study of 123 patients showed that 76% of children with uveitis developed complications and 19% even developed at least 1 blind eye[4].

3. Classification of uveitis

Uveitis can be subdivided based on specific characteristics, which can help to differentiate the underlying etiology. The Standardization of Uveitis Nomenclature (SUN) Working Group, set up by the 'International Uveitis Study Group' (IUSG), published classifications and descriptors in order to communicate uniformly about uveitis[5].

Depending on the onset (sudden, insidious), course (acute, chronic, recurrent), duration (limited ≤ 3 months, persistent > 3 months) or the site of inflammation (anterior, posterior, intermediate, pan-uveitis) different etiologies should be considered with varying prognosis and treatment[1, 6]. The intraocular inflammation may further be subdivided according to whether there is an associated infectious or non-infectious cause, and whether it is strictly confined to the eyes or associated with a systemic disease. Additionally searching for granulomatous signs in the eye may give more information, as it is more likely to develop in certain underlying diseases. Recognition of the exact localization is based on the primary site of inflammation. The clinical presentation may differ between the four possible localizations, which can help to differentiate:

Anterior uveitis refers to inflammation of the iris or the ciliary body. When acute, it is mainly characterized by photophobia or pain, ciliary injection/redness and miosis. Slit lamp examination makes it possible to see endothelial precipitates, inflammatory cells and proteins (flares) in the anterior chamber, and both peripheral anterior and posterior synechiae. In chronic anterior uveitis, the inflammation is more dormant, with ciliary injection and photophobia usually absent[5,6].

Intermediate uveitis is characterized by inflammation of the vitreous and the peripheral retina. Aggregates of inflammatory cells occur in the lower part of the vitreum, the so-called "vitreous snowballs". They are named "snow banks", when they occur in the pars plana and the ora serrata of the eye. Pars planitis is a subtype of the intermediate uveitis with snowball and bank formation where no associated infection or systemic disease is found, also referred to as idiopathic intermediate uveitis[6]. Notice that excessive intermediate inflammation can additionally cause a mild anterior uveitis, by spilling of inflammatory cells to the anterior chamber, to this extent where the anterior symptoms can masquerade an underlying intermediate uveitis.

Posterior uveitis can be subdivided into retinitis and choroiditis with focal or multifocal disease, where also the presence of a vasculitis needs to be assessed[6]. Usually infections are responsible, rather than autoimmune reactions. Both intermediate and posterior uveitis will have few to absent pain related symptoms, however nonspecific visual changes are more frequent compared to the anterior form.

In pan-uveitis, there is no preference in place of infestation. There is inflammation in the anterior chamber, the vitreum, the retina and/or the choroid[5, 6].

4. Etiology

The differential diagnosis of paediatric uveitis is diverse and can be divided into four main groups: infectious, non-infectious, masquerade or idiopathic. Etiology is very dependent on geographic, demographic, genetic and socio-economic factors. In Western Countries non-infectious anterior uveitis is most prevalent, where in developing countries mainly infectious causes should be excluded (table1). However even in developed countries infectious agents should be kept in mind, as they comprise approximately 11-13% of all childhood uveitis[7]. The idiopathic group of uveitis still remains the largest one in children, with a total of 60% [1]. Differential diagnosis of the underlying etiology can be more clarifying by categorizing the cases based on the classifications and descriptors mentioned above. The most

Table 1: Etiology of uveitis in children

Classification of etiology in childhood uveitis				
Anterior				Intermediate
Granulomatous		Non-granulomatous		
Sarcoidosis	Tuberculosis	Idiopathic	Systemic Lupus Erythematosus	Juvenile Idiopathic Arthritis
Inflammatory bowel disease	Syphilis	Juvenile idiopathic arthritis	Herpes simplex virus	Sarcoidosis Multiple Sclerosis
Behçet's disease	Herpes simplex virus	SpA* (AS, RD, Ps, IBD)	Lyme disease	Toxocariasis
Multiple sclerosis	Fungal disease	TINU	Leukemia	Lyme disease
Whipple's disease	Leprosy	HLA-B27 associated	Drug Induced	Pars planitis
Posterior				Pan-uveitis
Without vasculitis		With vasculitis		
Toxocariasis	Toxoplasmosis	Cytomegalovirus	Herpes Simplex/Herpes Zoster virus	Syphilis
Leukemia	Tuberculosis	Inflammatory bowel disease	Systemic Lupus Erythematosus	Sarcoidosis
Intraocular foreign body	VKH syndrome ***	Syphilis	Behçet's disease	VKH syndrome
Bartonella Henselae	Lyme Disease	Kawasaki's disease	Sarcoidosis	Behçet's disease
		Polyarteritis nodosa	Wegener's granulomatosis	Infectious endophtalmitis

* Spondyloarthrtitis (Ankylosing spondylitis, Reiter's disease, Psoriasis, Inflammatory bowel disease)
** Vogt-Koyanagi-Harada syndrome

common etiologies of childhood uveitis according to anatomical classification are listed in table 1. It is subdivided into following groups: anterior non-granulomatous, anterior granulomatous, intermediate, posterior with or without vasculitis and pan-uveitis[6,8].

5. Diagnostic entities in childhood uveitis

5.1 Juvenile idiopathic arthritis (JIA)

JIA is the most common rheumatic disorder in children. According to the international league of associations of rheumatology (ILAR), age below 16 years, arthritis in 1 or more joints and persistent symptoms longer than 6 weeks are the diagnostic criteria for JIA. JIA can be divided into 6 subgroups: systemic-onset JIA, oligoarthritis (persistent or extended), polyarthritis (RF positive or negative), psoriatic arthritis, enthesitis-related arthritis and undifferentiated arthritis[9].

JIA gives both musculoskeletal and extra-articular manifestations, with uveitis as most common one. JIA-associated uveitis accounts for approximately 20% to 40% of all childhood uveitis. On average, uveitis is expressed 1.8 years after the diagnosis of JIA. However, 10% develops uveitis before the diagnosis of JIA can be made[10]. The disease is bilateral in 70 to 80% of the patients. It manifests predominantly as an anterior, non-granulomatous uveitis, with an acute or chronic course. Risk factors for the development of chronic anterior uveitis are young age, oligo arthritis, female gender and positive antinuclear factor (ANF), while male sex, positive typing for human leukocyte antigen-B27 (HLA-B27) and enthesitis-related arthritis will predispose to an acute form[10].

Since chronic anterior uveitis is asymptomatic, different screening schemes have been developed for the early detection of uveitis in children with JIA[11,12]. Table 2 shows the current standards for ophthalmic exams to screen for uveitis set by the American Academy of Pediatrics[12].

The most common complications in JIA-associated uveitis are band keratopathy, cataract, posterior synechiae, glaucoma, maculopathy, hypotony and amblyopia[1].

5.2 Pars planitis - Idiopathic Intermediate Uveitis

The term "pars planitis" has been recommended, by the IUSG for a particular subset of idiopathic intermediate uveitis associated with snowbank and snowball formation in the absence of an infectious or systemic disease[5]. Pars planitis accounts for 5 to 26.7% of all pediatric uveitis, with a highest occurrence in 6 to 10 years old children[13].

Floaters, blurred vision, pain and photophobia are the most common symptoms, yet the disease can be asymptomatic and diagnosed incidentally during routine eye examination especially in young children[13].

Table 2: Overview of the principal auto-inflammatory diseases

Frequency of Ophthalmologic Examination in Patients With JIA					
Type JIA	ANA[1]	Age at onset (years)	Duration of disease (years)	Risk Category	Eye Examination Frequency (months)
Oligoarthritis or polyarthrtis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	-	≤6	≤4	Moderate	6
	-	≤6	>4	Low	12
	-	>6	NA[2]	Low	12
Systemic disease (fever, rash)	NA[2]	NA[2]	NA[2]	Low	12

[1]ANA: antinuclear antibodies; [2]NA; not applicable

Source: adapted from : Cassidy J. Ophtalmologic Examinations in Children with Juvenile Idiopathic Arthritis[12].

The most common clinical findings are diffuse vitreous cells, haze, snowballs and snowbanks. Usually the disease is bilateral[1]. Since the anterior segment is often quiet and symptoms are minimal, the diagnosis of pars planitis is often delayed, possibly leading to complications and permanent visual loss in small children[14]. The most frequent complications of pars planitis includes cataract, cystoid macular edema, vitreous opacities and optic disc edema[13,15].

In children, pars planitis should be differentiated from chronic anterior uveitis which may be idiopathic or associated with JIA. Also sarcoidosis, multiple sclerosis (MS) and masquerade syndromes must be included in the differential diagnosis. Because of the strong correlation between pars planitis and multiple sclerosis (MS), patients should also be screened for the association of MS on the long-term[14].

5.3 Behçet disease

Behçet disease is an idiopathic, systemic vasculitis that affects all types of blood vessels, although it has a preference for the middle/large veins in the body. Behçet is characterized by recurrent aphthous oral ulcers, genital ulceration, skin lesions (erythema nodosum, pseudofolliculitis, acneiform nodules, papulopustural lesions) and uveitis. Currently no internationally accepted diagnostic criteria for children are available[1,16].

The mean age of presentation in Behçet disease is 30 to 40 years, but in 4 to 26% of the cases Behçet disease starts before the age of 16[1]. The HLA-B51 allele strongly correlates with the disease and its ocular manifestations. Severe damage to the eyes and blood vessels is more common in boys, while girls are more likely to develop genital ulcers and erythema nodosum[17]. The uveitis is typically bilateral, with unilateral cases only occurring rarely, and has a non-granulomatous appearance. The recurrent course, often with attacks of explosive nature, is typical for the disease[6]. Posterior uveitis in combination with retinal vasculitis is the most distinguishing aspect of the disease and is what ultimately can lead to blindness. An anterior involvement, often an iridocyclitis, with an associated hypopion in about one third of the patients, would occur more frequently before the age of 10 and often evolves later into a pan-uveitis. Although the appearance of a hypopion is typical for Behçet, it's not pathognomic[6]. Intermediate uveitis is rare and is the first expression of the disease in less than 10% of cases[3]. Cataract, intraocular pressure elevation, macular edema, maculopathy and optic atrophy are the most frequent complications seen in Behçet disease[1].

5.4 Tubulo-interstitial nephritis and uveitis syndrome (TINU)

Tubulo-interstitial nephritis (TIN) is a frequent cause of kidney failure in children. Clinical diagnosis is based on non-specific constitutional complaints such as fever, weight loss, fatigue, anorexia, asthenia, flank or abdominal pain, arthralgia or myalgia in combination with renal impairment evidenced by increased serum creatinine levels, proteinuria, hematuria, glycosuria and elevated urinary beta-2-microglobulin[18].

In rare cases this disease can occur in association with uveitis, also known as TINU-syndrome. This was first described by Dobrin et al. in 1975[19]. TINU accounts for 1.7% of all cases of adult uveitis[20], the prevalence of TINU is higher in younger age groups (average age 15 years) and there is a female preponderance[21]. There seems to be no racial or ethnic predisposition[22]. The onset of the uveitis can occur before (21%), during (15%) and after (65%) the start of the kidney disease. The majority of cases develops a bilateral, sudden onset, anterior, non-granulomatous uveitis, with typical symptoms of redness, pain and photophobia.

The most common reported complication is the development of posterior synechiae, but also cystoid macular edema, macular pucker, and chorioretinal scar formation are described. In essence, it is critical to recognize flares in time and to keep in mind the possible presence of uveitis in patients with tubulo-interstitial kidney disease, even though the risk of vision loss due to TINU appears to be low.

5.5 Vogt-Koyanagi-Harada syndrome (VKH)

VKH is a systemic, autoimmune disease that affects melanocyte-containing tissues, like the eyes (uveitis), skin (vitiligo, poliosis, alopecia and sensory disorders), hearing system (sensory hearing loss) and meninges (meningitis). The disorder is common in Japan and certain parts of Latin-America, mostly in Brazil. In Northern-Europe it rather seems to be an unusual diagnosis6. The HLA-DR4 and DR1 alleles are associated with the disease.

The eye is typically affected bilaterally, by an anterior and/or intermediate uveitis with granulomatous findings (e.g. mutton-fat precipitates). A pathogenic feature is the perilimbal vitiligo (Sugiura sign) occurring in 85% of the Oriental patients. As the disorder evolves, it often affects the posterior segments of the eye[6].

VKH syndrome can mimic, despite a different etiology, a sympathetic ophthalmia, both ocular and extra-ocular[23]. Other diseases such as sarcoidosis and white-dot syndromes can also look like VKH syndrome and must always be included in the differential diagnosis[6].

5.6 Sarcoidosis

Sarcoidosis is a chronic, multisystem, noncaseating granulomatous disease of unknown etiology, affecting mostly young adults. The disease is rare in the paediatric population, where most cases have occurred in patients aged 13-15 years[24]. Essentially it can affect any organ system, but the lungs and lymph nodes are most commonly involved. Infants and children younger than 5 years typically present with a triad of dermatitis, arthritis and uveitis, without typical lung damage. In older children involvement of the lungs, lymph nodes and eyes are more frequent, as seen in adults[25]. Sarcoidosis affects more often patients of black than white ethnicity (10:1), even though it is more common in colder climates.

Ocular involvement typically affects both eyes with anterior uveitis as most common manifestation, occurring in 24% to 58% of childhood sarcoidosis[25]. Small granulomatous keratic precipitates, mutton fat precipitates and/or iris nodules (Koeppe and Busacca) are typically seen in this anterior involvement6. Posterior uveitis occurs less often but is more visually disabling than inflammation in the anterior segment. It is distinguished by presence of choroidal granulomata and peripheral multifocal choroiditis[6,26]. When intermediate uveitis is present moderate-to-severe vitreous inflammation, snowball and snow banking of the pars plana region can be seen. Other ocular involvements, such as conjunctival granulomata, keratitis, retinitis, glaucoma and involvement of the eyelids or lacrimal glands, are possible, which makes ophthalmological slit lamp examination mandatory in the evaluation of childhood sarcoidosis[26].

Very similar and difficult to differentiate from early onset sarcoidosis (<5 years) is Blau syndrome or familial juvenile systemic granulomatosis. It is a rare autosomal dominant disorder characterized by childhood onset of granulomatous manifestation of the skin (rash), eyes (panuveitis and multifiocal choroiditis) and joints (arthritis)[24]. Another specific subtype of sarcoidosis is Heerfordt syndrome, which is identified by uveitis associated with a facial nerve palsy and uveoparotid fever[6].

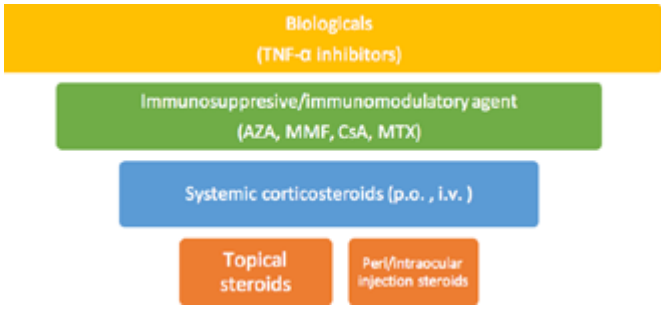
6. Treatment

The ultimate goal when treating uveitis is to avoid complications by suppressing the inflammatory response in the eye. There are no standardized treatment protocols for paediatric non-infectious uveitis, most clinicians follow a step-by-step drug strategy (see table3), which should be initiated early on and tapered off when activity has fully reduced during a period of 2 to 3 years. An effective communication between paediatric rheumatologist and ophthalmologist is therefore essential. In this article we limit ourselves to the treatment options for non-infectious uveitis[27].

6.1 Corticosteroids : topical, local injection or systemic use

The first-line treatment for anterior uveitis consists of topical corticosteroids, in the form of drops. The most commonly used topical corticosteroid is prednisolone acetate 1%. Association of cycloplegic agents is recommended to prevent the formation of posterior synechiae and to make the patient more comfortable[6,27]. If corticosteroids drops do not completely suppress the inflammation, periocular or intraocular injections with corticosteroids can be tried additionally. As topical steroids usually do not penetrate beyond the lens, local injections or systemic corticosteroids (oral, intravenously) are started immediately in intermediate, posterior and panuveitis[6,28].

Table 3: Step-by-step drug strategy for non-infectious uveitis



When topical corticosteroids are used, side effects such as intraocular pressure elevation and steroid-induced glaucoma should be kept in mind, as they occur more rapidly in children, and are more frequently refractory to treatment[1]. In patients who need more than 3 drops daily, the risk of cataract increases[29]. In these patients systemic immunosuppression with one of the DMARDs (disease modifying antirheumatic drugs) is indicated after 3 months of topical treatment[10].

Systemic corticosteroids continue to have an important role in the acute phase of non-infectious uveitis, but their use as a maintenance therapy is limited by their associated side effects[27]. The oral corticosteroids loading dose is usually 1 mg/kg/day of prednisolone, with a tapering over 3 months. In severe or sight-threatening uveitis, intravenous treatment with corticosteroids might be necessary.

6.2 Immunosuppressive agents

Immunosuppressive agents, called DMARDs, are used, alone or in combination with corticosteroids, in patients not responding adequately to local or systemic corticosteroids, in patients unable to reduce corticosteroid doses or experiencing side effects.

Inadequate response might be defined as worsening of active chorioretinal or retinal vascular lesions, anterior chamber cells, vitreous haze, macular edema and best corrected visual acuity[30].

In general, methotrexate (MTX) is used as first-line immunosuppressive agent, known as a safe and effective product. A dose of 15 mg/m² once weekly is commonly used, with a maximum of 20 mg/week following clinical response and systemic toxicity[13]. Full therapeutic effect is reached after 4-6 weeks. Side effects include gastro-intestinal discomfort, cytopenia, hepatotoxicity and interstitial pneumonitis. Adding 5 mg of folic acid the day after MTX is recommended to reduce the risk of side effects. MTX should be maintained for at least 12 months once uveitis is inactive[27].

Second-line immunosuppressive agents include Azathioprine (AZA), Mycophenolate Mofetil (MMF) and Cyclosporine (CsA).

Before starting AZA, genotype screening for TMPT (thiopurine methyltransferase) deficiency is recommended to avoid important drug toxicity, as gastrointestinal symptoms and myelosuppression. Close monitoring of blood count and liver enzymes is recommended during treatment. AZA is less commonly prescribed in children because of more frequent side effects and moderate-to-poor corticosteroid sparing effect[31].

MMF is used as second-line in MTX failures, and sometimes as first-line corticosteroid-sparing agent in non-JIA-associated uveitis. Side effects include gastrointestinal discomfort, leukopenia, thrombocytopenia and elevation of liver enzymes.

CsA is particularly effective in patients with Behçet disease-associated uveitis. In children with JIA-associated uveitis, CsA is more effective when combined with MTX. Hypertension, renal impairment, gingivitis and hirsutism are the most common side effects.

6.3 Biologicals

Biologicals have been recently introduced as rescue treatment. The majority are monoclonal antibodies, who directly act on the inflammatory cascade. The most effective agents at controlling ocular inflammation are the Tumor Necrosis Factor (TNF)-alpha inhibitors infliximab and adalimumab.
Infliximab and adalimumab are used as first line immunomodulatory agents for the treatment of Behcet disease, as second line immunomodulatory agents for juvenile idiopathic arthritis-associated uveitis after MTX treatment, as potential second-line immunomodulatory agents for treatment of posterior or panuveitis, severe uveitis associated with seronegative spondylarthropathy, or in patients who have failed to respond to classic immunomodulatory agents.

7. Conclusion

Because of the classifications and descriptors of uveitis, by the SUN, research and assessing the effect of new treatment options in uveitis has become more uniformly reliable. It has also proven to be an practical tool in helping to differentiate the etiology, estimating the prognosis and choosing the most effective treatment in children with uveitis.
Distinguishing infectious from non-infectious uveitis is key to start the proper treatment and prevent complications and permanent visual loss. The presence of a non-infectious uveitis needs to stimulate clinicians to search for associated systemic diseases and vice versa.
With the latest introduction of biologicals for treating uveitis, a new world of treating options has become available. Adalimumab and infliximab, both Anti-TNF-α biologic agents, have proven to be effective in non-infectious uveitis in adults and children, although more research is still needed. Mostly there is still a lack in paediatric treatment guidelines.

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New therapies for children with rheumatic conditions

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Key words

pediatric rheumatic diseases, biological therapies

Abstract

In recent years, the spectrum of pediatric rheumatic diseases as well as the understanding of the underlying pathogenesis has grown and in parallel the therapeutic possibilities for pediatric rheumatology patients have expanded. Standard treatment, comprising non-steroidal anti-inflammatory drug (NSAIDS), steroids and Disease modifying anti-rheumatic drugs (DMARDs) continues to be effective for the majority of juvenile idiopathic arthritis (JIA) patients. However, in patients refractory or intolerant to standard treatment, major advances have been seen since the introduction of biologicals, including TNF inhibitors and CTLA-4Ig in chronic arthritis patients and IL-1/IL-6 blockade in systemic JIA and in patients with autoinflammatory diseases. These new therapies interfere with the immune system and therefore the occurrence of side effects needs to be monitored. In the following article we discuss the mechanism of action of biological therapy, their indications and most common side effects.

Introduction

The spectrum of pediatric rheumatic diseases comprise more common entities such as juvenile idiopathic arthritis, but also rare diseases like early-onset systemic lupus, juvenile dermatomyositis, systemic vasculitis and the expanding spectrum of autoinflammatory diseases. Advances in understanding the underlying pathogenesis of these entities led to the development of novel therapies that target specific inflammatory cytokines, cell surface markers and/or cell signaling pathways. In 2000, Lovell first reported on the use of etanercept for the treatment of methotrexate resistant polyarticular juvenile idiopathic arthritis (JIA) in a multicentered, randomized, placebo-controlled, double-blinded trial.[1]

Since then, several additional cytokine antagonists, an anti–B-cell therapy, and a T-cell/B-cell coactivation signal inhibitor have been introduced in pediatric medicine. Since the introduction of these biological therapies, treatment options for patients with autoimmune and autoinflammatory diseases have been expanded, the use of corticosteroids is less and subsequently the outcome of these patients has dramatically improved, as measured by disease activity scores, functional assessments, radiographic progression and the impact on growth. The benefit of these new drugs is clear, but risks, especially on the long-term are not completely known.

As the number of children under these new therapies continues to grow, general pediatricians have an important role in close follow-up and early recognition of side effects.

In the following article, we will discuss the different biological therapies, most frequently used in pediatric rheumatology patients: TNF inhibitors, IL-1 blockade, anti-IL-6 therapy, CTLA-4 Ig and anti-B cell therapy. TNF inhibitors are mainly used to control articular inflammation (as seen in JIA), while IL-1 and IL-6 blockade are playing a central role in systemic inflammation (which is characteristic for autoinflammatory diseases). We will elucidate their mechanism of action, their indications and most common side effects.

TNF-α inhibitors

There is great evidence for the role of TNF-α in the initiation and perpetuation of the inflammatory process in patients with rheumatic diseases. Children with JIA have high levels of TNF-α in the synovial fluid and in the peripheral blood.[2,3] Studies in adults have shown an association between high levels of TNF-α and the presence with bone erosions.[4] There are at the moment three TNF-α inhibitors used for the treatment of pediatric rheumatic patients in Belgium: etanercept, adalimumab and infliximab (figure 1). They are added to standard therapy with methotrexate in polyarticular JIA patients in case of insufficient control of arthritis.

Etanercept is a fully human, dimeric protein containing the extracellular domain of the human TNF receptor fused to the Fc region of human IgG1. By binding to TNF-α, etanercept prevents the interaction of TNF-α with his cell surface receptor and consequently preventing effector responses of T cells and other immune cells. Etanercept can also modulate biological responses that are mediated by TNF: expression of adhesion molecules responsible for leukocyte migration, serum levels of cytokines and serum levels of matrix metalloproteases. Etanercept is administered subcutaneously, 0,8 mg/kg once or 0,4 mg/kg twice a week. The initial study, but also follow-up studies and registries report a dramatic reduction in active joints and markers of inflammation after three to four injections.[1,5] At the moment etanercept is indicated in children ≥ 2 years old with moderately to severe polyarticular JIA, for patients ≥ 12 years with juvenile psoriatric arthritis and enthesitis-related arthritis that are resistant or intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

Adalimumab is a fully human IgG1 monoclonal antibody that not only binds to TNF within the circulation, but also on the cell surface. It is administered subcutaneously every 2 weeks at a dose of 24 mg/m^2. As with etanercept results are seen quickly and efficacy is comparable in JIA patients. In 2008, Lovell et al published the results of the initial trial on efficacy and safety of adalimumab in JIA patients.[6] Today, adalimumab is reimbursed for ≥ 4 years old patients with moderately to severe polyarticular JIA and for patients ≥ 6 years with enthesitis-related arthritis that are resistant or intolerant to one or more DMARDs. In JIA patients with uveitis, adalimumab is the preferential treatment given the superior effect in the treatment of the uveitis.

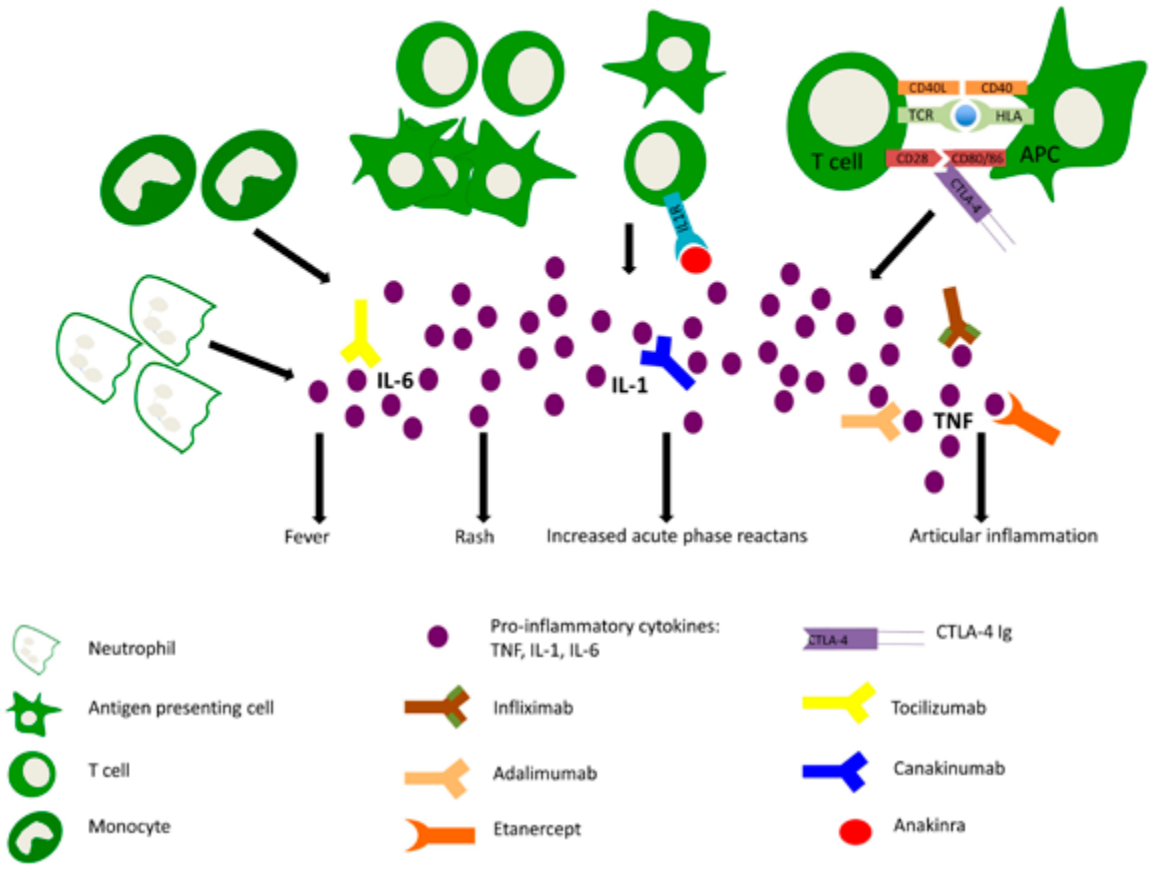
Infliximab is a chimeric monoclonal antibody that contains the murine antigen-binding region against human TNF-α attached to the constant regions of human IgG1. Mechanism of action is similar to adalimumab. Ruperto et al published in 2007 a randomized, double-blind, placebo-controlled trial on the use of infliximab in patients with polyarticular JIA.[7] Administration of infliximab is via intravenous route every 4-8 weeks at a dose of 6-10mg/kg depending on clinical response. Because of the murine part, there are concerns about the development of infusion related allergic reactions, probably related to the development of anti-infliximab antibodies. The latest are also related to accelerated clearance of infliximab. At the moment reimbursement is only available for pediatric patients > 6 years with refractory Crohn's or Colitis Ulcerosa disease.

In addition to the treatment of JIA, TNF-blockade, especially adalimumab also was shown to be successful in the treatment of children with refractory uveitis,[8] and both infliximab and adalimumab have proven to be efficacious in inflammatory bowel disease.[9,10] Finally, in small case series, benefit has been reported in hidradenitis suppurativa, and rare autoinflammatory disorders like Behcet's disease, Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), hyperIgD syndrome, Deficiency of ADA2 (DADA2), …

To date, and in general, TNF-α antagonists have been very well tolerated. Infusion reaction (mild allergic reactions to anaphylactic reactions) can be associated with the administration of infliximab. Injection site reactions can be observed with adalimumab and etanercept, but are usually mild. During treatment with TNF-α blockers, patients may be more prone to infections: mild upper respiratory tract are the most common, but patients must be monitored for the development of systemic and opportunistic

Figure 1: Biologic therapies and their mechanism of action in pediatric rheumatology.

Depending on the type of rheumatological disease, different immune cells play a dominant pathogenic role. T cells and antigen presenting cells are central players in the inflammatory process in autoimmune diseases like juvenile idiopathic arthritis. Monocytes and neutrophils, both cells of the innate immune system, are important in the pathogenesis of autoinflammatory diseases like systemic juvenile idiopathic arthritis and cryoperin associated periodic syndrome (CAPS). During the inflammatory response pro-inflammatory cytokines are secreted in the environment. TNF-α is important in articular inflammation, whereas IL-1 and IL-6 are mainly responsible for the systemic features. Etanercept is a fusion protein containing a human FcIgG1 linked with a TNF receptor. Etanercept binds circulating TNF-α, thus preventing cellular binding and cell activation. Adalimumab and infliximab are both anti-TNF monoclonal antibodies but differ in that infliximab is a chimeric antibody whose antigen-binding region uses a mouse component. Abatacept binds the CD80 and CD86 family of B proteins on antigen-presenting cells, thereby preventing the costimulatory signaling needed to activate T cells via CD28. Anakinra binds to the IL-1 receptor and thereby prevents binding of IL-1 and subsequent cell signalling. Canakinumab is a fully human anti-IL-1β monoclonal antibody that selectively blocks Il-1β. Tocilizumab is a humanized, mAb to the IL-6 receptor. Tocilizumab competes with both the soluble and the membrane-bound IL-6 receptor preventing cell signaling.



infections (bacterial, viral (such as varicella) but also granulomatous (Tuberculosis)).[1,5–7] In view of reactivation of TBC seen in adult rheumatoid arthritis patients receiving TNF-inhibition, all patients are screened for latent tuberculosis with a tuberculosis skin test before start of treatment. In case of a serious infection, treatment with the TNF antagonists should be discontinued. We recommend that patients, starting on biological therapy, are made up-to-date with all immunizations in agreement with current immunization guidelines before start of treatment if possible. Similar as for patients receiving methotrexate we recommend to prescribe yearly the flu vaccine. Following the current guidelines from the Belgian Health Authorities for immunosuppressed patients, children receiving biologics should receive the 13-valent conjugated anti-pneumococcal vaccine and 8 weeks later the 23-valent non-conjugated anti-pneumococcal vaccine. For life-attenuated booster vaccines, limited data so far indicate that these are safe in patients treated with regular methotrexate dosage, low-dose corticosteroids and anti-TNF agents. However, firm conclusions on the safety cannot be drawn, and currently it is not recommended to administer live attenuated vaccines while on biological therapy. Various other side effects have been reported: vasculitic or psoriatic skin rashes, cytopenia, development of drug induced lupus, lupus-like reactions, sterile cholecystitis,[11]… There has been a particular concern regarding the possible development of malignancy, particulary lymphoma, under treatment with TNF antagonists, especially in adults, but also in children. The initial warning given by the US Food and Drug Administration in 2009 was based on the analysis of voluntary post-marketing reports of malignancies in pediatric patients receiving TNF inhibitors for various conditions. Subsequent studies however have shown that patients with JIA have an increased rate of malignancies compared with the general population, even without biological drug exposure.[12] In addition, more recent studies could not reveal an increased malignancy rate in JIA patients

Table 1: Guidelines in the use of biologicals in children

Clinical monitoring
Document absence of latent or active tuberculosis before starting
Monitor initially after 1-2 months, then every 3-6 months, depending on course
Hold if suspected bacterial infection, varicella
Vaccination with life attenuated vaccines is contraindicated
Laboratory Monitoring
Complete blood cell count with white blood cell count, differential and platelet count, AST, ALT at start and afterwards at least 1x/3-4 months

upon receiving TNF-inhibitors highlighting the need for more long-term studies with a relevant control population rather than historical controls.[13] Similar concerns exist for the development of demyelinating syndromes, including multiple sclerosis. While some reports warn for an association between inflammatory demyelinating events, other failed to demonstrate a higher incidence than what would be expected.[14] At this stage, this complication is very rarely seen in children. Currently, patients with previous demyelinating syndromes should not be treated with TNF inhibotors and patients with a positive family history should be closely monitored for symptoms of demyelinisation.

In case of surgery, guidelines developed for adults suggest withholding biologic DMARDs for at least 1 week before and after surgery.

Finally TNF antagonists were shown to confer a risk of worsening congestive heart failure in adults. Therefore the use of these drugs are contra-indicated for these children.[15]

In the follow-up of children under TNF inhibitors, laboratory monitoring (complete blood cell count with white blood cell differentiation and liver transaminases) is recommended every 3 months.

IL-1 blockade

IL-1β is a strong pro-inflammatory cytokine. It not only plays a role in chronic arthritis by stimulating synoviocytes and chondrocytes to produce small inflammatory mediators and MMP's that lead to joint damage, but also in systemic inflammation which is typical of auto-inflammatory diseases.[16] IL-1 function is tightly regulated by its natural occurring receptor IL-1Ra: an imbalance between IL-1 and IL-1Ra can lead to uncontrolled inflammation. Today there are 3 IL-1 inhibitors used in pediatric rheumatology: anakinra, canakinumab and rilonacept (figure 1). Anakinra and canakinumab are reimbursed in Belgium for patients with a specific autoinflammatory syndrome, named CAPS (cryopyrin associated periodic syndrome). Recently canakinumab has also been approved to treat patient with refractory systemic juvenile idiopathic arthritis (sJIA), colchicine resistant Familial Mediterranean Fever and rare autoinflammatory diseases like TRAPS and hyperIgD.

Anakinra is a human recombinant form of IL-1 Ra that is given subcutaneously once daily at a dose of 1-4 mg/kg. Patients with sJIA as well as patients with CAPS and deficiency in IL-1 Ra (DIRA), two monogenic autoinflammatory syndromes, showed a dramatic response to Anakinra in several studies, supporting its use in the pediatric population.[17–19] Canakinumab is a fully human anti-IL-1β monoclonal antibody that selectively blocks Il-1β. Because of his longer half-life, canakinumab is administered every 4 to 8 weeks. The dose used is 4 mg/kg, but can be increased up to 8 mg/kg depending on clinical response. Randomized controlled trials with canakinumab in pediatric patients with CAPS and sJIA have proved its great efficacy and a good safety profile.[20]

Injection site reactions, often mild and decreasing with time, are more frequently seen for anakinra than for canakinumab. Ice packs and application of a topical corticosteroid can be helpful. It is seldom a reason to interrupt the treatment. Patients treated with IL-1 blockade have an increased susceptibility to infections, especially when there is a concomitant use of corticosteroids.[18,20] Therefore it is recommended to discontinue anti-IL1 treatment in case of a serious infection. Cytopenia and elevations in liver transaminases, sometimes dramatic, were seen in a few patients included in the clinical trials with canakinumab.[20]

The relation between IL-1 inhibition in sJIA and development of macrophage activation syndrome (MAS) is not completely elucidated. During the pivotal clinical trials in sJIA, a few patients treated with IL-inhibition were found to develop MAS. Conversly, L-1 inhibition with anakinra has been used successfully to treat MAS in sJIA. Monitoring a complete blood cell count and liver transaminases is recommended 1 month after start of treatment and subsequently every 3 months.

IL-6 blockade

IL-6 is a pro-inflammatory cytokine contributing to the host defense through stimulation of the acute-phase responses, immune reactions and hematopoiesis. Dysregulated continual secretion of IL-6 plays a pathological role in several autoinflammatory diseases.[21] IL-6 levels were shown to correlate with fever spikes, thrombocytosis and joint involvement in patients with sJIA.

Tocilizumab is a humanized anti-IL-6 receptor antibody that can bind to the soluble and membrane bound IL-6 receptor (figure 1). A proof of principle study in sJIA patients showing its benefit was published in 2005.[22] Randomized, double-blind, placebo controlled trials in sJIA and polyarticulair JIA patients have proven their efficacy[23,24] with quick and persistent control of systemic and articular inflammation. Tocilizumab is reimbursed in Belgium for children with refractory sJIA and very recently also for children with polyarticular JIA. In addition there is evidence for the benefit of Tocilizumab in refractory uveitis patients[25], autoinflammatory diseases that are IL-6 mediated like Castleman disease, Takayasu arteritis… Intravenous administration at a dose ranging from 8 mg/kg to 12 mg/kg depending on weight and indication, occurs every 2 weeks for sJIA patients and every 4 weeks for polyarticular JIA patients. A subcutaneous form is under investigation. Clinical and laboratory response can be seen in 48 hours.

Infections were the most common adverse event in clinical trials conducted in children with sJIA and polyJIA. Patients should be screened for tuberculosis before initiation of the treatment, as is the case for TNF blockers and IL-1 blockade. Also elevation in liver transaminases and neutropenia occurred more frequently in patients on tocilizumab treatment. Other important adverse events reported included anaphylactoid reactions, development of MAS, occurrence of pulmonary hypertension and intestinal hemorrhage.[23,24] Therefore a complete blood cell count with white blood cell differentiation and liver transaminases are checked before each administration of tocilizumab. Echocardiography is done regularly in follow-up of patients treated with tocilizumab.

CTLA-4 Ig (Abatacept)

Before a T cell can be activated by an antigen presenting cell (APC), 2 molecular signals are required: 1. the interaction between the T cell receptor and the MHC molecule on the APC and 2. the interaction of CD28 on T cells and CD80/86 on the APC (figure1). Besides CD80/86, CTLA-4 is also a receptor for CD28, but with an opposite effect: it prevents the second signal required for T cell activation. Binding of CTLA-4 to CD28 therefore results in T cell anergy. Abatacept is a fusion protein consisting of the extracellular domain of the human CTLA-4 and a fragment of the Fc portion of human IgG. It inhibits T cell activation by preventing the 2nd activation signal (figure1). Forms for intravenous or subcutaneous administration exist. In Belgium there is reimbursement for the IV administration of abatacept in children above 6 years with polyarticular JIA, resistant to therapy with DMARD's and at least 1 TNF blocker. Prior to start, tuberculosis screening (mantoux test and X-ray of the thorax) is necessary. In an international, multicenter prospective study of 190 subjects with polyarticular course JIA using a randomized, double-blind, placebo-controlled withdrawal design, IV abatacept was well tolerated and no serious adverse events were recorded.[26] Recently, a Phase III Open-Label Study showed effectiveness and safety of subcutaneous abatacept treatment over 24 months in patients with polyarticular JIA.[27] Long-term follow-up of patients enrolled in the abatacept IV trial, demonstrate that abatacept has a very good safety profile: no cases of tuberculosis, opportunistic infections, or malignancies.[28] Apart from treatment of polyarticular JIA patients, there are indications that abatacept is successful in the treatment of refractory uveitis patients.[25]

Guidelines for the use of abatacept suggest to interrupt treatment if a bacterial infection is suspected or in children with varicella. Laboratory monitoring (complete blood cell count, liver transaminases) is recommended every 3 months.

Rituximab

Rituximab is a chimeric mouse-human monoclonal antibody that binds to the CD20 receptor on pre-B and mature B cells, but not on antibody producing plasma cells, resulting in B cell depletion. Rituximab is given intravenously. Two dosing regimes are actually used: a dose of 375 mg/m2/week for 4 weeks or 2 doses of 500 mg/m^2 (max 1000mg) with an interval of 2 weeks. Because of his mechanism of action, Rituximab will be beneficial in the treatment of auto-antibody mediated diseases. The most common indication for rituximab therapy is refractory systemic lupus with renal involvement, vasculitis, cytopenia and neuropsychiatric disease.[29–31] Other indications are refractory dermatomyositis, primary systemic vasculitis especially refractory ANCA associated vasculitis, …

Before administration of Rituximab, pretreatment with an antihistamine and corticosteroids is recommended to prevent allergic infusions reactions. As rituximab deplete B cells, prolonged reduction of immunoglobulin levels is possible and more common in children than in adults, leading to an increased susceptibility for infections including opportunistic infections.[32] It may require immunoglobulin replacement therapy, especially in patients who have developed serious infection or who are on other immunosuppressive therapy. As reactivation of a hepatitis B virus occurred in patients under treatment with Rituximab, children need to be screened for hepatitis B infection, before start of treatment and if positive, Rituximab treatment cannot be initiated. Under treatment with Rituximab B-cell numbers need to be checked before and 1 month after infusion. Immunoglobulin levels are recommended to be monitored every 3 months.

Summary

In recent years, possibilities for treatment of pediatric rheumatology patients have grown thanks to the better understanding of the underlying pathogenesis. Standard treatment, comprising NSAIDs, (local or temporary systemic) steroids and DMARDs (especially methotrexate) continues to be effective for the majority of JIA patients. However, in patients refractory or intolerant to standard treatment, major advances have been seen since the introduction of biologicals, including TNF inhibitors and CTLA-4Ig in chronic arthritis patients and IL-1/IL-6 blockade in sJIA patients. Being biological drugs, these new therapies may theoretically interfere with the physiological immune defense. As such, surveillance of patients under this therapy for intercurrent infections and more rarely autoimmune phenomena is important.

With the discovery and expansion of knowledge on autoinflammatory diseases (see article on autoinflammatory diseases in this journal), the often dramatic response to biological drugs in these conditions has been apparent and their role is increasing. This is illustrated by the use of IL-1 blockade in IL-1 driven pathologies like CAPS. In addition, new insights in disease mechanism continue to incite targeted drug development, such as the JAK kinase inhibitors, which seem to have promising effects in the autoinflammatory interferonopathies.

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1 paquet =
1 vaccin pour une vie*

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An adjusted Bristol Stool Scale for non-toilet-trained children: the Brussels Infant and Toddler Stool Scale (BITSS).

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Key words

Infants, Toddlers, Stool consistency, Stool scale, Bristol Stool Scale, Brussels Infant and Toddler Stool Scale

Abbreviations

AISS: Amsterdam Infant Stool Scale
BSS: Bristol Stool Scale
BITSS: Brussels Infant and Toddler Stool Scale
HCP: Healthcare professionals

Abstract

Background and objective

Stools of infants and young non-toilet-trained children differ considerably from the illustrations in the Bristol Stool Scale (BSS), which was developed for adults. Nevertheless, the BSS is also widely used to describe stool consistency in non-toilet trained children. The objective of this study is to evaluate the adequacy of an adjusted BSS based on photos of infant stools in diapers.

Methods

At first, out of 28 photos, seven photos of infant stools in diapers best matching the drawings in the original BSS were selected by 11 international key-opinion leaders in the field of paediatric gastroenterology. Then they were shown to 261 parents, 145 paediatricians and 160 nurses in paediatric departments throughout Belgium. They were asked to match each of the 7 photos with the best corresponding BSS type.

Results

The overall proportion of perfect assignments for each photo with their matching BSS description was 45.9% (parents 36.4%, paediatricians 58.6%, nurses 50.0%; p<0.001), which increased to 56.4% when perfect match according to the 4 BSS consistency groups was considered (parents 43.7%, paediatricians 69.7%, nurses 65.0%; p<0.001). Fleiss' kappa values were higher in paediatricians and nurses (respectively 0.667 (95% CI 0.480 – 0.745) and 0.620 (95% CI 0.446 - 0.701), corresponding with substantial agreement) than in parents (0.582 (95% CI 0.318 – 0.689), moderate agreement).

Conclusions

We developed an adapted stool scale for non-toilet-trained children, the Brussels Infant and Toddler Stool Scale (BITSS). Healthcare professionals assessed stool consistency better than parents, who experienced most difficulties in differentiating hard from normal formed stools. Watery stools were best recognized by all groups.

Introduction

Defining a normal stool pattern in infants and young children is challenging as stool patterns are highly fluctuating and vary widely in frequency and consistency according to age and nutrition[1,2]. These variations are normal and common, but cause considerable concern to many parents[3–6], resulting in frequent consulting of healthcare professionals (HCP) which may lead to unneeded dietary modifications, investigations and medical treatments[6].

The description of stool consistency is very subjective. Several studies have shown differences in the perception of "normal stool" between parents and HCPs[3,7]. An objective instrument to assess stool consistency is required in order to better diagnose constipation and diarrhoea, and to evaluate treatment efficacy. In adults, the Bristol Stool Scale (BSS, figure 1)[8] is the most commonly used instrument for the description of stool consistency. The BSS consists of a descriptive visual scale categorizing stools in seven illustrated types from type 1 (separate hard lumps) to type 7 (watery, no solid pieces). For children, several alternatives have been developed[9–12]. However, none of these alternatives has succeeded to replace the BSS in daily practice, illustrating their shortcomings. In infants and non-toilet-trained children, stool assessment is very challenging because stools in diapers differ from the BSS illustrations and tend to deform over time.

The objective of this study is to propose a new tool to describe stool consistency in non-toilet trained children, starting from the original BSS descriptions of stool consistency but replacing the drawings with photos of real stools in diapers in order to obtain a more realistic presentation of stools and to validate this scale.

Methods

Study design

In a first phase, photos of stools from non-toilet-trained children were selected to represent the drawings of stools in the original BSS. These colour photos of diapers with stools from hospitalized infants and young children were taken by nurses in the hospitalization wards of the KidZ Health Castle of the UZ Brussel between February and April 2016. Stools with blood or mucus were excluded. The type of feeding was not considered as an exclusion- or inclusion criterion. Parental consent for taking the photos was obtained.

The four best matching photos for each of the original types of the BSS were selected by a team consisting of 12 nurses and three staff members of the UZ Brussel, resulting in 100% agreement in the 4th anonymous voting round. These 28 pictures were sent out to a core-group composed of five international paediatric gastroenterologists doing research in this field, who selected the seven photos best representing the original BSS descriptions, each corresponding with one specific type of the BSS (figure 2). A 100% full consensus was reached after two voting rounds. The order of these seven photos was then randomly mixed. These mixed photos as well as the original BSS with the descriptions were sent to six other international key-opinion leaders in paediatric gastroenterology. When they were individually asked to combine the 7 photos with the best corresponding BSS type, the kappa value of the first voting round was 0.86 for photos combined per BSS consistency group, indicating an excellent interobserver agreement between the key opinion leaders.

In the second phase, this selection of photos was shown to individual paediatricians, nurses and parents, who were asked to match the photos with the corresponding

Figure 1: Illustration of the Bristol Stool Scale (8)

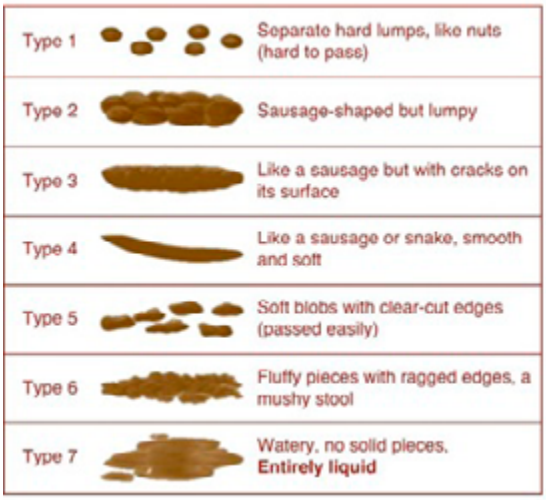
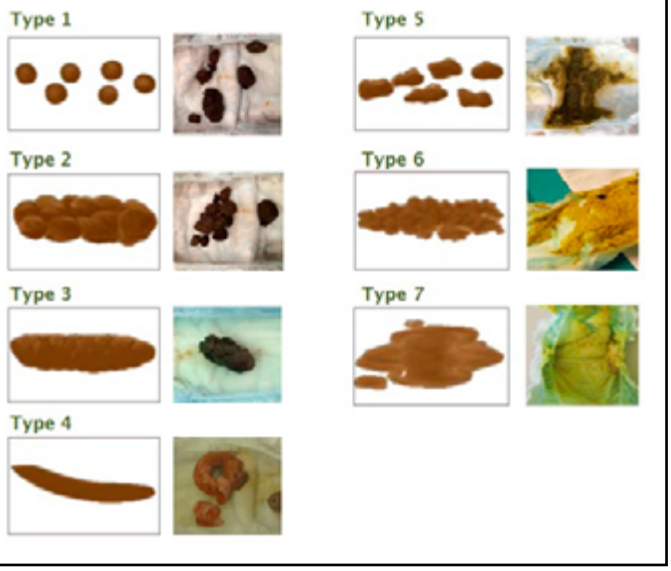


Figure 2: BITSS stool photos compared to the original BSS drawings



BSS type. They were allowed to look at the seven photos before assigning each photo to the best matching BSS type. For parents, as most of them are not familiar with the BSS, they were asked to put the photos in the correct order from "hard" to "watery" stools, corresponding with the original BSS order. The purpose of this phase was to investigate whether parents, nurses and paediatricians achieved similar results in matching our seven photos to the corresponding BSS type. If this is confirmed, this Brussels Infant and Toddler Stool Scale (BITSS) could be used as a more adequate and reliable alternative for the BSS for describing stool composition of non-toilet-trained children.

In a following phase, the study was enlarged from a Belgian to an international study, involving Europe, Asia and The Americas (data not reported, accepted for publication). The protocol of the international study was registered at Clinical Trials.gov NCT02913950. The study was approved by the Medical Ethical Committee of the UZ Brussel. No funding was received to the benefit of this study.

Data collection

Data were collected in the KidZ Health Castle of the UZ Brussel of the Vrije Unviersiteit Brussel and in other paediatric departments throughout Brussels and the Flanders. Data were obtained from October 2016 until the end of January 2017.

Language

Explanations about the test and the original BSS descriptions were given in the language of the participant. Languages spoken were Dutch, French and English. Participants speaking any other language were not included in absence of an interpreter.

Participants

Participating paediatricians are general paediatricians, paediatric gastroenterologists and other subspecialists in paediatrics. Trainees in paediatrics were also allowed to participate. Nurses were working in paediatric hospitalization wards or in ambulatory paediatric medical services. Parents were recruited in waiting rooms of ambulatory medical services of the hospitals. They were attending a planned consultation with a paediatrician and the study was conducted while they were waiting for the clinical visit of their child.

Statistical analysis

A total amount of 250 parents, 125 paediatricians and 125 nurses was preset as the number to be obtained. Data were analysed using R version 3.1.2. Results are expressed as absolute percentages of appropriate assignments. The level of interobserver agreement between parents, paediatricians and nurses was evaluated based on the proportion of exact agreement as well as on the Fleiss' kappa coefficient [13], which allows assessing the interobserver agreement between multiple raters in the assignment of categorical variables. This is in contrast with the classic Cohen's kappa, which measures the interobserver reliability between only two observers. The following kappa values will be calculated: overall, per observer group and per gender. Kappa values are interpreted as follows: 0.01-0.20 = poor agreement; 0.21-0.40 = fair agreement; 0.41-0.60 = moderate agreement; 0.61-0.80 = good/substantial agreement; 0.81-1.00 = excellent agreement) [14]. Differences of the proportion of exact agreements among rater groups and among sexes was calculated using χ^2-analyses.

Results

In total, 566 participants were recruited (Table 1).An overview of the number of correct assignments is illustrated per photo in Figure 3.

Regarding photo 2 (BSS type 1), parents scored the lowest results (68.6%); nurses performed slightly better and paediatricians scored the best, however still not very good (respectively 73.1% and 76.6%).

Photo 5 (BSS type 2) appeared to be the most difficult to interpret. In nearly all groups photo 5 got the worst scores: only half of the parents matched this photo with the according BSS type 2, and results were also poor for paediatricians and nurses. Parents mostly misattributed photo 5 to BSS type 3 (40.6%), whereas HCP equally mismatched the photo with BSS type 1 and 3 (both 15.4%).

For photo 4 (BSS type 3), results in parents were very poor (49.8%), whereas HCP did much better (79.0%; $p < 0.001$). Misattributions were equal to BSS type 1 and 2, but in HCP this was around 10% for both, whereas in parents it was much higher: 26.8% incorrectly assigned photo 4 as BSS type 2 and 22.6% even as BSS type 1.

Photo 6 (BSS type 4) was interpreted very well by all groups, as 91.9% of all observers classified the photo to the corresponding BSS.

Photo 3 was very well recognized as BSS type 5 by parents (85.8%), even slightly better than by HCP (81.6%), although this difference was not significant (p=0.181). Parents confused photo 3 more frequently with BSS type 4 (9.6%), whereas HCPs rather falsely interpreted it as BSS type 6 (11.1%).

Paediatricians and parents performed similar in scoring photo 1 as BSS type 6. Parents confused photo 6 mostly with BSS type 7 (8.1%), whereas paediatricians more often wrongly assigned it as loose stools (8.3%). In nurses, the results were lower comprising comparable mismatching with BSS types 5 (11.9%) and 7 (10.0%).

Paediatricians (94.5%) achieved the best scores in matching photo 7 with BSS type 7, compared to 91.6% of the parents and 88.8% in nurses. In all groups, photo 7 was mostly confused with BSS type 6. All rater groups achieved highest average combined scores for watery stools, suggesting this is the easiest category to identify.

Other findings

Overall proportion of correct answers

The overall number of correct assignment of every photo was 45.9%. The proportion of entirely correct assignments was significantly different among parents (36.4%), paediatricians (58.6%) and nurses (50.0%) (p<0.001).

Correctness within maximum one type deviance from the correct type

As shown in Table 2 all photos reached >90% correct assignments when results that fall within one type deviance from the correct BSS type are combined, except for photo 4 (type 3) in parents, due to the fact that 12% of them assigned it as type 1 instead of type 3 (2 category types away). This suggests that our photos (except for photo 4) are easily recognised by all rater groups.

Figure 3: Correct assignments of the BITSS photos

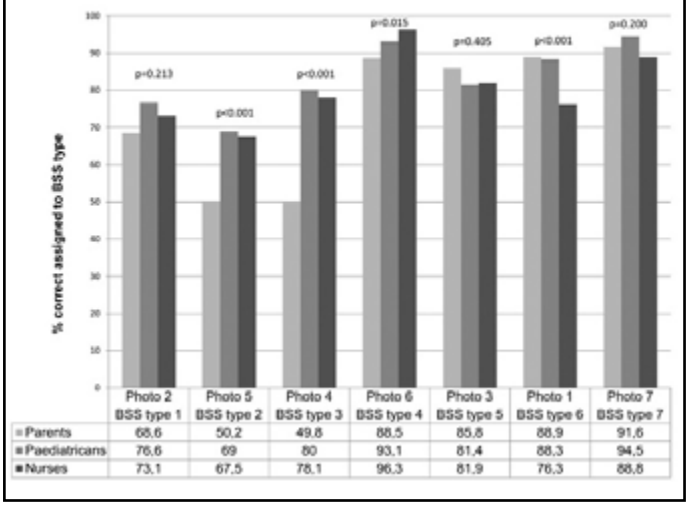


Table 1: Overview of the participants

	Parents (%)	Paediatricians (%)	Nurses (%)
Brussels	**174 (67)**	**76 (52)**	**69 (43)**
UZ Brussel	174 (67)	33 (23)	44 (28)
St-Pieter		18 (12)	12 (8)
HUDERF		16 (11)	6 (4)
St-Anna St-Remi		9 (6)	7 (4)
West Flanders	**27 (10)**	**24 (17)**	**36 (23)**
AZ St Jan Brugge	20 (8)	9 (6)	20 (13)
AZ Groeninge Kortrijk	7 (3)	15 (10)	8 (5)
Zeepreventorium			8 (5)
Antwerp	**25 (10)**	**24 (17)**	**32 (20)**
Koningin Paola	25 (10)	15 (10)	19 (12)
St-Vincentius		9 (6)	13 (8)
East Flanders	**35 (13)**	**21 (14)**	**23 (14)**
UZ Gent	26 (10)	13 (9)	15 (9)
OLV Aalst	9 (3)	8 (6)	8 (5)
TOTAL	261 (100)	145 (100)	160 (100)

Overall interobserver agreement

The overall fleiss κ value is 0.604 (95% CI 0.382-0.692). The interobserver agreement is moderate in parents (κ= 0.582 (95% CI 0.318 - 0.689)), and good in HCP (κ= 0.667 (95% CI 0.480 - 0.745) for paediatricians and κ= 0.620 (95% CI 0.446 - 0.701) for nurses)).

Differences due to gender

Out of the 261 parents, sex was known for 231 (88.5%); 52 of these were male (22.5%) and 179 (77.5%) female. There were 137/145 (94.5%) paediatricians for whom the sex was registered, 44 (32.1%) of these were male and 93 (67.9%) were female. There was a registered sex for 141/160 (88.1%) nurses, of whom only 9 nurses were male, the influence of gender was not analysed for this group.

The kappa score for agreement between fathers was moderate (0.543; 95% CI 0.259-0.649), whereas the kappa value indicated substantial agreement for mothers (0.606; 95% CI 0.342-0.714). The overall number of perfect assignments for all photos was significantly higher for mothers than for fathers (40.2% vs 21.2%; p=0.012).

Regarding paediatricians, the kappa value was also considerably better in female than in male paediatricians (respectively 0.697 (95% CI 0.531-0.756) vs0.571 (95% CI 0.338-0.682)). The overall number of perfect assignments for all photos was not significantly different among female and male paediatricians (61.3% vs 47.7%; p=0.134).

Discussion

Stool composition is a primary outcome in many clinical trials on constipation and diarrhoea. Therefore, a reliable tool to describe stool composition is of major clinical relevance. Up to now, the BSS is used most of the time, although this scale is not adapted for non-toilet trained children. Several attempts have been made to overcome the shortcomings of the BSS. Bekkali et al developed the "Amsterdam Infant Stool Scale" (AISS), and described consistency (4 types), amount (4 groups) and colour (6 categories), represented by photos [15]. They reported 78% agreement on consistency when photos were identified by (every time) the same medical student and doctor, with an interobserver weighed kappa of 0.68 (κ 0.62-0.74). Ghanma et al compared the scores obtained by two nurses identifying in vivo infant stools based on the BSS and the AISS and found only a minor difference (69% vs 65% agreement) [16]. The AISS is quite complex and therefore appears to be too complicated for routine use, in particular by parents.

Recently, Wojtyniak et al examined the variability in stool assessment when infant stools were evaluated in vivo by their parents and a physician using the AISS, compared to interpretation by another doctor based on photographs of these stools [17]. Interobserver agreement between parents and physicians appeared to be remarkably higher in an in vivo assessment as compared to observations based on photos (90% vs 64% agreement for consistency, κ 0.87 vs 0.50), suggesting that interpretation of stool characteristics based on photos might be less accurate. Nevertheless, stools "in vivo" will always need to be compared to illustrations and descriptions for daily clinical observations and clinical trials. Koppen et al examined the degree of agreement between the BSS and parental report of stool consistency as rated by the parents of infants and toddlers and found only fair agreement (overall κ 0.34) between parental report and the BSS [18]. Therefore, we evaluated seven selected photos of stools in diapers, representing the seven descriptions as in the BSS.

General differences between the groups of respondents

Overall, HCP achieved better scores than parents in interpreting stool consistency based on our photos. Differences were apparent for the harder type of stools (BSS types 2: ±20% lower scores), suggesting that parents tend to categorize hard stools as normal. Parents have more difficulties in recognizing the harder stools. This supports earlier data reporting that parents and HCP seem to have different perception of normal stools for infants [7]. This finding is likely to be induced by the fact that a lot of non-breast-fed infants have harder stools, according to the opinion of HCP. Regarding loose and watery stools (BSS types 5 to 7), all groups achieve similar scores, suggesting loose and watery stools are easier to recognize.

The proportion of exact rating of all photos by paediatricians is lower (46 %) as in a previous study [10] with paediatric gastroenterologists using a modified BSS (5 categories; 83 %), and the results of Bekkali et al [13] (78%, 4 categories), but kappa values are almost identical in both studies (0.67 vs 0.68).

Although studies found a close correlation between stool form evaluations as performed by untrained subjects compared to by a trained observer [19], others warned for a parent-child discrepancy in reporting both physical and emotional plaints [20]. However, infants' parents are thought to be more capable of identifying stool consistency than parents of older children, because of the frequent diaper care. This was nevertheless not the case in a study [18], where only fair agreement was found (κ 0.34) between parental report of their infants' stool form and evaluation by those parents with the BSS (descriptions/images). To the best of our knowledge, no other study compared the capability of identifying stools by parents and by HCP on a large scale. Only Wojtyniak et al assessed the agreement between a parent and a physician. However, the difference in agreement (κ 0.87 vs 0.50) was mainly due to technical features of the photographic evaluation, and not to a different interpretation between parents and paediatricians in se [17].

Differences for individual photos

Over 40% of the parents misclassified photo 5 (BSS type 2) as normal, formed stools, while this was the case for only 15 % of the HCP. This finding may indicate that many infants are producing hard stools, which are then falsely recognized by the parents as normal. On the other hand, our photos were classified based on the BSS, which is said a priori to be not applicable to the evaluation of infants' stools. Thus, the illustration for BSS type 2 in the original BSS might not be representative for type 2 stools as seen in infants. Furthermore, almost 50% of all parents misinterpreted photo 4 (type 3, normal, formed stools) as hard stools, while this was significantly less in HCP (20%), again suggesting that many parents experience difficulties in differentiating hard from normal, formed stools. The study by Koppen et al 18 also showed the discrepancy between how parents describe and how they interpret their infants' stools: from the children classified (by their parents) as having hard stools, more than 50% of the parents chose BSS types 3-5 (normal stools) as best representing their child's stools, while 37% of the children with stools represented by BSS types 1-2 (hard stools) were reported as having normal stools.

Table 2: Assignments (in percentage) that deviated with max 1 from the reference BSS type

	Photo 1 BSS type 6	Photo 2 BSS type 1	Photo 3 BSS type 5	Photo 4 BSS type 3	Photo 5 BSS type 2	Photo 6 BSS type 4	Photo 7 BSS type 7
Parents	100.0	91.6	98.5	77.4	99.2	98.1	98.5
Paediatricians	99.3	95.2	93.8	90.3	97.9	98.6	97.2
Nurses	98.1	92.5	98.1	90.0	100.0	98.8	98.8
Overall	**99.3**	**92.8**	**97.2**	**84.3**	**99.1**	**98.4**	**98.2**

Our results are also in line with findings from Chumpitazi et al [21], who showed that even gastroenterologists have more difficulties evaluating stool consistency with pictures representing the boundaries of normal vs abnormal stools, more particularly for types 2 vs 3 and types 5 vs 6, and they stated that for this reason the use of the BSS to differentiate one stool type from another is compromised. In another study with a simplified modified BSS, types 3 and 5 were excluded from the scale: even in this scale, non-adjacent types were better discriminated than boundary types [10,11]. Contrarily, photo 6 (BSS type 4) was much easier recognized as normal stools in all groups (>88%).

In identifying loose stools, all groups achieved excellent and similar results (81-86%), but parents tended to mismatch photo 3 (BSS type 5) more frequently with normal stools (11%), whereas HCPs rather mismatched it with watery stools (13%). This may be explained by the finding from Colon and Jacob that half of paediatricians considered loose stools as abnormal after the age of 6 months, whereas parents believed it was only abnormal after the age of 18 months7. However, all study groups scored >80% for this photo, which is in contrast to observations by Parés et al showing that parents (40%) and nurses (20%) scored low in identifying this stool type [22]. In the modified BSS, this type was also excluded [10,11].

For watery stools, no significant differences were found between parents and HCP: excellent scores were achieved. Indeed, BSS types 7 and 4 were best correlated by all groups in earlier research [22].

Gender differences

Again, the largest differences were found in the harder stool types. When it comes to identifying hard stools, fathers scored around 20% below the scores of mothers and male doctors scored 10% below female results. Population studies show that women experience more hard stools and constipation, with a female/male ratio of 1.5 [23–28]. This might partly explain why women are more familiar with hard stools and thus recognize them more adequate.

Other possible influencing factors

Worldwide, defecation patterns do not significantly differ among children [5], though several studies mentioned the association between stool characteristics and differences in feeding habits [4,7,24,29,30], besides cultural differences in the perception of normal bowel habits [31]. Another factor we did not consider is the socioeconomic background and education level of parents. Parés et al [22] stated that in a Spanish BSS validation study, the worst results were obtained in older patients with lower education levels. In our study, no information on age nor on level of education was gathered. Moreover, as stated by Wojtyniak et al [17], technical features play a part in the ultimate photo quality. In their study, a huge difference in interrater agreement was found between evaluations based on in vivo stools vs photos (κ 0.87 vs 0.5). To reduce influences of these factors, we used 3 identical cameras and photos were printed in high quality.

Strengths and limitations

The main strength of this study is the multicentre evaluation: a large number of observers was included from paediatric departments throughout the country, suggesting a representative sample of the population, allowing results to be accurately generalized. Secondly, the use of photos instead of drawings not only permits a closer resemblance to real infant stools, but also has the advantage of a uniform assessment between a large number of raters. Unlike in other studies, quality issues of the photos probably did not interfere with our results. Furthermore, all Belgian participants were tested by one researcher, with the advantage of a uniform execution in all participants.

This study has also some limitations. The major limitation is that only 7 photos were evaluated, each corresponding to one BSS type. This allowed participants to identify more obvious photos first, and to assign the remaining, more confusing photos to the other categories. In addition, no intra-observer reliability was determined in this study. Another limitation is that no other information about the respondents than their gender was noted. It might have been interesting to have more details about ethnic origin, socioeconomic status, educational level, age of child(ren) …, as well as their own stool characteristics, as all of these factors can influence their interpretation of bowel habits. However, the aim of this study was merely to validate a new scale, and not to explore possible influencing factors to the full extent.

Conclusion

In this study, an adapted stool scale for infants and young non-toilet-trained children, the Brussels Infant and Toddler Stool Scale (BITSS), was developed. Overall, HCP assessed stool consistency better than parents, and they also achieved a higher degree of agreement. Parents experience more difficulties in recognizing hard stools. Watery stools were best recognized by all groups.

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Congenital pulmonary malformations: Case series and review of the literature.

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Key words

Congenital pulmonary malformations, neonatal presentation

Abstract

Congenital pulmonary malformations are a spectrum of different pathologies which include congenital pulmonary airway malformation, pulmonary sequestration, bronchogenic cysts and congenital pulmonary emphysema. With improvements in ultrasound technology more malformations are detected prenatally. However, correct diagnosis and management of these conditions remains a challenge. The best treatment and timing of surgery, if indicated, is unclear as some of these conditions may regress or remain asymptomatic. We present a review of the current literature on the diagnosis and management, illustrated by clinical and radiographic data of 4 neonates with a suspected diagnosis of congenital pulmonary malformation.

Review of the literature

Congenital pulmonary malformations were thought to be relatively uncommon with an estimated incidence of 1 in 10.000 to 1 in 35.000 but recent data suggest an incidence of 1 in 2400 live births [1,2]. In the last years, the terms congenital pulmonary airway malformations, congenital masses of the lung and congenital thoracic malformations are used to describe the spectrum of different pathologies which include congenital pulmonary airway malformation (CPAM), pulmonary sequestration, bronchogenic cysts and congenital pulmonary emphysema (CPE)[3-5]. The underlying pathophysiologic mechanism is still unclear, however, bronchial atresia is found in resected specimens of different types of malformations [6]. Obstruction of the developing foetal airway may be a common pathway that results in different types of malformations [4-6]. CPAM are intrapulmonary lesions that contain various types of epithelial linings and maintain communication with the normal trachea and bronchial tree unlike bronchogenic cysts. They retain a normal blood supply [1]. There are 5 types of CPAM according to the classification of Stocker dependent upon the size and epithelial lining of the cyst (Table 1). Type 0 has a tracheal or bronchial origin and is acinar dysgenesis or dysplasia, type 1 has a bronchial or bronchiolar origin, type 2 has a bronchiolar origin, type 3 has a bronchiolar–alveolar duct origin (adenomatoid type), and type 4 has a distal acinar origin [7]. Pulmonary sequestration is generally thought to result from an abnormal accessory tracheobronchial bud arising from the foregut. The lesion is not connected to the tracheobronchial tree and has a systemic arterial supply, usually from the thoracic or abdominal aorta. There are two types of sequestrations, intralobar or extralobar, based on whether the visceral pleura is shared with the adjacent normal lobe or not [1,7,8]. Bronchogenic cysts result from abnormal budding of the foregut. The cysts are usually single and unilocular, filled with fluid or mucous. Pathologic examination shows lining by pseudostratified ciliated columnar respiratory epithelium and presence of cartilage, smooth muscle and glands. There is no communication with the bronchial tree [1,7,8]. CPE presents as a distended hyperlucent lobe which is thought to be caused by a partial bronchial obstruction. The obstruction may be intrinsic (focal bronchomalacia, bronchial atresia) or extrinsic (due to compression) [8,9].

Other congenital abnormalities are frequently associated depending on the type of congenital lung malformation. Cardiac malformations are the most frequent [10,11]. Renal and limb abnormalities have also been described, especially in CPE [12].

More and more malformations are diagnosed prenatally (85%) due to better prenatal follow up and improvements in ultrasound technology. This has the advantage of making a diagnosis prior to development of symptoms, although it is still unclear how to handle it. CPE is usually not diagnosed prenatally but clinically suspected postnatally [3]. If a congenital pulmonary malformation is suspected antenatally, close follow up with serial ultrasounds is required. Delivery is preferably planned in a tertiary and specialised centre depending on the evolution and size of the lesion [4]. It is not possible to make a definitive diagnosis based on prenatal ultrasound alone. Magnetic resonance imaging during pregnancy does not have any additional benefit [5]. Many lesions appear to decrease in size over time on serial prenatal ultrasound scans. But even if the

Table 1: CPAM types

TYPE 0	1-3 % of cases	Small cysts < 0,5 cm	Involves entire lung, 100% mortality at birth
TYPE 1	60-70 % of cases	Distinct thin walled cysts 2 to 10 cm Pseudostratified columnar epithelium	Only 1 lobe involved, malignant potential
TYPE 2	15-20 % of cases	Multiple Cysts 0,5 to 2 cm Cuboidal or columnar epithelium	Associated with other abnormalities
TYPE 3 = ADENOMATOID TYPE	5-10 % of cases	Microcysts < 5 mm Cuboidal epithelium	Typically involves an entire lobe or several lobes
TYPE 4	10-15 % of cases	Unlined cysts maximum 7 cm Flattened epithelial cells	Affects a single lobe, strongly associated with malignancy

lesion seems to have disappeared, postnatal evaluation, preferably by CT scan, is recommended as complete resolution is rare [4]. More than 90% of foetuses with a congenital pulmonary malformation will do well during pregnancy and also postnatally. Hydrops due to impairment of cardiac return by caval vein and cardiac compression has a bad prognosis. Prenatal treatment by fetal surgery is possible but difficult, the indication is based on foetal echocardiogram. [4]

The current practice for diagnosis is to start with an X-ray of the lungs after birth followed by a CT angiography in the first 6 months. The timing of the CT scan depends on the symptomatology. Imaging is not fully reliable to make the definitive diagnosis. Pathological analysis of the resected specimen is needed [3,5,6]. Additionally echocardiography needs to be done because of possible associated (cardiovascular) anomaly [4,5,10]. Depending on the suspected diagnosis an ultrasound of the abdomen should be added.

The time of clinical presentation depends on the type of malformation. Overall, 70% of patients who are diagnosed antenatally will be symptomatic at birth [5]. In CPE, clinical signs are evident in the early neonatal period. Pulmonary sequestrations usually remain asymptomatic until infection develops [4]. Symptoms can develop later due to cyst infection, haemorrhage, pneumothorax, surinfection or malignant transformation. Deterioration can be very fast in children if one of these complications occurs.

Most types of congenital pulmonary malformations imply the risk of complications, including secondary infection and malignant transformation. The exact prevalence of these complications is still unknown [5]. CPE compromises the lowest risk for any complication [4,11]. Secondary infection is a very frequent complication in bronchogenic cysts and pulmonary sequestration and less frequent in CPAM [13]. Development of bronchoalveolar carcinoma has been reported in cases of CPAM type I [14]. Additionally CPAM type IV is associated with malignancy, especially with pleuropulmonary blastoma. Malignant transformation of epithelial cells of bronchogenic cysts has also been described. Very rarely pulmonary sequestrations have been linked with malignancy. The overall risk of malignancy is not known and even the protective effect of prophylactic resection in asymptomatic patients is not clear [9].

The management of congenital pulmonary malformations consists of two main options: surgery or watchful waiting. For pulmonary sequestrations there is a third option for small lesions, namely endovascular embolization, but surgical resection is the treatment of choice [15,16]. Surgery, either by lobectomy or segmentectomy, remains the standard treatment of all symptomatic lesions, but the postnatal management of asymptomatic patients is still controversial [5]. The main arguments for watchful waiting in asymptomatic patients are the largely unknown natural history of these lesions, the possibility of postnatal regression and above all the burden and the risks of thoracotomy and lung resection [9]. One of the difficulties with an expectant management is that a definitive diagnosis without histology is not possible given the known high frequency of hybrid malformations [6,9]. An argument pro relative early surgery is that if urgent surgery is needed after a complication has occurred, the morbidity and mortality of the procedure will be higher. A systematic review and meta-analysis of Stanton et al showed a risk ratio of 2,8 when comparing complications after elective surgery with emergency surgery [17]. Given the risk of surinfection and small but probable risk of malignancy in pulmonary sequestration, bronchogenic cysts and CPAM, most clinicians advice elective surgery in these children [3,17,18]. Though individual evaluation should be performed as the risk of asymptomatic cases developing symptoms may be small depending on the type and size of the lesions. In these patients a conservative approach may be appropriate [17,19,20]. For asymptomatic pulmonary emphysema, watchful expectation and follow-up is mostly advised [21,22]. But we have to keep in mind that there is a risk of combination of CPAM and polyalveolar changes, which can look like pulmonary emphysema on imaging [6].

Additionally, there is discussion about the best timing of surgery. There is consensus to wait at least until the child is 3 months old when the anaesthetic risks and surgical difficulties have diminished. As many complications occur already in the first 2 years of life, it is advised not to delay the surgery that long. Waiting too long implies the possibility of more extensive parenchymal abnormalities of adjacent tissue due to long term compression. Another reason why not to wait too long is the probable compensatory alveolar growth after resection which has the best chance in the first two years of life. Elective lobectomy appears to be well tolerated without any subsequent long term limitation in physical activity [9]. Video assisted thoracoscopic surgery has been proposed as preferred treatment for elective resection in the future as surgical risks and complications with thoracoscopic surgery should be lower as shown in a recent systematic review from 2017 wherein outcomes of thoracoscopic versus open excision of asymptomatic congenital pulmonary malformations were compared. Meta-analysis showed that regarding thoracoscopic procedures, the total number of complications was significantly less (OR 0.63, 95% CI 0.43, 0.92; p<0.02, 912 patients, 404 thoracoscopic) [23]. However, there is a lack of long term prospective studies [5].

A recent prospective study from Italy examined the outcome of infants operated on for congenital pulmonary malformations in comparison with a control group of term infants operated on for inguinal hernia. Patients operated on for congenital pulmonary malformations had significantly higher prevalence of wheezing (OR 4.9, p <0.006), need for bronchodilators (OR 3.4, p<0.03), lower respiratory tract infection (OR 16.8, p<0.005) and chest X-rays abnormalities (OR 11.4, p<0.0001). Overall 50% of patients with congenital pulmonary malformation present with one or more of these long-term sequelae, regardless of type of malformation. Therefore, long-term follow-up of patients operated on for congenital pulmonary malformation is recommended [24].

Case presentations and discussion

This case series of 4 neonates with suspected congenital pulmonary malformation illustrates the different neonatal presentations, clinical course and definitive diagnosis which are unpredictable and make it therefore challenging to choose the best management strategy.

In the first patient, a girl, the diagnosis of macrocystic CPAM was postulated on prenatal ultrasound. The lesion was first seen at a gestational age of 24 weeks and remained stable throughout pregnancy. She was born at a gestational age of 38 weeks and 6 days by caesarean section. There was a short need for respiratory support by continuous positive airway pressure (CPAP). A computed tomography (CT) of the thorax was suggestive of a CPAM type I with extended cystic degeneration of the right upper lobe. Echocardiography was normal. Because of tachypnoea, respiratory support with high flow nasal cannula was started. Due to a rapid deterioration with expansion of the lesion and atelectasis of the left lung, the child was intubated and mechanically ventilated (Figure 1A, 1B). A lobectomy of the right upper lobe was performed at the age of 1 month. She was discharged 2 weeks after surgery. Pathological examination was compatible with CPAM type I, without signs of malignancy. This case shows how an infant can deteriorate very rapidly making surgery much more complex. As this infant was symptomatic from birth, surgery was immediately proposed, but the problem to determinate the best timing remained.

Figure 1A: First X-ray taken on day 1

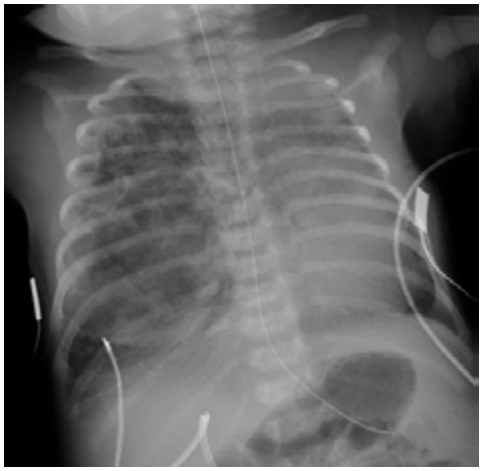
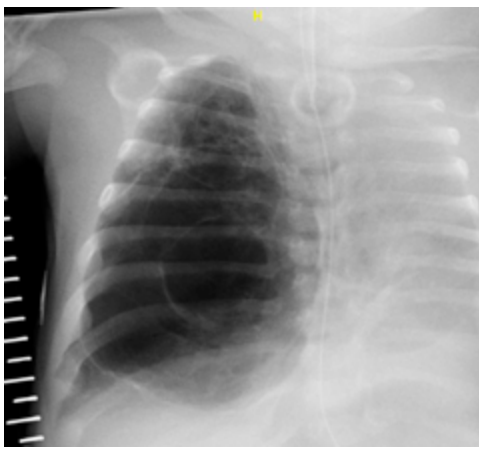


Figure 1B: X-ray taken prior to surgery



The second patient is a boy born at a gestational age of 30 weeks and 3 days by caesarean section. Prenatal ultrasounds were normal. After birth the baby was in need for respiratory support with CPAP. Surfactant was given by the less invasive surfactant administration (LISA) procedure, but respiratory distress persisted and invasive ventilation was needed. X-ray of the lungs showed an inhomogeneous image of the lungs with respiratory distress syndrome (RDS) grade 3 and the impression of hyperinflation of the left upper lobe (Figure 2A). A second dose of surfactant was given. He was extubated after 1 day with immediate switch to CPAP. Respiratory support could be stopped after 1 week, but tachypnoea and subcostal retractions persisted. A new X-ray of the lungs showed a hyperlucent and hyperinflated left upper lobe with a shift of the mediastinum to the right and partial atelectasis of the right lung (Figure 2B). Additional imaging with CT showed an emphysematous aspect of the left upper lobe with a focal interruption of the left upper lobe bronchus. Bronchoscopy showed an inflammatory aspect of the left bronchus and a bronchomalacia of the left upper lobe. Based on these examinations the diagnosis of CPE was made. Additional workup with echocardiography and CT angiography of the lungs showed a small atrium septum defect (ASD) and normal pulmonary vasculature. Because there was no need for respiratory support a conservative management with watchful expectation was implemented. At the postnatal age of 5,5 months a lobectomy of the left upper lobe was performed because of infectious respiratory exacerbations urging hospital admissions. Pathologic examination confirmed the diagnosis of congenital pulmonary emphysema. The postoperative course was uneventful. This case shows the need for additional workup if CPE is suspected to find the underlying cause and exclude hybrid malformations and associated anomalies. An expectant management was followed because the boy had no symptoms, but surgery was needed after a couple of months because of repeated infections.

Figure 2A: First X-ray of the lungs taken on day 1: RDS grade 3, impression of better aeration of the left upper lobe

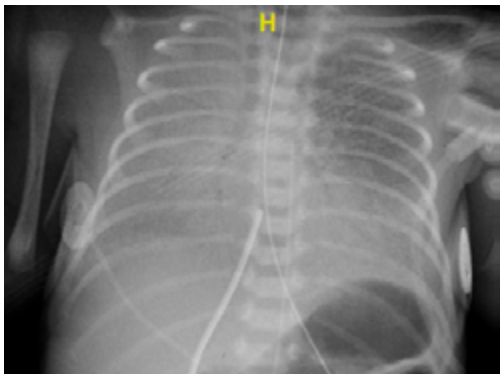
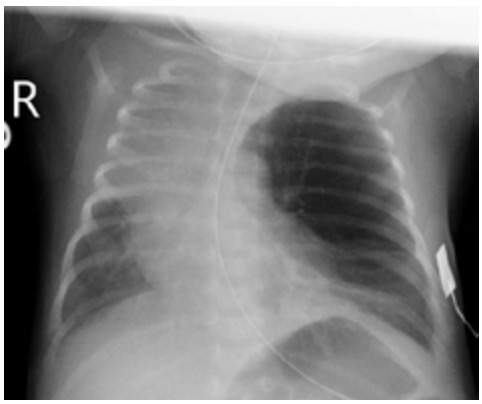


Figure 2B: X-ray of the lungs showing a hyper lucent and hyper inflated left upper lobe with a shift of the mediastinum to the right side and partial atelectasis of the right lung



The third patient is a girl born at a gestational age of 32 weeks and 1 day by caesarean section due to maternal pre-eclampsia. CPAP was started because of respiratory distress, but the respiratory distress worsened and X-ray of the lungs showed a pneumothorax at the right side. This was treated by intubation, surfactant administration and a chest tube that could be removed after 4 days. After 6 days there was a recurrence of the pneumothorax on the right with placement of a new chest tube. After two days the girl developed tachycardia and high oxygen demand. X-ray of the lungs showed expansion of the pneumothorax (Figure 3A). A second chest tube was placed with good result. The drains could be removed 1 and 2 days later but there was a fast evolution to tension pneumothorax and a new chest tube was reinserted. Additional investigations were performed because of this atypical course. Genetic screening for cystic fibrosis was negative. CT imaging of the thorax showed a cystic lesion with destruction of the right middle lobe (Figure 4A). The differential diagnosis of CPAM was considered, but an infectious cause or a sequel of manipulation or barotrauma could not be excluded. Echocardiography and an ultrasound of the abdomen were normal. The patient could be extubated 5 days after the last chest tube was placed. The chest tube was successfully removed 2 weeks after placement. The girl remained clinically stable without need for respiratory support. There was no tachypnoea although serial X-rays of the lungs showed an increase of the cystic lesions with probable need for lobectomy in the near future (Figure 3B). To plan this operation a new CT of the lungs was made 1 month later. Surprisingly, there was an almost complete resolution of the lesion (Figure 4B). We know from the literature that postnatal resolution of a CPAM is possible but rare. Because of the fast resolution the most probable diagnosis is interstitial pulmonary emphysema secondary to barotrauma. This case shows the importance of making the good diagnosis and the possibility to postpone surgery if the clinical evolution is positive.

Figure 3A: X-ray of the lungs showing an extended pneumothorax on the right

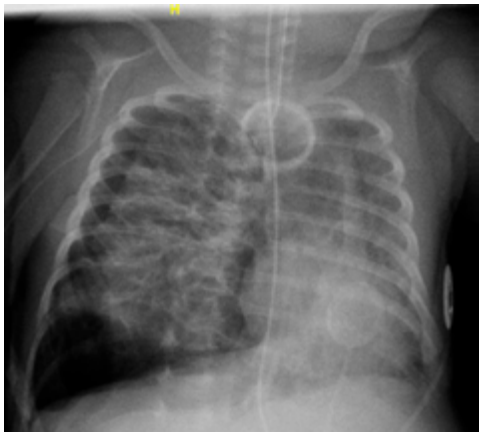
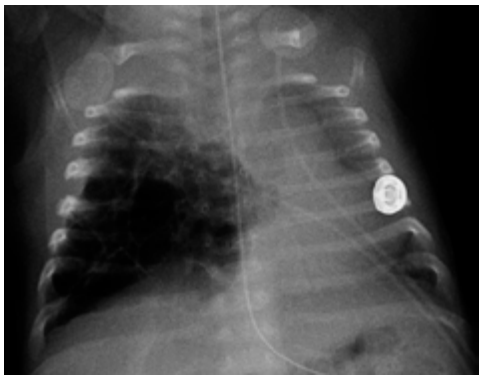


Figure 3B: X-ray of the lungs showing an increase of the cystic lesions



The fourth patient is a boy born at a gestational age of 33 weeks due to premature contractions. At 31 weeks of gestation a cystic malformation in the right hemithorax was diagnosed and a CPAM was suspected. The first postnatal X-ray of the lungs showed a diffuse white right lung (Figure 5A). CT imaging of the lungs showed normal pulmonary vascularity, and confirmed the proposed diagnosis of CPAM type 3. Surgery appeared to be necessary because of the extensiveness of the lesion but was postponed as the boy had no clinical symptoms. After 2 months progressive tachypnoea was noted with severe deterioration probably due to a respiratory infection wherefore acute mechanical ventilation and semi-urgent lobectomy of the right upper lobe was needed. X-ray of the lungs before surgery showed a cystic lesion with mediastinal shift (Figure 5B). CT imaging confirmed a cystic structure with septa. The pathological examination of the resected specimen revealed a bronchogenic cyst, no CPAM 3. This case is an example that the definitive diagnosis of a congenital pulmonary malformation can only be based on the histopathological examination. Bronchogenic cysts have a high infection rate.

Conclusion

Congenital pulmonary malformations are diagnosed more frequently antenatally. The initial follow up and diagnostic evaluation is clear cut, but the best management and treatment remains controversial. For symptomatic patients surgery with lobectomy or segmentectomy is the main procedure. For asymptomatic patients the proposed treatment largely depends on the size and type of malformation. Whereas for congenital pulmonary emphysema expectant management is mostly accepted, this is not the case for pulmonary sequestrations, bronchogenic cysts and congenital pulmonary airway malformations where most clinicians promote early elective surgery, if possible by thoracoscopy. From all our cases we can conclude that it is important to continuously re-evaluate clinical symptoms and adapt the management plan accordingly. If a child remains without or with only mild symptoms, watchful waiting and follow up for at least a couple of months seems the best option, depending on the suspected diagnosis. If a child tends to deteriorate, fast intervention is needed to prevent short and long term complications. The need for surgical resection in asymptomatic patients remains controversial and therefor long-term outcome studies are necessary.

Figure 4A:
CT scan of the lungs showing a cystic lesion with destruction of the right middle lobe

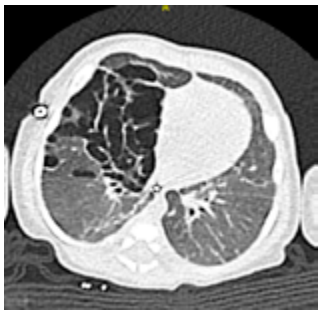


Figure 4B:
CT scan of the lungs showing an almost complete resolution of the previous lesions

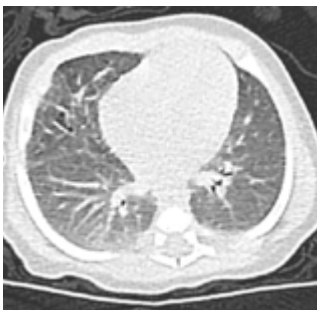


Figure 5A: First postnatal X-ray of the lungs showing a diffuse white right lung

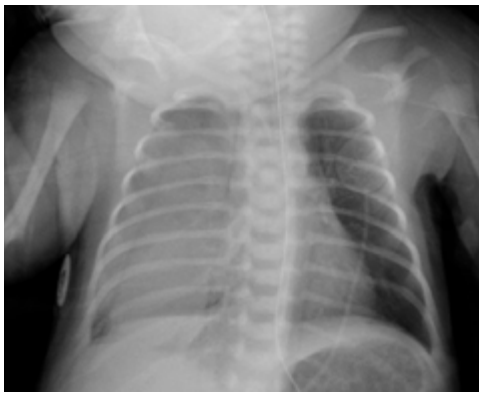
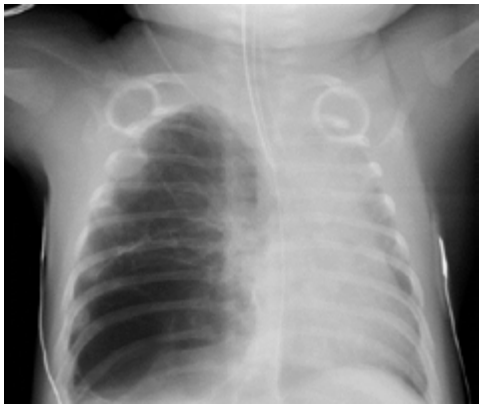


Figure 5B: X-ray of the lungs before surgery showing a cystic lesion with mediastinal shift



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Le traitement doit être instauré chez les enfants âgés de 5 semaines à 5 mois. **POSOLOGIE ET MODE D'ADMINISTRATION:** Le traitement doit être instauré par un médecin expérimenté dans le diagnostic, le traitement et la prise en charge des hémangiomes infantiles, dans un environnement clinique contrôlé dans lequel des installations adéquates pour la prise en charge des réactions indésirables, y compris celles nécessitant des mesures d'urgence, sont disponibles. Posologie: La posologie est exprimée en propranolol base. La dose initiale recommandée est de 1 mg/kg/jour, répartie en deux prises séparées de 0,5 mg/kg. Il est recommandé d'augmenter la dose jusqu'à la dose thérapeutique, sous surveillance médicale, de la manière suivante : 1 mg/kg/jour pendant 1 semaine, puis 2 mg/kg/jour pendant 1 semaine, puis 3 mg/kg/jour en dose d'entretien. La dose thérapeutique est de 3 mg/kg/jour, administrée en 2 prises séparées de 1,5 mg/kg, le matin et en fin d'après-midi, avec un intervalle d'au moins 9 heures entre deux prises. Le médicament doit être pris pendant ou juste après un repas. Si l'enfant ne mange pas ou vomit, il est recommandé de ne pas administrer la dose. Si l'enfant recrache une dose ou ne prend pas tout le médicament, il convient de ne pas lui administrer une autre dose et d'attendre la dose suivante prévue. Au cours de la phase de titration, chaque augmentation posologique doit être réalisée sous surveillance médicale dans les mêmes conditions que pour l'administration de la dose initiale. Après la phase de titration, la dose sera réajustée par le médecin en fonction de l'évolution du poids de l'enfant. Une surveillance clinique de l'état de l'enfant et un réajustement de la posologie doivent être effectués au moins une fois par mois. Durée du traitement: HEMANGIOL doit être administré pendant une période de 6 mois. L'arrêt du traitement ne nécessite pas de diminution progressive de la dose. Chez la minorité de patients qui présentent une rechute des symptômes après l'arrêt du traitement, celui-ci peut être réintroduit dans les mêmes conditions avec une réponse satisfaisante. Populations particulières: En l'absence de données d'efficacité clinique et de sécurité, HEMANGIOL ne doit pas être utilisé chez l'enfant âgé de moins de 5 semaines. Il n'y a pas de données d'efficacité et de sécurité dans les essais cliniques menés avec HEMANGIOL permettant de recommander l'instauration d'un traitement par HEMANGIOL chez l'enfant âgé de plus de 5 mois. Enfants insuffisants hépatiques ou rénaux: En l'absence de données, l'administration du produit n'est pas recommandée chez l'enfant insuffisant hépatique ou rénal. Mode d'administration. Voie orale. HEMANGIOL doit être administré pendant ou juste après un repas afin d'éviter le risque d'hypoglycémie. Il doit être administré directement dans la bouche de l'enfant à l'aide de la seringue pour administration orale graduée en mg de propranolol base fournie avec le flacon de solution buvable (voir les instructions d'utilisation à la rubrique 3 de la notice). Le flacon ne doit pas être agité avant utilisation. Si nécessaire, le médicament peut être dilué dans une petite quantité de lait pour bébé ou de jus de pomme et/ou d'orange adapté à l'âge de l'enfant. Ne pas verser le produit dans un biberon plein. Le mélange peut être effectué avec une cuillérée à café (environ 5 ml) de lait pour les enfants pesant jusqu'à 5 kg ou avec une cuillerée à soupe (environ 15 ml) de lait ou de jus de fruit pour les enfants pesant plus de 5 kg et administré dans un biberon. Le mélange doit être utilisé dans un délai de 2 heures. HEMANGIOL et le repas doivent être donnés par la même personne afin d'éviter le risque d'hypoglycémie. Si plusieurs personnes sont impliquées, une bonne communication est essentielle pour garantir la sécurité de l'enfant.**CONTRE-INDICATIONS:** Prématuré n'ayant pas atteint l'âge corrigé de 5 semaines (l'âge corrigé étant calculé en soustrayant le nombre de semaines de prématurité de l'âge réel) • Nouveau-né allaité par sa mère traitée par des médicaments contre-indiqués avec le propranolol • Hypersensibilité à la substance active ou à l'un des excipients • Asthme ou antécédent de bronchospasme • Blocs auriculo-ventriculaires des second et troisième degrés • Maladie du sinus (y compris bloc sino-auriculaire) • Bradycardie au-dessous des limites suivantes : Age: 0-3 mois/ 3-6 mois/ 6-12 mois - Fréquence cardiaque (battements/min): 100/90/80. Hypotension artérielle au-dessous des limites suivantes: Age: 0-3 mois/ 3-6 mois/ 6-12 mois - Pression artérielle (mm Hg): 65/45 / 70/50 / 80/55. Choc cardiogénique • Insuffisance cardiaque non contrôlée par un traitement • Angor de Prinzmetal • Troubles artériels périphériques sévères (syndrome de Raynaud) • Enfants prédisposés à l'hypoglycémie • Phéochromocytome. **EFFETS INDÉSIRABLES:** Résumé du profil de tolérance: Dans les essais cliniques conduits dans les hémangiomes infantiles proliférátifs, les effets indésirables les plus fréquemment rapportés chez les enfants traités par HEMANGIOL ont été des troubles du sommeil, des infections respiratoires majorées telles que bronchite et bronchiolite associées à une toux et une fièvre, des diarrhées et des vomissements. Globalement, les effets indésirables rapportés au cours du programme d'autorisation temporaire d'utilisation et dans la littérature ont été des hypoglycémies (et les événements associés tels que des crises convulsives hypoglycémiques) et des infections respiratoires majorées associées à une détresse respiratoire. Liste tabulée des effets indésirables: Le tableau suivant présente les effets indésirables rapportés, quelles que soient la dose et la durée du traitement, dans trois études cliniques conduites chez 435 patients traités par HEMANGIOL à la dose de 1 mg/kg/jour ou de 3 mg/kg/jour sur une durée maximale de traitement de 6 mois. La fréquence des effets indésirables est définie en utilisant la convention suivante : très fréquent (≥ 1/10) ; fréquent (≥ 1/100 à < 1/10) ; peu fréquent (≥ 1/1000 à < 1/100) ; rare (≥ 1/10 000 à < 1/1000) ; très rare (< 1/10 000) ; fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Compte tenu de la taille de la base de données des essais cliniques, les catégories Rare et Très rare ne sont pas représentées. Au sein de chaque classe de systèmes d'organes, les effets indésirables sont présentés par ordre décroissant de gravité. Infections et infestations: Très fréquent (Bronchite) - Fréquent (Bronchiolite). Troubles du métabolisme et de la nutrition: Fréquent (Diminution de l'appétit). Affections psychiatriques: Très fréquent (Troubles du sommeil) - Fréquent (Agitation, Cauchemars, Irritabilité). Affections du système nerveux: Fréquent (Somnolence) - Fréquence indéterminée (Crise convulsive hypoglycémique). Affections cardiaques: Peu fréquent (Bloc AV) - Fréquence indéterminée (Bradycardie). Affections vasculaires; Fréquent (Extrémités froides) - Fréquence indéterminée (Hypotension artérielle, Vasoconstriction, Syndrome de Raynaud). Affections respiratoires, thoraciques et médiastinales: Fréquent (Bronchospasme). Affections gastro-intestinales: Très fréquent (Diarrhées, Vomissements) - Fréquent (Constipation, Douleur abdominale). Affections de la peau et du tissu sous-cutané: Fréquent (Erythème) - Peu fréquent (Urticaire, Alopécie). Investigations: Fréquent (Diminution de la pression artérielle) - Peu fréquent (Diminution de la glycémie, Diminution de la fréquence cardiaque, Neutropénie) - Fréquence indéterminée (Agranulocytose,Hyperkaliémie). Description d'effets indésirables sélectionnés. Concernant les infections des voies respiratoires inférieures telles que la bronchite ou la bronchiolite, une aggravation des symptômes (y compris de bronchospasme) a été observée chez des patients traités par HEMANGIOL en raison de l'effet bronchoconstricteur du propranolol. Ces effets ont dans de rares cas conduit à l'arrêt définitif du traitement. Les troubles du sommeil recouvrent l'insomnie, un sommeil de mauvaise qualité et l'hypersomnie. Les autres affections du système nerveux central ont principalement été observées en début de traitement. Des diarrhées ont été fréquemment rapportées sans être systématiquement associées à une maladie gastro-intestinale infectieuse. La survenue de diarrhées semble dose-dépendante entre 1 et 3 mg/kg/jour. Aucun cas n'a été d'intensité sévère et n'a conduit à l'arrêt du traitement. Les événements cardiovasculaires rapportés au cours des études cliniques ont été asymptomatiques. Lors des 4 heures de surveillance cardiovasculaire réalisée pendant les jours de titration, une diminution de la fréquence cardiaque (d'environ 7 bpm) et de la pression artérielle systolique (< 3 mm Hg) a été observée après l'administration du médicament. Un cas de bloc cardiaque auriculoventriculaire du second degré chez un patient avec des troubles de la conduction sous-jacents a entraîné l'arrêt définitif du traitement. Des cas isolés de bradycardie symptomatique et d'hypotension artérielle ont été rapportés dans la littérature. Les baisses de la glycémie observées au cours des études cliniques ont été asymptomatiques. Toutefois, plusieurs cas d'hypoglycémie associée à une crise convulsive hypoglycémique ont été rapportés au cours du programme d'autorisation temporaire d'utilisation et dans la littérature, notamment en cas de jeûne lors d'une maladie concomitante. Le traitement concomitant par corticoïdes systémiques peut majorer le risque d'hypoglycémie . Une hyperkaliémie a été rapportée dans la littérature chez quelques patients avec un hémangiome ulcéré étendu. 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 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 **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ:** PIERRE FABRE DERMATOLOGIE - 45 place Abel Gance - F- 92100 Boulogne. **NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ.** EU/1/14/919/001. **DATE DE PREMIÈRE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION.** Date de première autorisation : 23 avril 2014. **DATE DE MISE À JOUR DU TEXTE.** 09/2014. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne du médicament http://www.ema.europa.eu. **CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE.** Sur prescription médicale.

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Pierre Fabre
DERMATOLOGIE

* Nécessitant un traitement systémique

Lactose breath tests in pediatrics: "A tailwind towards diagnosis or a whiff of confusion?"

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Key words

Pitfalls of lactose breath tests in diagnosing lactose malabsorption. Breath testing. H_2 breath test. Hydrogen breath test. $^{13}CO_2$ breath test. ^{13}C-breath test. Children. Pediatrics. Lactose intolerance. Lactose malabsorption.

Abstract

Lactose malabsorption is a common clinical condition that is caused by a reduced activity or expression of lactase in the intestinal wall. Currently there is no worldwide gold standard diagnostic test for this condition. In clinical practice breath testing is widely accepted for diagnosing lactose malabsorption thanks to its non-invasiveness. However, a reliable breath test starts with a good preparation of the patient. We illustrate the difficulties of interpreting the lactose breath test in daily practice with a practical example, namely the case of a five-year-old Caucasian girl with conflicting results of two lactose breath tests.

Introduction

Lactose, a disaccharide present in dairy products, cannot be absorbed by the intestine unless it is enzymatically cleaved into its monosaccharides, glucose and galactose. Lactase is the enzyme needed for hydrolysis of lactose and is located in the small intestinal brush border membrane. The activity of lactase is highest at birth and decreases after 2-3 years of age reaching its final levels at the age of 5-10 years[1]. A reduced expression or impaired activity of the enzyme lactase causes 'lactose malabsorption' (LM). The literature shows a wide variation in the prevalence of LM both as a primary condition and secondary due to gastrointestinal pathology[2]. LM can induce abdominal symptoms like pain, flatulence, bloating, nausea, diarrhea or constipation. This clinical syndrome is called 'lactose intolerance' (LI). It is important to know that not all patients with LM have LI[3]. Breath testing has become popular in clinical practice for diagnosing LM. As we illustrate in this case report the interpretation of the lactose breath test (BT) can be challenging.

Case report

A five-year-old Caucasian girl was referred to us with the complaint of 'nutritional hypersensitivity'. According to the mother she was fatigued and she had nausea, bloating and abdominal cramps after eating milk-derived food products for some time now. She had no infectious or inflammatory symptoms. Her stool frequency and consistency were variable. Her past medical history was uneventful. There was no family history of gastrointestinal disease. She did not take any medications or dietary supplements. At presentation her biometry was normal (weight and height at the 50th percentile). No abnormalities could be detected during the clinical systemic examination. Her abdomen was non-tender, liver and spleen were not palpated and there was normal peristalsis. Rectal examination was normal. A blood examination, consisting of a complete blood count, electrolytes, erythrocyte sedimentation, C-reactive protein, IgE, CAP tests (cow milk protein, goat milk, egg, pea, cheese and kiwi), tissue transglutaminase and vitamin levels, was normal. In order to exclude LI a lactose BT was performed. As her parents are divorced both have independently completed a lactose BT with their daughter within the time span of 1.5 months. One was requested by the family physician and one by our clinic; yet both test have been processed at the Laboratory Medicine Department of the University Hospitals in Leuven. Our facility performs a combination of an H_2-BT and a ^{13}C-BT, the results of both tests are shown in figure 1. The first test showed a LM (Figure 1A) while the second test showed a normal lactose digestion (Figure 1B). Both tests were performed and assessed in the same way and by the same person.

Discussion

Lactose malabsorption may be primary or secondary. Congenital lactase deficiency, characterized by complete absence of lactase activity in the small intestines, is a rare autosomal recessive disorder. The most frequent cause of LM is primary LM, also called lactase non-persistence. This condition is characterized by a gradual decrease in lactase activity and usually develops during childhood. Yet LM can also be secondary to underlying intestinal diseases damaging the brush border of the small intestine, such as gastroenteritis, small intestinal bacterial overgrowth, celiac disease, inflammatory bowel disease or food allergy. It can occur at any age and is mostly transient.

The diagnosis of LM cannot be predicted on the basis of a specific complaint. The sensitivity of self-reported symptoms, such as bloating, diarrhea, flatulence, and abdominal pain, can range from 0 to 90% and the specificity from 18 to 96%[4]. There is no generally accepted gold standard diagnostic test to quantify lactase expression or activity and provide an unequivocal diagnosis of LM.

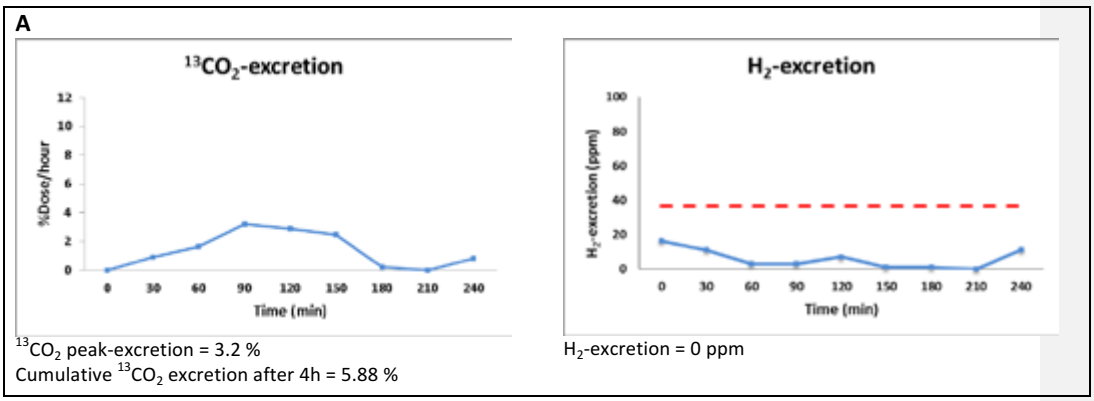
In case of a patient with clinical symptoms presumably occurring after the ingestion of lactose-containing foods, a tentative diagnosis of LI can be made. Several objective tests can be used to validate the diagnosis of LM. In table 1 an overview of the possible tests can be found with a comparison between the tests[1,5-6]. All the tests of lactose malabsorption can be compared with the most invasive test, the small bowel mucosal biopsies. In this test the lactase concentration and activity can be measured directly. However, even this test has its limitations as lactase is not expressed homogenously across the epithelium and as the acquisition of biopsies is invasive[7]. Other invasive tests are the genetic tests and the lactose tolerance test (LTT) because a phlebotomy is needed. Genetic testing can identify alleles associated with lactase persistence in Caucasian patients, indicated by -13910 T/C polymorphism. It cannot be used in subpopulations where lactase persistence is linked to different polymorphisms[1]. Moreover it cannot identify secondary causes of LM. Genetic testing has a sensitivity of 93% and a specificity 100% compared with jejunal biopsy in a selected population[8]. LTT is based on the evolution of serum glucose levels after ingestion of a standard dose of lactose. The test is indicative of LM if the blood glucose rises by less than 20 mg/dL or 1.1 mmol/L (normal > 30 mg/dL or >1.6 mmol/L) after ingestion of a specific amount of lactose. A noninvasive method to test LM is the measurement of pH and reducing substances in stools. The patient is considered to have LM if the stool becomes acidic after consumption of lactose. This test can be used in infants or children who cannot undergo other types of testing, but the diagnostic value is limited. Today the most widely used tests for LM are the standardized BTs. In these tests lactase activity is not measured directly, but indirectly by the determination of lactose digestion and absorption. The use of BT can limit the

number of jejunal biopsies that have to be performed in the diagnostic workup of LM. They are safe, rapid, noninvasive and easy to perform. More than two decades ago researchers already showed a good correlation between the result of the lactose BT and the lactase activity in small bowel biopsies[9].

For LM there are two BTs available: the H_2- and the combined ^{13}C-H_2 BT. The H_2-BT assesses malabsorption of lactose based on the principle that H_2 (hydrogen) is not produced by human enzymes but only by anaerobic bacteria upon fermentation of unabsorbed carbohydrates. If lactose is not absorbed in the small intestine, it will be fermented by the bacteria in the large intestine and converted to H_2. Part of the hydrogen is absorbed through the intestinal wall, transported in the bloodstream and will take part in the gas-exchange in the lungs. Presence of hydrogen in the breath indicates contact of lactose with bacteria and is suggestive of LM. Studies in Caucasian populations have shown high correlations between the H_2-BT, intestinal lactase levels, and genetic tests[10-13]. However, false negative results may occur in subjects with a methanogenic microbiota that converts the produced H_2 into methane preventing appearance of H_2 in breath. The combined ^{13}C-H_2 BT aims to address this shortcoming by measuring both the digestion (from $^{13}CO_2$-excretion) and the malabsorption (from H_2-excretion) of ingested ^{13}C-labelled lactose. In the small intestine, ^{13}C-lactose is digested and hydrolyzed into the monosaccharides ^{13}C-glucose and ^{13}C-galactose. After transport through the intestinal circulation into the portal vein, the ^{13}C-galactose is converted to ^{13}C-glucose in the liver. After glycolysis, the metabolically produced $^{13}CO_2$ is also exhaled[14-15]. Thus a timely $^{13}CO_2$ excretion indicates a normal activity of lactase, whereas a low cumulative excretion is compatible with lactase deficiency. As ^{13}C is a stable isotope that does not involve any radiation, the ^{13}C-lactose test can be used safely in pediatric population [9]. In the context of LM the sensitivity and specificity for H_2-BT is 69% and 90% and for ^{13}C-BT it is 84% and 96%, respectively[16]. The combination of the H_2- and ^{13}C-BTs results in a higher sensitivity (85%) and a lower specificity (65%)[9,16]. It becomes easier to distinguish between different pathologies by combining both tests. But as all tests the BTs

Figure 1: ^{13}C-H_2 BTs for assimilation of lactose.

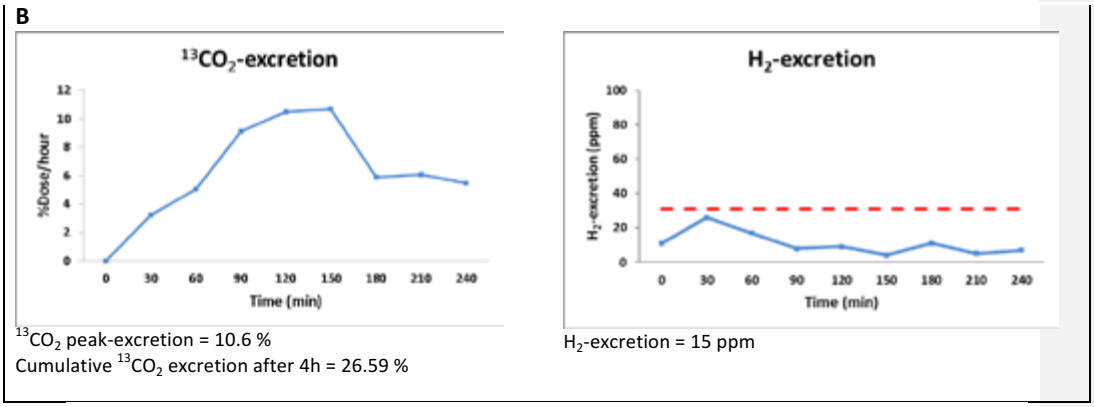
Figure 1A: Low lactose digestion resulting in a lactase deficiency with lactose malabsorption.



$^{13}CO_2$ peak-excretion = 3.2 %
Cumulative $^{13}CO_2$ excretion after 4h = 5.88 %

H_2-excretion = 0 ppm

Figure 1B: Normal lactose digestion.



$^{13}CO_2$ peak-excretion = 10.6 %
Cumulative $^{13}CO_2$ excretion after 4h = 26.59 %

H_2-excretion = 15 ppm

Table 1: Summary of available tests for diagnosing lactose malabsorption and tolerance.

	Small bowel biopsy	Genetic test	Lactose tolerance test	Stools / urine	Lactose breath tests
Test principle	Assessment of lactase enzyme activity	Genetic polymorphism 13910 upstream of lactase gene	Evolution of serum glucose after lactose challenge	Measurements of pH and reducing substances	Assessment of lactose absorption after lactose challenge
Test comparisons					
-Cost	High	High	Low	Low	Low
-Invasiveness	Yes	Yes	Yes	No	No
-Availability	Rare	Variable	Excellent	Good	Good
-Secondary causes LM	Excluding	Not excluding	Not excluding	Not excluding	Not excluding
-Assessment of symptoms (LI)	Not possible	Not possible	Possible	Not possible	Possible
-Sensitivity	95%	93%	+/- 75%	Low	70-100%
-Specificity	100%	100%	+/- 96%	Low	90-100%
-Shortcomings / conditions changing interpretation of test	Variable expression of lactase at jejunal brush border	Range of genetic polymorphisms (race)	Fluctuations of serum glucose (diabetes) Abnormal gastric emptying	Low diagnostic value Wrong collection of stools	Abnormal gastric emptying Bacterial overgrowth Non-H2-producers Wrong test-preparation Antibiotics - Laxative - motility changing drugs Acute diseases - Fever

needs to be performed in standardized and controlled conditions to be reliable.

The ingested agent for the BTs can be pure lactose or a lactose-containing product, like full fat liquid milk[15,17-18]. In case of the combined ^{13}C-H_2 BT, ^{13}C-labelled lactose is required. There is no agreement in the pediatric literature about the quantity and concentration of lactose to be used in BTs. Doses can range between 0.5 g to 2 g per kg body weight at 10% or 20% concentrations with a maximum dose varying between 20 – 50 g[15,17]. A physiological level corresponds most likely with a dose of 1 g lactose/kg (maximum 25 g) at a concentration of 10%[15,19]. When a higher dose (50 g lactose) is used, there is a possibility of overestimating the frequency of LM[20]. During the BTs every 15 - 60 minutes end-expiratory breath samples are collected for a duration of 4 hours in the pediatric population[11,21]. It is also important to note if symptoms develop following ingestion of lactose, indicating LI. In the pediatric context there is no unanimity about the diagnostic cut-off[15]. A rise in H_2 concentration to 20 ppm or more above baseline is acknowledged as positive for LM[22]. LM is considered in ^{13}C-H_2 BT if the cumulative percentage of $^{13}CO_2$ -excretion at 4 hours is less than 14.5% of administered dose, irrespective of an increase in breath H_2-excretion9. Figure 2 shows a representation of different possible results of ^{13}C-H_2 BTs. The diagnosis of either normal (Figure 2A) or low (Figure 2C) lactose absorption is most reliable if the results of the H_2- and $^{13}CO_2$-BT are concordant. A normal digestion of lactose in combination with increased H_2 excretion (Figure 2B) might suggest bacterial overgrowth or LM due to other reasons than lactase insufficiency such as a fast transit resulting in a too short contact time between the carbohydrate and the lactase enzyme[9]. If the results are discordant without any explanation by history then further examination by jejunal biopsy is needed.

As mentioned above different conditions can cause discordant results between the BTs. Conditions causing false-positive results in H_2-BT are high-fiber diet, small intestinal bacterial overgrowth (SIBO) and alterations of respiratory rates. For this reason a good preparation is needed. Ideally a BT is performed after a night of fasting. The day before the H_2-BT it is necessary to avoid slowly absorbed carbohydrates and fiber cereals to prevent H_2-production from other sources than lactose[15,23]. An early rise in H_2-excretion combined with a normal $^{13}CO_2$-excretion is seen in case of SIBO or in case of fermentation by oral bacteria. For this reason it is important to interrupt the treatment with pro-and anti-motility drugs during the BT[23]. Concomitant measurement of methane - which can be high in case of SIBO - may help to differentiate SIBO from other early H_2-excretion conditions[3]. Asking patients to brush their teeth and rinse their mouth with antiseptic mouth wash, like chlorhexidine, can eliminate oral bacteria and prevent an early H_2-excretion. During breath testing chewing gum cannot be tolerated, because of the possibility of fermentation of sorbitol to form H_2 in the intestine[15].

The range of false-negative results of H_2-BT are between 2.5% and 15%[24-25]. Other factors, like antibiotics and laxatives, which cause alterations in intestinal motility or microbiota composition also lead to false negative results. This explains why H_2-BT can only be conducted as early as 4 weeks after bowel lavage, enteroscopy of discontinuation of antibiotics[15]. The most important reason for a false-negative result is a microbiota containing methanogenic bacteria such as Methanobrevibacter smithii. This occurs in about 15-30% of the population[23,26]. Consequently, the concentration of exhaled hydrogen will be lower. In this case, a simultaneous measurement of serum glucose (LTT) or breath methane concentration can be helpful and might enhance the specificity of H_2-BT. The use of breath methane concentration is still not conclusive in pediatric literature[17]. In non-hydrogen-excretors ^{13}C-BT can be reliably applied.

In ^{13}C-BT, the results can be influenced by changes in the endogenous CO_2 production and excretion induced by food ingestion, physical activity, respiratory diseases, thyroid dysfunctions and fever[9,15,27]. In general, breath tests assume a constant ventilation. Hyper-and hypoventilation may cause changes in the respiratory $^{13}CO_2$ and H_2 excretion. Therefore, both physical activity and sleeping state should be avoided before and during breath testing.

Once the diagnosis has been established, the treatment of LT will consist of a lactose free or lactose poor diet. A restriction of lactose is usually sufficient because of the persistence of some lactase activity, the main exception is in the case of congenital lactase deficiency[17]. Lactase enzyme preparations are commercially available and can be taken orally with lactose-containing food to reduce the symptoms of LI.

In case of our girl with the discordant BTs, a clear diagnosis proved to be challenging. Based on the history of the mother, the girl was symptomatic after ingestion of lactose containing foods while the father reported almost no symptoms. This discrepancy also became clear in the symptoms that were reported by the parents during and after the BTs. At the consultation to discuss the results, the girl claimed that she had performed both tests in a different way, namely she had not taken the full amount of lactose at the first testing. This may account for the low $^{13}CO_2$-result of that test (Figure 1A). As the two tests were performed at home by either parent, we have no relevant details on test preparation and execution. Moreover the height of the girl was reported differently for both tests. For the first test her height was documented to be 105 cm whereas it was 113 cm for the second test. As this measure is used to calculate the basal CO_2 production (14.35 mmol/kg h versus 14.56 mmol/kg h) in the ^{13}C-BT, it may influence the interpretation of the test itself. As the H_2-test was not suggestive of LM on both occasions, and as one ^{13}C-BT was normal and one may have been performed without the normal dose of lactose, we concluded that the girl did not have LM. Most likely her symptoms were related to another gastro-intestinal condition, but as she had very few objective symptoms (and discordant complaints based on the history of father and mother) with almost no relevance to her daily functioning, we did not advocate endoscopic biopsies and advised against the removal of lactose from her diet. In this case the mercurial nature of her BT results did not expedite our diagnostic process, nor did the parental dichotomy facilitate our clinical management.

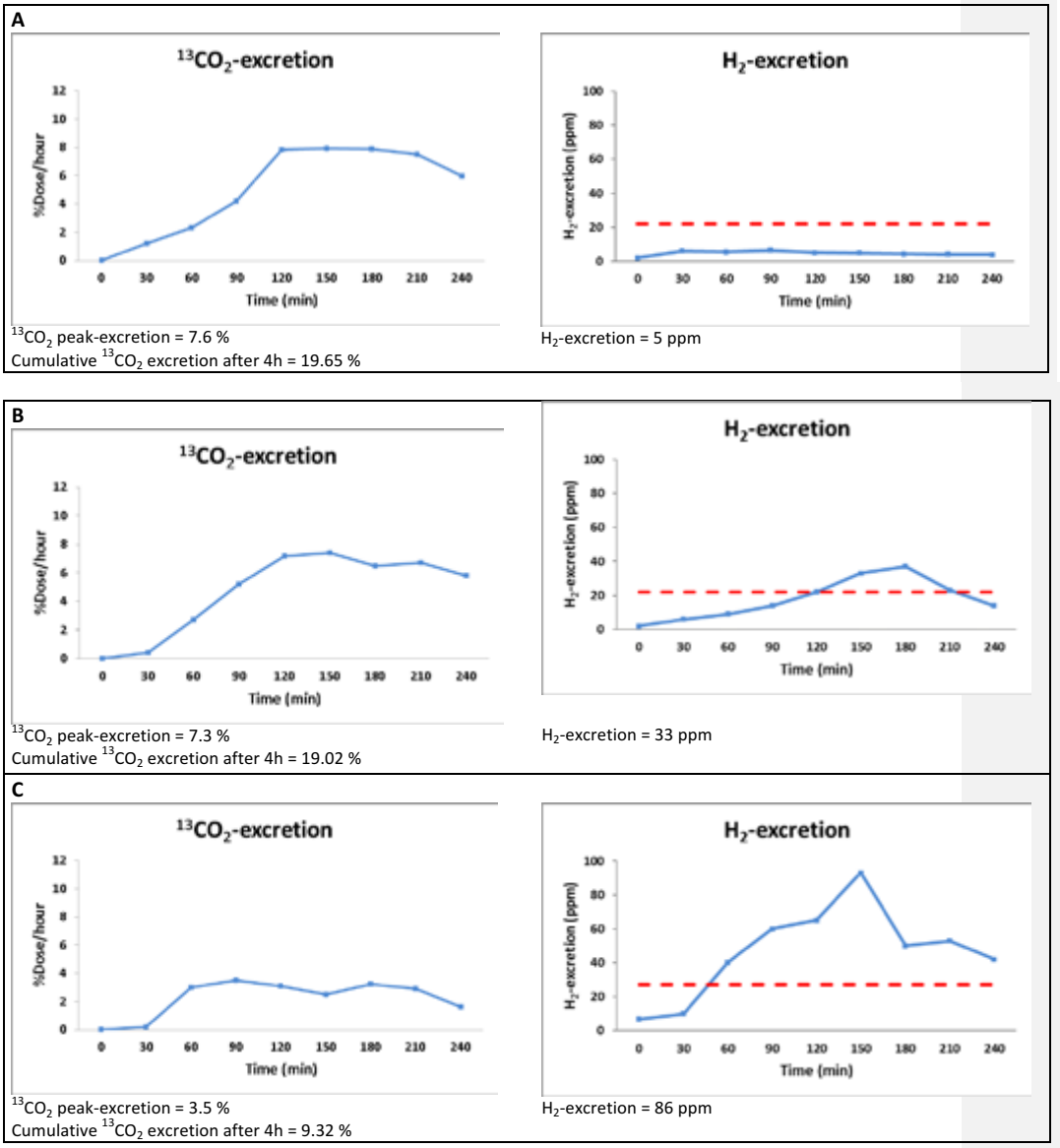
Conclusion

If there is a clinical suspicion of LM, lactose BTS are the preferred diagnostic tool. The combination of the H_2- and ^{13}C-BT can result in a higher test sensitivity. If the results are concordant the diagnosis of normal and low lactose absorption is relatively easy. In case of discordant results a jejunal biopsy may be needed to confirm the presence of LM. As mentioned above the interpretation of BTs can be challenging and a good preparation and test execution is paramount. Table 2 shows a brief overview of all necessary precautions for the busy clinician.

Table 2: Overview of the measures to be taken in breath testing.

Before breath testing
- No high-fiber meal and avoid slowly absorbed carbohydrates day before testing
- Overnight fasting (young children at least 4 hours)
- No use of antibiotics 4 weeks before testing
- Interrupt pro-and anti-motility medication
- Brushing teeth and rinsing out mouth with antiseptic mouth wash
During breath testing
- No eating or drinking
- No chewing gum
- Keep the children calm during testing
- No exercise or sleeping (avoid hyper-and hypoventilation)
- No smoking
- No fever / no acute respiratory disease

Figure 2: Overview of typical results of ^{13}C-H_2 BTs.



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Pacemaker implantation as a successful treatment of complicated breath holding spells: a case report and review of the literature

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Key words

Breath-holding spells – asystole – insertable cardiac monitor (Reveal) - pacemaker implantation

Abstract

Breath-holding spells are a well-known benign clinical entity of early childhood, characterized by sudden pallor or cyanosis, limpness and loss of consciousness during a short period of time. In most cases spontaneous resolution is seen between 5 and 8 years of age and no treatment is needed. In some cases breath-holding spells are more severe and may be complicated by prolonged asystole and/or convulsions. In these cases further treatment is indicated. We present a case of a 14 month old girl with severe pallid breath-holding spells causing prolonged loss of consciousness and convulsions. Trials with oral benzodiazepines and oral iron supplementation were unsuccessful. An insertable cardiac monitor (Medtronic Reveal) was implanted and showed an asystole of 20 seconds. A pacemaker was implanted and resolution of breath-holding spells was seen. This case shows that cardiac pacing can be a successful treatment in children with severe pallid breath-holding spells complicated by prolonged asystole.

Introduction

Breath-holding spells are benign paroxysmal non-epileptic events occurring during childhood[1]. Prevalence is estimated at 0.1-4.6% of all children and there seems to be a family predisposition[1,2]. Breath-holding spells are slightly more frequent in boys than in girls and are characterized by sudden pallor or cyanosis, change of postural tone and loss of consciousness. Episodes are short in duration and resolve spontaneously[1,3]. Breath-holding spells typically have an onset between 6 and 18 months of age and in 90% of children spells have completely resolved by the age of 6[2]. Therefore the mainstay of therapy is reassurance and parental education[4]. However, in some cases episodes are complicated by severe bradycardia or asystole, convulsions or even status epilepticus and specific treatment is indicated[1]. In the past breath-holding spells were treated with a variety of medications, all with varying degrees of success. In this paper we present a case of a 14 month old girl with breath-holding spells and associated asystole, who was successfully treated with pacemaker implantation.

Case report

A 14 month old girl was presented at our clinic because of recurrent syncopes of unknown origin. During the previous five weeks she had fainted six times and her parents were extremely anxious. The first episode occurred while she was playing and she became angry when her father left the room. When her father returned she was lying on the ground, she was pale and her body was limp. The girl was aresponsive for 2 to 3 minutes. No convulsions, urine loss or tongue bite were observed. There was no postictal phase. Clinical examination revealed no abnormalities. Working diagnosis of first epileptic insult was made and she was sent home with a rescue treatment of benzodiazepines.

During the next 4 weeks there were 5 new events. Every episode was precipitated by anger, frustration or minor trauma and was characterized by sudden loss of consciousness and a paleness of the face. Once convulsions of both arms and legs were observed. During another event a purple/blue color of the lips was reported. Duration of unconsciousness ranged from 1 to 15 minutes after which she recuperated spontaneously. During the longest episode, when the girl was unconscious for 15 minutes, basic life support was initiated by one of the neighbors. There was no postictal phase. Medical history was unremarkable. Familial history was negative for epilepsy, cardiac problems or sudden unexpected death.

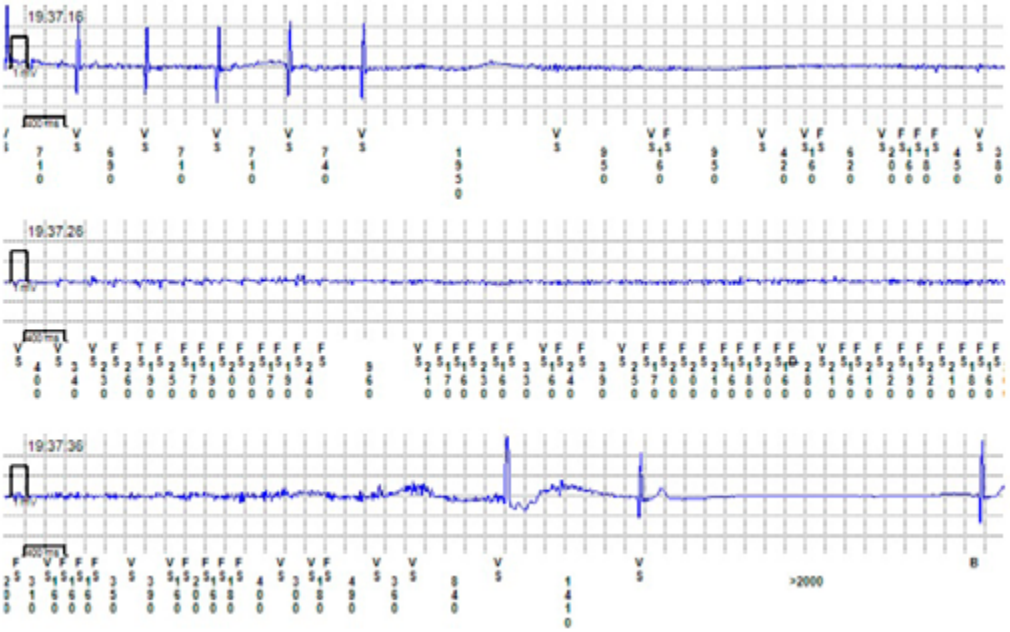
By the time the girl was examined in our center, she had already undergone multiple investigations. Laboratory testing showed an iron deficiency anemia. A 24-hours electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain were normal. Holtermonitoring during 48 hours revealed nothing remarkable, but unfortunately there was no syncope during the time monitored. Electrocardiography (ECG) and echocardiography were also normal. Ocular compression test, performed in a regional hospital, was positive and showed a bradycardia/asystole for 3.6 seconds. Therapy with oral iron supplementation had already been started, but was unsuccessful. During her stay in our hospital she was monitored continuously during 6 days, but then again no event could be witnessed. Because of the pronounced events and important impact on the quality of life we decided to implant an insertable cardiac monitor (Medtronic Reveal). One week later another, rather short, event happened at home and registrations of the Medtronic Reveal showed an asystole for 20 seconds (Fig 1). Because of the life threatening events and the documented asystole an epicardial pacemaker with 1 atrial and 1 ventricular lead (type Medtronic ADAPTA ADDRL1) was implanted for pacing in the VVI-mode (lower rate 80/min). Six months after pacemaker implantation no new episodes occured. Therefore, we expect that no more major events with prolonged syncope or even no events at all, will appear and that spells will completely resolve without sequelae when she grows older.

Discussion

Breath-holding spells are well-known, usually benign paroxysmal events occurring during childhood[1]. These events typically start between 6 and 18 months of age and a positive family history may be present[1,2,5]. Prognosis is good and in 90% of children symptoms have spontaneously resolved by the age of 6[2].

Breath-holding spells can be divided into two main categories based on the skin color: cyanotic and pallid breath-holding spells[3]. Cyanotic breath-holding spells or blue spells are the most common ones (54-62%) and are characterized by cyanosis, initially around the lips, change in muscle tone and loss of consciousness during a short period of time[2]. Events are always precipitated by a stimulus such as anger, frustration or minor trauma[2]. Therefore repeated detailed history taking is indispensable. The underlying pathophysiologic mechanism still remains unclear. Several theories were already brought forward. It has been postulated that in children with cyanotic breath-holding spells there is an autonomic dysregulation. Di Mario et al. suggested that during breath-holding spells there is initially an excessive sympathetic response with a subsequent excessive rebound parasympathetic (vagal) response[6]. It is thought that the initial violent crying causes hypocapnia and forced expiratory apnea, resulting in cerebral and systemic hypoxia. Since the child is in respiratory spasm during expiration, increased thoracic pressure arises, causing reduced right ventricular output and a decreased venous return. Furthermore, adrenergic and hypoxia mediated pulmonary arterial vasoconstriction is provoked, resulting in an intrapulmonary right to left blood shunt[1,2].

Figure 1: ECG detail



Pallid breath-holding spells or white anoxic seizures on the other hand are characterized by a gasp or a brief cry, diaphoresis and paleness followed rapidly by loss of consciousness[4,5]. More severe spells may be accompanied by clonic movements and urine loss[4]. Pallid breath-holding spells are almost always provoked by distress or a painful stimulus, causing an exaggerated vagal discharge resulting in a low cardiac output, bradycardia and finally asystole for several seconds[1,2,7]. Sometimes children show symptoms of both cyanotic and pallid breath-holding spells. These events are categorized as mixed breath-holding spells.

Diagnosis of breath-holding spells is mainly based on an accurate and detailed history taking. Clinical examination and neurological evaluation are normal in children with breath-holding spells[2,5]. Laboratory testing adds little or no information[5]. An EEG is only recommended if there is a concern of underlying epileptic activity[4]. Since long-QT syndrome may present similar to breath-holding spells, an ECG should be considered in all patients with breath-holding spells[4]. In children with pallid breath-holding spells an occular compression test can be performed. By applying pressure on closed eyes the occulocardiac reflex is elicited, leading to anoxic seizure or vagal cardiac inhibition and inducing a prolonged asystole[5]. However, this test should be used with caution because of the risk of inducing retinal bleeding.

Simple breath-holding spells are self-limiting. Prognosis is good and intellectual and developmental outcome are normal[4]. Therefore reassurance and parental education are the mainstay of therapy. During a breath-holding spell the child should be placed in a lateral recumbent position to increase venous return and to reduce the period of cerebral anoxia[4]. Sometimes breath-holding spells are more severe, causing an important impact on daily life and adjuvant medical therapy should be considered. Various pharmaceutical therapies have already been used for breath-holdings spells, all with varying degrees of success. It has been observed that breath-holding spells can be associated with anemia and iron deficiency. Jain et al. reported a prospective study with 100 children that has shown a good response to iron supplementation[8]. A Cochrane review of 2010 concluded that iron therapy reduces severity and frequency of breath-holding spells in children with iron deficiency anemia[8,9]. Besides iron supplementation also successful trials and case reports of treatment with atropine, piracetam, theophylline, glycopyrrolate and fluoxetine have been described[10-14].

In some cases, breath-holding spells, mainly pallid breath-holding spells, are complicated by bradycardia or prolonged asystole causing an acute life-threatening event and sudden death[1,4,7]. In these children implantation of an epicardial pacemaker with ventricular leads for back-up pacing, is indicated. A recent review article of Sartori et al describes 48 patients with severe breath-holding spells (bradycardia or prolonged asystole, prolonged loss of consciousness, ophistotonus, convulsions, epileptic seizures or status epilepticus), where a pacemaker was implanted successfully. Pacemaker implantation was effective in all cases and in 86.4% there was a complete resolution of the complications of breath-holding spells[1]. Implantation of a pacemaker nowadays is a relatively easy and uncomplicated procedure, requiring a hospital stay of no more than 48 hours. Insertion of a pacemaker carries some risks, such as infection, loss of capture, fracture of pacing wires and a finite battery life[15]. Therefore a pacemaker should only be implanted in certain conditions. Following indications were suggested: 1) frequent and severe breath-holding spells with prolonged loss of consciousness, subsequent lethargy or epileptic convulsions, 2) important impact on daily life despite parental education and medical treatments, 3) prolonged asystole on cardiac monitoring[1].

Conclusions

Breath-holding spells are a benign and well-known clinical entity of early childhood. In general, prognosis is good and in most cases spells resolve spontaneously over time. However, in rare cases breath-holding spells are complicated by severe bradycardia or asystole, causing risk at sudden death. When arrhythmia is suspected, placing an insertable cardiac monitor may be helpful. With proven bradycardia or asystole, implanting a pacemaker seems to be indicated.

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Two cases of pyelonephritis following voiding cystourethrography: why this warrants a different approach.

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Key words

VCUG, postprocedural pyelonephritis, complications, fluoroquinolones

Abstract

Voiding cystourethrography (VCUG) is a valuable diagnostic procedure for investigating vesicoureteral reflux and lower urinary tract anatomy. Its invasive nature and possible complications force us to critically consider indications for VCUG. Postprocedural pyelonephritis significantly differs from community acquired pyelonephritis and should be considered in any febrile patient after VCUG, particularly in children with medium to high grade vesicoureteral reflux (VUR). In this article, we outline the clinical course of two patients and attempt to shine a light on important topics regarding complications of VCUG, antibiotic choice and follow-up care.

Introduction

A voiding cystourethrography (VCUG) is a frequently performed diagnostic procedure during childhood. It is the gold standard test for investigating lower urinary tract anatomy and for diagnosis and classification of vesicoureteral reflux (VUR). Indications for VCUG after urinary tract infection (UTI) and to a much lesser extent after antenatal hydronephrosis are being vigorously debated. The historically described link between VUR and renal scarring may not be as robust as previously thought and the routine administration of uroprophylaxis is being re-assessed with contradicting literature resulting in a huge variation in current practice. The RIVUR trial was the largest study looking into antimicrobial prophylaxis in children with VUR and found that the risk of UTI was reduced by half among children receiving prophylaxis in comparison to placebo[1]. Critics argued that although this finding was statistically significant, its clinical value was doubtful, requiring 16 up to 22 patient years of antibiotics to prevent one UTI or febrile UTI respectively[2]. Moreover there was no demonstrable effect on scar formation and a propensity to induce bacterial resistance together with a debatable cost-effectiveness[3-5]. The results of this study did not alter the British or American guidelines, that reject routine prophylaxis and VCUG, and use renal and bladder ultrasound (RBUS)-centred clinical decision protocols. VCUG has several drawbacks: it is costly and invasive, as it requires both ionising radiation and retrograde instillation of contrast substance via either transurethral catheterisation or suprapubic puncture. Furthermore, VCUG increases the risk of postprocedural pyelonephritis, since contrast medium infusion potentially provides an ascension vehicle for pathogens into the upper urinary tract. Therefore, different guidelines recommend prophylactic antibiotics during VCUG, although prophylaxis regimens strongly vary, and a standard peri-VCUG prophylactic protocol is inexistent[6]. A recently published randomised controlled trial showed a clear reduction in postprocedural pyelonephritis in children under prophylaxis[7]. At our institution, it has been common practice to perform VCUG under antibiotic prophylaxis for more than two decades, doubling the dose the day of the exam and on the following day. Still, postprocedural pyelonephritis remains a risk to consider after VCUG. Two infants presented to our clinic with VCUG-related pyelonephritis in a short time. These infections significantly differedfrom community acquired pyelonephritis in many aspects. In this article, we outline the clinical course of the two patients and review important topics regarding complications of VCUG, antibiotic choice and follow-up.

Cases

Patient A was a one-month-old, term born girl, who presented to our paediatric emergency department, because of a sudden onset of fever, vomiting and groaning, which started one hour before admission. She had undergone a VCUG under trimethoprim prophylaxis the day before presentation to the emergency department, in the context of antenatal hydronephrosis, for which uroprophylaxis was started on the first day of life. The VCUG revealed a bilateral grade V VUR (fig 1), for which uroprophylaxis was continued. A urine culture, collected during catheterisation for VCUG was sterile. At presentation, the patient had a temperature of 38.3°C, a pulse rate of 188 beats per minute (bpm) and a central capillary refill time of 4 seconds. There was no febrile focus on physical examination. She received a volume expansion with isotonic saline and broad-spectrum antibiotics were commenced according to the neonatal sepsis protocol in our hospital (ampicillin and cefotaxim), after which a catheterised urine specimen and a liquor sample were obtained. There was a significant leucocytosis and an elevated C-reactive protein (CRP), while urine microscopy showed gross pyuria (table 1). She was hospitalised for presumed postprocedural urosepsis. Within the first two days of hospitalisation, she remained febrile. After 48 hours, Pseudomonas aeruginosa grew in both blood and urine culture. Empiric antibiotics were switched to piperacillin-tazobactam, after which the patient soon became afebrile. At the sixth day of hospitalisation, a major venous access problem occurred, necessitating a switch to the only oral alternative: ciprofloxacin for a total antibiotic therapy duration of 3 weeks, after which uroprophylaxis was resumed.

Table 1: laboratory results of both index cases.

	Patient A	Patient B	Reference
Haemoglobin (g/dL)	11.8	12.3	9.8-13.8
Haematocrit (%)	34.0	36.1	29.4-42.0
Platelets (10^3/mm^3)	313 x 10^3	577 x 10^3	158-470
White blood cell count (10^3/mm^3)	6.0 x 10^3	16.7 x 10^3	3.5-17.3
C-reactive protein (mg/L)	85.8	8.7	<5
Urine white blood cells (wbc/hpf)	>1600	440	Absent
Urine culture	Pseudomonas aeruginosa, resistant to aztreonam	Pseudomonas aeruginosa, resistant to aztreonam.	Sterile
Blood culture	Pseudomonas aeruginosa, resistant to aztreonam	Sterile	Sterile
Cerebrospinal fluid culture	Negative	Negative	Sterile

Patient B was an eleven-weeks-old, term born boy, who presented to our paediatric emergency department because of fever, moaning and refusal to drink. One day before presentation he had undergone a VCUG under trimethoprim prophylaxis in the context of bilateral hydronephrosis diagnosed by renal and bladder ultrasound (RBUS) during an episode of Klebsiella oxytoca pyelonephritis during the seventh week of life. Culture of urine collected during catheterisation for VCUG was negative, while VCUG revealed a bilateral high-grade VUR (fig 2) on the right and an apparent normal urethra. At physical examination, we saw an irritable, ill-appearing boy with cutis marmorata. The rectal body temperature was 40.4°C, the pulse rate 220 bpm, central capillary refill time was 3 seconds. A peripheral intravenous catheter was inserted and blood for laboratory tests and culture was drawn. Then a volume expansion with isotonic saline and broad-spectrum antibiotics (ampicillin and cefotaxim) were administered. Shortly thereafter, a catheterised urine specimen and cerebrospinal fluid were obtained. Laboratory results are displayed in table 1. As soon as the urine culture grew Pseudomonas aeruginosa antibiotics were switched to piperacillin-tazobactam. The blood culture remained sterile. During his stay at the hospital, our patient was circumcised, and a per-operative cystoscopy revealed gaping ureteral orifices with the presence of a small ureteral valve, that was incised. After completion of this ten day intravenous antibiotic course, prophylaxis by means of nitrofurantoin was initiated. No further UTIs have occurred since then.

Complications of VCUG

During VCUG, the bladder is gradually, retrogradely filled with a contrast agent via gravity drip after transurethral catheterisation or suprapubic puncture. Image acquisition can be by either fluoroscopy, radionuclide or ultrasonography. Fluoroscopic VCUG provides superior anatomical detail and grading of VUR[8]. Yet, there is no consensus on the recommended VCUG modality in current UTI guidelines. The reported incidence and predictors of postprocedural pyelonephritis are highly variable, and data of older series are clouded by use of bacteriuria alone as a diagnostic criterion for UTI[6,7]. Two retrospective studies, in Israel and the United States, have systematically re-evaluated children some days after VCUG. In Israel, a low incidence (1.7%) of VCUG-induced pyelonephritis was observed with a relatively high rate of Pseudomonas aeruginosa infections while using prophylaxis[9]. In the United States, the risk of postprocedural pyelonephritis was as low as 1% (95% CI 0.4-1.6%), rejecting a standard preventive use of antibiotic prophylaxis for the sole purpose of postprocedural UTI prevention[6]. Both studies found the presence of, and (higher) grade of VUR to be predictive of febrile postprocedural pyelonephritis. However, at least a significant proportion of the boys in both studies were probably circumcised, what is known to protect against pyelonephritis. This benefit is similar with regard to UTI risk reduction in boys with hydronephrosis, regardless of the underlying diagnosis as is the case for high-risk urological abnormalities such as the presence of posterior urethral valves and high-grade VUR[10]. A systematic review in which the authors looked into the lifetime risk of UTI in the male population with and without circumcision, found a lifetime risk of UTI of 32% (95% CI 15.6-49.8) in uncircumcised males and 8.8% (95% CI 4.15-13.2) in circumcised males, thus a RR of 3.65 (95% CI1.15-11.8). The difference, 23.2%, represents the percentage of UTIs during the lifetime attributable to lack of circumcision as a single risk factor[11].

A recently published prospective trial in India, randomised children undergoing VCUG to either an antibiotic group or non-antibiotic group. 120 children were included, 1.4% of children who were assigned to the antibiotic prophylaxis group were later diagnosed with post-VCUG acquired pyelonephritis, compared to 17% of children undergoing VCUG without antibiotic prophylaxis (OR = 14.2, 95% CI 1.7-117). The risk of postprocedural pyelonephritis was increased in children with abnormal ultrasound scans[7]. It is hypothesised that the pathogenesis of postprocedural pyelonephritis follows the direct introduction of bacteria into the upper urinary tract. Pseudomonas aeruginosa, which was cultured in both of our patients, is both a nosocomial bacterium and a skin commensal. Therefore, it could have been introduced in the bladder via transurethral catheterisation, and subsequently ascended to the renal tissue as both of our patients had high grade VUR. A percutaneous cystography could to some extent circumvent this problem, but prior trials comparing transurethral and suprapubic techniques had to be discontinued because families clearly considered suprapubic puncture to be too invasive and more distressful9. In theory, the contrast medium is shortly evacuated out of the bladder during voiding. The aforementioned presence of (moderate to severe) VUR as a risk factor in developing post-VCUG UTIs, could in part be explained by late emptying of the ureters leading to post-void residual contrast. Ideally a second bladder catheterisation should take place to make sure all contrast material is eliminated. However, the pathogenesis of postprocedural

Figure 1: bilateral grade V reflux according to the International Reflux System classification representing reflux into a markedly dilated and tortuous ureter.

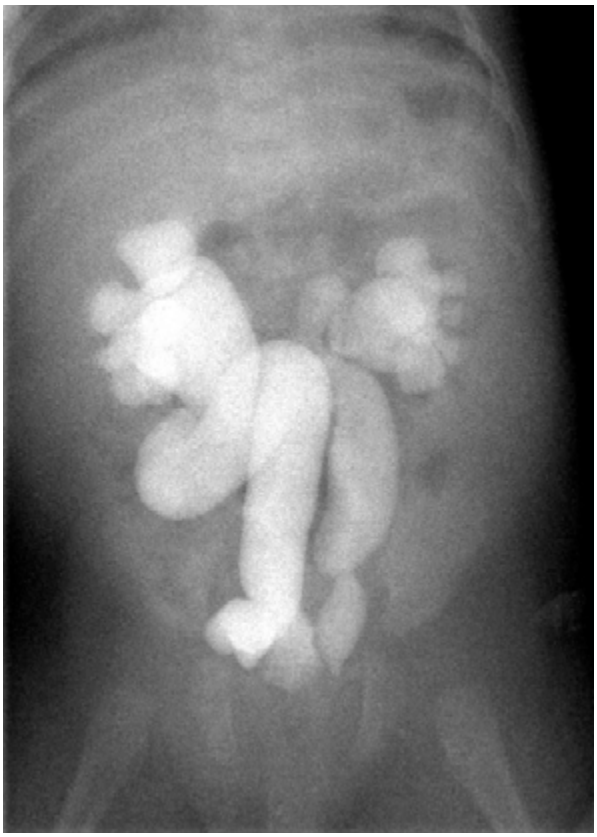
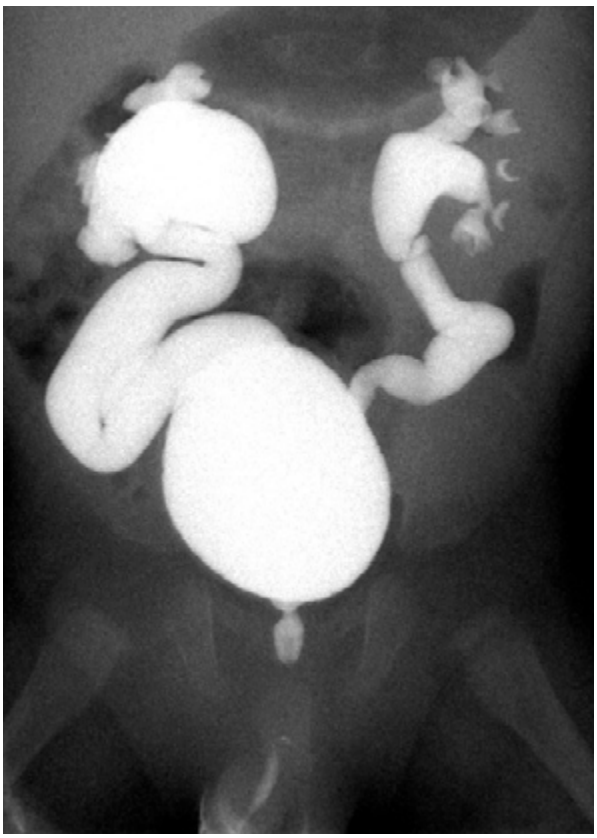


Figure 2: anteroposterior voiding cystourethrogram obtained with patient B in supine position demonstrating grade V primary vesicoureteral reflux at filling initiation on the right and grade IV reflux on the left.



pyelonephritis remains incompletely understood. Other reported complications, albeit rare, are catheter trauma and bladder rupture[12]. Clinicians should be aware of such possible complications, and be even more vigilant in case of pre-existing urologic diagnoses and acquainted with their centre's local VCUG protocol. Another point of disarray regards the timing of the VCUG with a traditional interval of 4-6 weeks to avoid false positives. A British retrospective study compared the presence and severity of VUR in children receiving a VCUG within 4 weeks and 8 weeks after index UTI. They concluded that an early cystogram does not lead to an overestimation of the presence or grade of reflux[13].

Toxicity profile of fluoroquinolones in children

Pseudomonas aeruginosa is intrinsically resistant to different classes of antibiotics. Ciprofloxacin, a second generation fluoroquinolone, is usually the only effective oral antibiotic against Pseudomonas strains. However, prescribing fluoroquinolones for children has long been seen as controversial, because cartilage tissue damages had been observed in weight-bearing joints of juvenile animals to which fluoroquinolones were administered. Yet, a meta-analysis of 16.184 children who had been prescribed ciprofloxacin showed that the risk of arthropathy is relatively low and reversible with management. Moreover there was no dose dependent or duration dependent risk of toxicity[14].

Concluding remarks

VCUG is a valuable diagnostic tool in the evaluation of vesicoureteral reflux and lower urinary tract anatomy. Its invasive nature and possible complications force us to critically consider indications for VCUG. Postprocedural pyelonephritis should be considered in any febrile patient after VCUG. Periprocedural antibiotic prophylaxis certainly seems to be recommended in children with a pre-existing uropathy, who are particularly at risk of developing a VCUG-induced UTI. . Pseudomonas aeruginosa should be covered in treatment of postprocedural pyelonephritis pending culture results. Since the risk of ciprofloxacin-induced arthropathy seems to be relatively low and reversible, clinicians should be less reluctant in prescribing it to this high-risk group.

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Op het leven

Seasonality of respiratory syncytial virus (RSV) in Belgium

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Abstract

The timing and duration of the respiratory syncytial virus (RSV) season is crucial for efficient administration of immunopropfylaxis to prevent infection in vulnerable infants. We describe a retrospective study of the seasonal RSV pattern in Belgium over a 13-year period, from July2004 till June 2017. The RSV season begins mostly at the beginning of October. The end of the season is less clearly definable with a range between mid-February to the end of March.

Introduction

Respiratory syncytial virus is the most frequent cause of bronchiolitis and pneumonia in infants and young children and an important source of morbidity, mortality and financial burden worldwide[1]. Immunoprophylaxis to prevent RSV infection with neutralizing monoclonal antibodies, palivizumab, is available for monthly administration during the season to high-risk infants: preterm birth, cyanotic or complicated heart disease and chronic lung disease[2]. In Belgium only 5 injections are reimbursed annually. The exact timing and duration of the RSV season is crucial for efficient administration.

Objectives

To guide the timing of RSV prophylaxis, we investigated the seasonal pattern of RSV in Belgium over a 13-year period: July 2004 – June 2017.

Methods

Data collection was retrospective. Nine hospitals throughout Belgium (16 % of pediatric beds) participated. All RSV detection test from out- and inpatients performed in children < 3 years old from July 1st 2004 until May 31th 2017 were eligible for the study.

Onset and offset of the RSV season was defined as the first respectively the last 2 consecutive weeks with at least 10% positive tests and a minimum of 10 samples tested that week[3]. Peak week was defined as the highest percentage of positive tests.

Results (Table, Figure)

Over the study period, 87.574 were retained for analysis from which 22.239 (25.4 %) tested positive (56.3 % boys) (and 97 % within the identified epidemics (green area in figure)). Most often season starts around week 41 (second week of October) or 42. The onset was remarkably early in 2008-2009 (week 30) and 2015-2016 (week 37). In 2016-2017, after an early start (week 30), two times there was a switch-off for 3 to 4 weeks in between. Offset ranged from week 7 to week 10, except for 2007-2008 (week 14), 2008-2009 (week 4), 2009-2010 (week 13), 2010-2011 (week 15), 2014-2015 (week 15) and. 2016-2017 (week4). Median peak week was week 49 (range: 47 – 52). Season duration ranged from 13 to 28 weeks (mean: 20.9 weeks), except for the longest epidemics in 2007-2008 (28 weeks), 2008-2009 (26 weeks) and 2010-2011 (25 weeks).

Conclusion

Although the start of the RSV season was relatively consistent (at the beginning of October), the end of the season is more difficult to define. Our data are in line with the findings of the WIV/ISP[4]. Prophylaxis should start "before" the season taking into account a mean season duration of 20.9 weeks and knowing that 5 monthly doses give sustained exposure to a therapeutic level of antibodies for more than 150 days after the 1st dose[5].

Table 2: Number of (positive) RSV tests and epidemic characteristics among children <3 years in 9 hospitals in Belgium, July 2004 – June 2017.

Season	N tests	N positive tests	Onset (week)	Offset (week)	Peak (week)	Duration (N weeks)
2004-2005	2533	752	44	7	52	17
2005-2006	4255	1339	40	8	48	21
2006-2007	5017	1391	42	9	49	20
2007-2008	4684	1159	42	17	52	28
2008-2009	6813	1751	30	3	47	26
2009-2010	6485	1814	43	10	50	21
2010-2011	7307	1751	41	13	50	25
2011-2012	7405	1753	41	8	49	20
2012-2013	7496	2177	39	6	48	20
2013-2014	8691	2154	43	8	50	18
2014-2015	9298	2144	43	10	50	20
2015-2016	8900	1991	37	6	48	23
2016-2017	8690	2063	40	4	48	13

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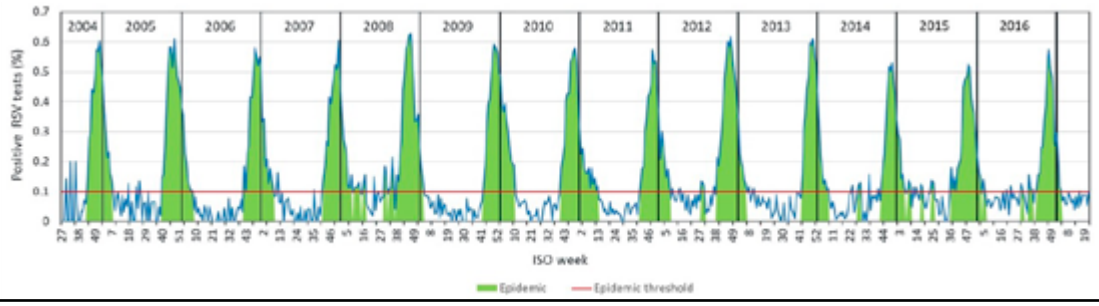
Figure: Weekly percentage of positive RSV tests (inpatient + ambulatory) among children <3 years in 9 hospitals in Belgium, July 2004 – June 2017.



DENOMINATION DU MEDICAMENT Enterol 250 mg, poudre pour suspension buvable. Enterol 250 mg, gélules. *Saccharomyces boulardii CNCM I-745*.COMPOSITION QUALITATIVE ET QUANTITATIVE Enterol 250 mg, poudre pour suspension buvable : Chaque sachet-dose de poudre pour suspension buvable contient 250 mg de *Saccharomyces boulardii CNCM I-745* sous forme lyophilisée (soit au minimum 6 x 10^9 cellules reviviscentes au moment de la fabrication et 1 x 10^9 cellules lyophilisées reviviscentes à la date de péremption). Enterol 250 mg, gélules : Chaque gélule contient 250 mg de *Saccharomyces boulardii CNCM I-745* sous forme lyophilisée (soit au minimum 6 x 10^9 cellules reviviscentes au moment de la fabrication et 1 x 10^9 cellules lyophilisées reviviscentes à la date de péremption). Excipient(s) à effet notoire : Enterol 250 mg, poudre pour suspension buvable : fructose, lactose. Enterol 250 mg, gélules : lactose. Pour la liste complète des excipients, voir rubrique 6.1 du RCP. FORME PHARMACEUTIQUE Enterol 250 mg, poudre pour suspension buvable. Poudre pour suspension buvable. Enterol 250 mg, gélules. Gélule. DONNEES CLINIQUES : Indications thérapeutiques : Prévention de la diarrhée associée à l'antibiothérapie à large spectre chez des sujets prédisposés à développer une diarrhée à *Clostridium difficile* ou rechute de diarrhée à *Clostridium difficile*. Traitement des diarrhées aiguës chez les enfants jusqu'à 12 ans, en complément de la réhydratation orale. Posologie et mode d'administration : Posologie : Adulte : 2 à 4 gélules ou 2 à 4 sachets-doses par jour, en 2 prises. Population pédiatrique : Enfant : 2 gélules ou 2 sachets-doses par jour, en 2 prises. Mode d'administration : Gélules : avaler avec un peu d'eau. Sachets-doses : diluer la poudre dans un verre d'eau. Précautions à prendre avant la manipulation ou l'administration du médicament : En raison d'un risque de contamination aéroportée, les sachets ou gélules ne peuvent pas être ouverts dans les chambres des patients. Les professionnels de la santé doivent porter des gants durant la manipulation de probiotiques en vue de leur administration, puis les jeter immédiatement après usage et se laver les mains avec soin. Durée du traitement : Prévention des récurrences ou rechute de diarrhée à *Clostridium difficile* : 4 semaines. Traitement de la diarrhée en comp lément à la réhydratation orale chez l'enfant : 1 semaine. Contre-indications : Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP. Patients porteurs d'un cathéter veineux central, patients dans un état critique ou immunodéficients en raison du risque de fongémie. Allergie aux levures, spécialement *Saccharomyces boulardii CNCM I-745*. Effets indésirables : Les effets indésirables sont classés ci-dessous par système-organe et par fréquence comme définies ci-après : très fréquents (≥ 1/10), fréquents (≥ 1/100, < 1/10), peu fréquents (≥ 1/1.000, < 1/100), rares (≥ 1/10.000, < 1/1.000), très rares (< 1/10.000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Infections et infestations : Très rares : Fongémie chez des patients porteurs d'un cathéter veineux central, et chez des patients dans un état critique ou immunodéficients, mycose à *Saccharomyces boulardii CNCM I-745*. Affections du système immunitaire : Très rare : choc anaphylactique. Affections vasculaires : Très rare : choc anaphylactique. Affections respiratoires, thoraciques et médiastinales : Très rare : dyspnée. Affections gastro-intestinales : Très rares : constipation, épigastralgies, météorisme abdominal (épigastralgies et météorisme abdominal ont été observés lors d'études cliniques). Affections de la peau et du tissu sous-cutané : Très rares : prurit, exanthème, Œdème de Quincke. Troubles généraux et anomalies au site d'administration : Très rares : soif. 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 : http://www.afmps.be, adversedrugreactions@fagg-afmps.be; Luxembourg : http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE BIOCODEX Benelux NV/SA - Square Marie Curie 20 - 1070 Bruxelles - Belgique - Tél : 0032(0)23704790. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE : Enterol 250 mg, poudre pour suspension buvable : BE269026. Enterol 250 mg, gélules en flacon en verre : BE269035. Enterol 250 mg, gélules en plaquette: BE397896. MODE DE DELIVRANCE : Délivrance libre. DATE DE MISE A JOUR DU TEXTE : Mise à jour : 01/2018. Approbation : 03/2018.

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Antibiotics may be effective to treat prolonged wet cough in children.

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Clinical question

Is the use of antibiotics to treat prolonged wet cough in children safe and effective?

Context

Wet cough is a frequent presenting symptom for paediatricians. Wet cough is prolonged when lasting more than 4 weeks, with the presence of lower airway secretions. A common cause of prolonged wet cough is protracted bacterial bronchitis, which is defined in clinical guidelines worldwide as a prolonged wet cough without presence of signs or symptoms of alternative cause that responds to two weeks of appropriate antibiotic therapy. This Cochrane review reviewed the evidence for the current recommendation (recommended by e.g. American College of Chest Physicians' (ACCP) cough guideline panel) to prescribe antibiotics as first line therapy in children without signs or symptoms of an alternative cause. This review included randomized controlled trials that compared antibiotics to placebo or a control intervention in children with prolonged wet cough (without underlying illnesses, including bronchiectasis). The review excluded cluster-RCTs and cross-over trials.

Summary of the results

This review is an update of a review that was first published in 2005. One new trial was identified, bringing the total number of trials in this review to three, including 190 children. The studies all compared antibiotics to placebo, but differed in the intervention used (two studies used amoxicillin/clavulanic acid, one erythromycin) and the duration of treatment (7 days to two weeks). The age range of children included in the trials was 21 months to 6 years.

The main outcome of this review was the proportion of children that was not cured or substantially improved after treatment and was reported in all three studies (190 children). This number was decreased after antibiotics treatment, compared to placebo (placebo: 76 per 100 vs antibiotics: 32 per 100, 95% CI* from 18 to 49, corresponding to a NNTB^ of 3, 95% CI from 2 to 4).

The two older papers (125 children) also reported the number of children requiring additional treatment, which was also lower in the group receiving antibiotics treatment (placebo: 36 per 100 vs antibiotics: 5 per 100, 95% CI from 2 to 16, corresponding to a NNTB of 4, 95% CI from 3 to 5).

The number of adverse events (e.g. diarrhoea, vomiting, rash, allergic reactions) was reported in all three trials, and was reported not to differ significantly between antibiotics and placebo (placebo: 5 per 100 vs antibiotics: 10 per 100, 95% CI from 3 to 25).

Remarks

The certainty of the evidence presented in this review was judged to be moderate for the proportion of children not cured or substantially improved and proportion of children requiring additional treatment, which means we are fairly confident in the estimate made. The certainty for the outcome adverse events was low, which means that the true number of adverse events may differ substantially from the number estimated in this review. Reasons for downgrading our level of confidence were a high risk of bias in the two older studies, affecting all three outcomes reported, and imprecise results for the outcome adverse events.

Conclusion

A cure of antibiotics probably decreases the number of children with prolonged wet cough that are not cured after treatment and probably also decreases the number of children requiring further treatment. Antibiotics may have little or no effect on the incidence of adverse events.

Implications for practice

Antibiotics seem useful for children with prolonged wet cough without signs and symptoms of other underlying illness.

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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
^ **NNT:** number needed to treat for benefit

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Bexsero: het eerste vaccin tegen meningokokken van serogroep B.

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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

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

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1 pak =
1 levensreddend vaccin*

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1. Salazar-Lindo et al - New England Journal of Medicine 2000; 343: 463-7
2. Turck D et al - Alimentary Pharmacology and Therapeutics 1999; 13(Suppl.6) 27-32
3. Cézard JP et al - Gastroenterology 2001; 120: 799-805
4. Alfredo Guarino et al - Journal of Pediatric Gastroenterology and Nutrition 46:S81–S122, 2008

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DENOMINATION DU MEDICAMENT Tiorfix Baby 10 mg granulés pour suspension buvable -Tiorfix Junior 30 mg granulés pour suspension buvable - Tiorfix 100 mg gélules COMPOSITION QUALITATIVE ET QUANTITATIVE • 10 mg : Chaque sachet contient 10 mg racécadotril et 966,5 mg sucrose. 30 mg : Chaque sachet contient 30 mg racécadotril et 2,9 g sucrose. 100 mg : Chaque gélule contient 100 mg racécadotril et 41 mg de lactose monohydrate. Pour la liste complète des excipients, voir le RCP. FORME PHARMACEUTIQUE 10 et 30 mg : Granulés pour suspension buvable. Poudre blanche à l'odeur caractéristique d'abricot. 100 mg : Gélule de couleur ivoire (taille 2) contenant une poudre blanche, à l'odeur de soufre. INDICATIONS THERAPEUTIQUES 10 et 30 mg : Traitement symptomatique adjuvant de la diarrhée aiguë chez les nourrissons (âgés de plus de 3 mois) et les enfants, en association avec une réhydratation orale et les mesures de soutien habituelles, dans le cas où elles ne suffisent pas à elles seules à contrôler l'affection clinique, et si on ne peut pas remédier à la cause de la diarrhée. Le racécadotril peut être administré comme médication complémentaire si le traitement de la cause est possible. 100 mg : Tiorfix est indiqué pour le traitement symptomatique de la diarrhée aiguë chez les adultes dans le cas où elles ne suffisent pas à elles seules à contrôler l'affection clinique, et si on ne peut pas remédier à la cause de la diarrhée. Le racécadotril peut être administré comme médication complémentaire si le traitement de la cause est possible. POSOLOGIE ET MODE D'ADMINISTRATION 10 et 30 mg : Tiorfix Baby et Tiorfix Junior sont administrés par voie orale en association avec une réhydratation orale (voir le RCP). Tiorfix Baby est destiné aux enfants de poids <13 kg. Tiorfix Junior est destiné aux enfants de poids ≥13 kg. La dose recommandée dépend du poids corporel: 1,5 mg/kg par prise, (correspondant à 1 ou 2 sachets), trois fois par jour, à des heures régulières. Chez les enfants de moins de 9 kg : un sachet de 10 mg 3 fois par jour. Chez les enfants de 9 kg à 13 kg : deux sachets de 10 mg 3 fois par jour. Chez les enfants de 13 à 27 kg: un sachet de 30 mg 3 fois par jour. Chez les enfants de plus de 27 kg: deux sachets de 30 mg 3 fois par jour. • La durée du traitement dans les essais cliniques chez les enfants était de 5 jours. Le traitement doit se poursuivre jusqu'à ce que deux selles normales peuvent être observées. Le traitement ne devra pas être poursuivi au-delà de 7 jours. Le traitement au long cours par le racécadotril est déconseillé. Il n'existe pas d'études cliniques chez les nourrissons de moins de 3 mois. • Populations particulières: Il n'existe pas d'études chez les nourrissons et les enfants souffrant d'insuffisance rénale ou hépatique (voir le RCP). La prudence est de mise chez les patients insuffisants hépatiques ou rénaux. Les granulés peuvent être ajoutés à la nourriture, dissous dans un verre d'eau ou dans un biberon. Le tout doit être bien mélangé et immédiatement administré. 100 mg : Seulement pour adultes: Une gélule d'emblée quelque soit le moment de la journée. Ensuite une gélule trois fois par jour de préférence avant les repas principaux. Le traitement doit être poursuivi jusqu'à ce que deux selles normales sont observées. Le traitement ne devrait pas durer plus de 7 jours. Populations particulières: Personnes âgées: la posologie ne doit pas être ajustée pour les personnes âgées. La prudence est de mise chez les patients insuffisants hépatiques ou rénaux. CONTRE-INDICATIONS Hypersensibilité à la substance active ou à l'un des excipients mentionnés dans le RCP. Tiorfix Baby et Tiorfix Junior contiennent du sucrose. Ces médicaments sont contre-indiqués chez les patients présentant une intolérance au fructose, un syndrome de malabsorption du glucose et du galactose ou un déficit en sucrase/isomaltase (maladies héréditaires rares). EFFETS INDESIRABLES 10 et 30 mg : Les données disponibles émanent d'études cliniques incluant 860 enfants atteints de diarrhée aiguë traités par racécadotril et 411 enfants traités par placebo. 100 mg : Les données disponibles émanent d'études cliniques incluant 2193 patients atteints de diarrhée aiguë adultes traités par racécadotril et 282 patients traités par placebo. Les effets indésirables suivants ont été observés plus fréquemment avec racécadotril qu'avec le placebo, ou ont été rapportés après la mise sur le marché. La fréquence des effets indésirables est définie selon la convention suivante: très fréquent (≥1/10), fréquent (≥1/100, <1/10), peu fréquent (≥1/1 000, <1/100), rare (≥1/10 000, <1/1 000), très rare (<1/10 000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). 10 et 30 mg : Infections et infestations Peu fréquent: amygdalite. Affections de la peau et du tissu sous-cutané (voir le RCP) Peu fréquent: éruption cutanée, érythème. Fréquence indéterminée: érythème polymorphe, œdème de la langue, du visage, des lèvres ou de la paupière, angio-œdème, urticaire, érythème noueux, éruption cutanée papuleuse, prurigo, prurit. 100 mg : Affections du système nerveux Fréquent: mal de tête. Affections de la peau et du tissu sous-cutané (voir le RCP) Peu fréquent: éruption cutanée, érythème. Fréquence indéterminée: érythème polymorphe, œdème de la langue, du visage, des lèvres ou de la paupière, angio-œdème, urticaire, érythème noueux, éruption cutanée papuleuse, prurigo, prurit, nécrolyse épidermique toxique. 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 MARCHE Bioprojet Europe Ltd., 101 Furry Park road, Killester, Dublin-5, Irlande NUMERO D'AUTORISATION DE MISE SUR LE MARCHE 10 mg : BE400723 30 mg : BE400732 100 mg : BE400741 MODE DE DELIVRANCE 10 et 30 mg : Médicament soumis à prescription médicale 100 mg: Délivrance libre DATE DE MISE A JOUR DU TEXTE 05/2017

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