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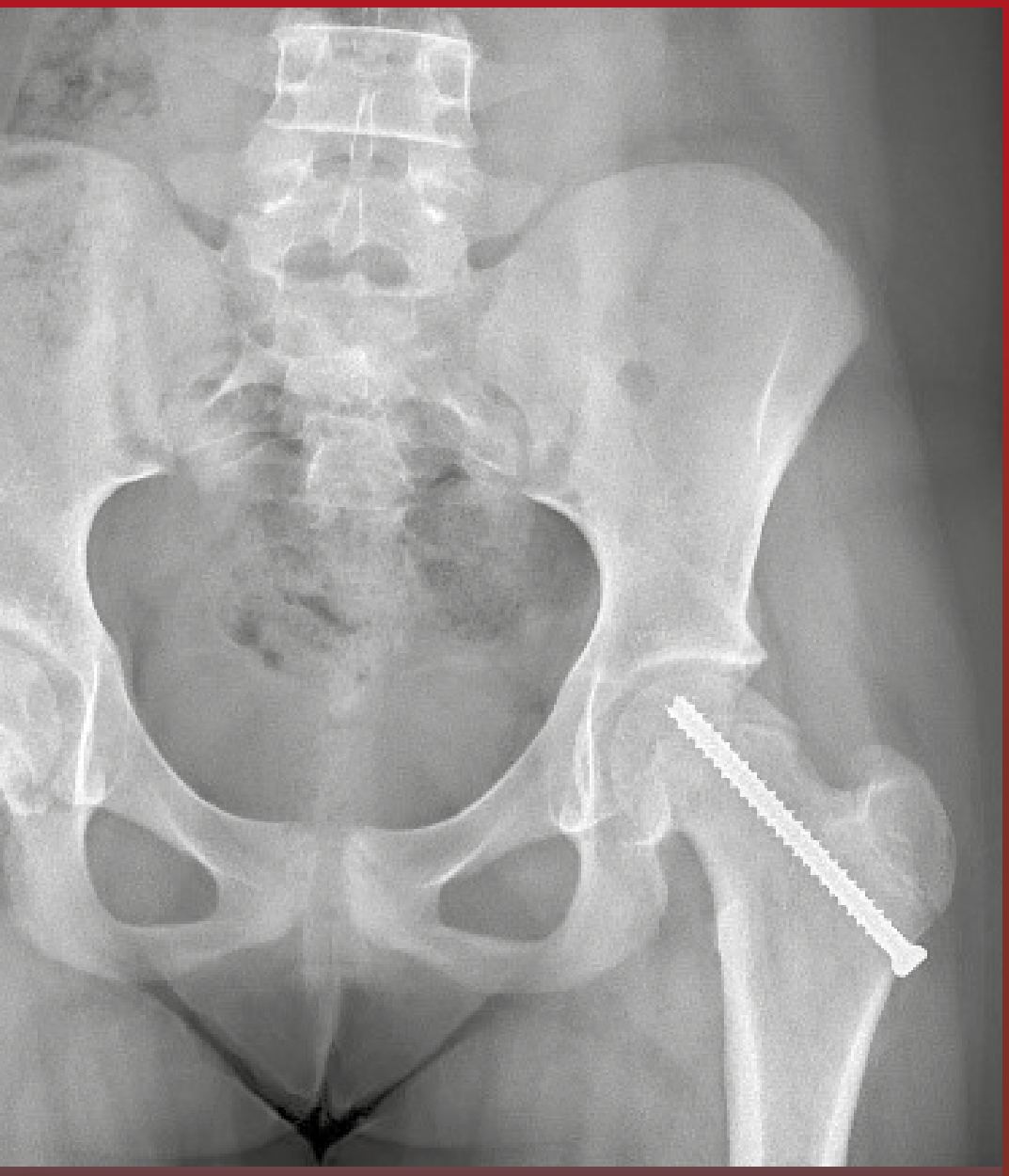

Articles

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Paediatric Cochrane Corner

Focus on Symptoms

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Editorial

The Winter issue concludes not only the year 2019 but also puts a term to the “teens” decade. Although the initial name TBK-JPB (Tijdschrift van de Belgische Kinderarts-Journal du Pédiatre Belge) was replaced by the title BJP (Belgian Journal of Paediatrics) in 2016 the layout and the main aims remained very similar. During these three years we have been lucky to recruit and welcome new young paediatricians, Anne Rochtus, Christophe Chantrain and Stephanie De Rechter who have joined the core of the editorial board. We are grateful to them and consider them as the future of the BJP.

We would like to promote a permanent dialogue with the staff of the different paediatric faculties of our country where the specializing paediatricians are trained in order to incite and encourage them to send manuscripts to our journal as complements to the numerous seminaries held in the different departments. Our secretariat and our editorial board can guide and help them because we consider that the BJP represents the ideal tribune to circulate and inform the paediatric community about the clinical work and also the research studies performed in Belgium.

In the present issue we expect our readers to enjoy the detailed article concerning “Difficult, misleading and atypical clinical presentations of Kawasaki disease”. It describes thoroughly this complicated disease and displays spectacular pictures of the lesions.

The next article “The effect of a rehabilitation program on BMI and pulmonary function in youngsters with CF” stresses the importance of the rehabilitation program to cope with the increasing number of CF patients reaching adulthood. As they live longer than a few decades ago they need cautious and rigorous support.

Another article “Pulmonary embolism: about two paediatric observations” concerns a rare pathology of the respiratory tract, often underestimated in children. It focuses on specific paediatric risk factors that should be recognized in order to establish the currently lacking standard paediatric guidelines.

The MIB is devoted to “Innovation in monitoring and treatment of nephropathic cystinosis” a sound rationale for a PhD thesis.

Our traditional paediatric Cochrane corner concerns “Faster growth comes with increased risks of severe bowel problems when using formula rather than donor breast milk in preterm or low birth weight infants” highlights the pros and cons of formula instead of donor breast milk in low birth weight preterm infants and the necessary caveats due to the threatening development of necrotizing enterocolitis.

An interesting enquiry studies the “Differences in empathy between Flemish paediatricians and surgeons” using the Jefferson Scale of Physician Empathy (JSE). As could be expected paediatricians with a longer relationship with their patients score higher than surgeons. In any case it is noteworthy that physicians caring for children need (and express) a more empathic behaviour than those caring for adult patients.

The section “Focus on symptoms” illustrates a largely underdiagnosed problem “Slipped capital femoral epiphysis: think about it!”. This article prompts us to renew the section “the surgeon’s corner” because we believe that paediatricians (and general practitioners) should benefit from better awareness of these symptoms that can aggravate the outcome when misdiagnosed.

Hoping you will enjoy the reading, the editorial board of the BJP is committed to pursue its efforts to improve the scientific quality of this review and wishes to our readers joyful last days of the current year and a very happy New year 2020.

Samy Cadranel and Marc Raes

Uw vragen of commentaar
Vos questions ou commentaires

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Difficult, misleading and atypical clinical presentations of Kawasaki disease.

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Key words

Kawasaki disease, mucocutaneous lymph node syndrome, clinical presentation, incomplete Kawasaki disease, atypical Kawasaki disease

Abstract

The diagnosis of Kawasaki disease is essentially made clinically and based on well-defined criteria that, in the classical form, are fairly well recognizable by an alert clinician. There are however difficult, misleading and atypical presentations of Kawasaki disease in which the clinical criteria, although present, are more difficult to recognize and where a high index of suspicion is needed to make the diagnosis. All these presentations share the risk of late diagnosis and increased rate of development of coronary artery aneurysms, the most feared complication. In this article we provide an overview of clinical features of these unusual forms in the hope that this can contribute to the timely recognition and decrease of complications. This article only deals with the clinical aspects and does not address treatment.

Introduction

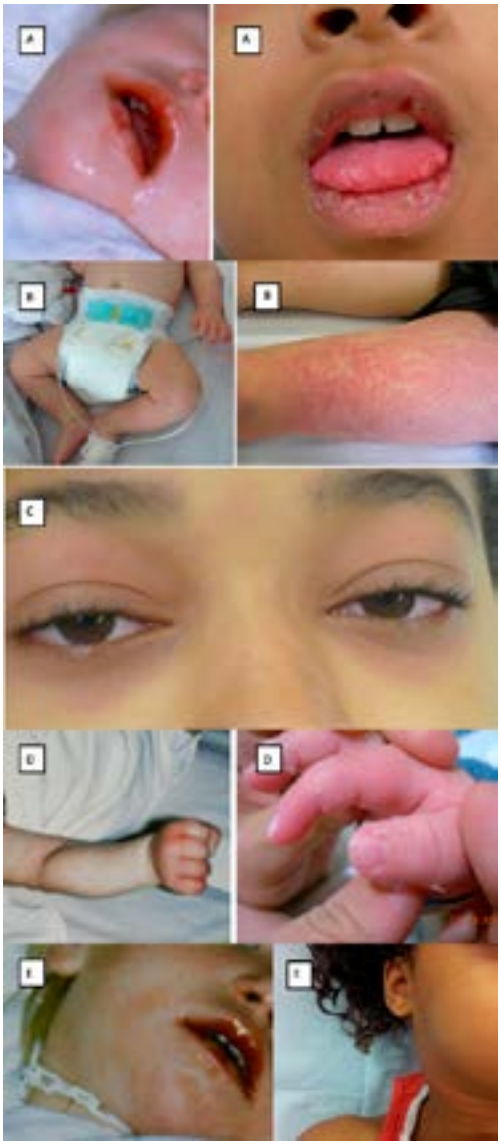
Kawasaki disease (KD) is the second most common vasculitis of childhood affecting medium-sized arteries, with a predilection for coronary arteries. The peak incidence is between 6 months and 5 years. The etiology is unknown. However, the most common hypothesis is an infectious cause in a genetically susceptible individual, although no single agent has been identified formally [1].

The diagnosis is essentially clinical and is based on well-defined criteria [2]. These are: fever without any explanation lasting at least 5 days plus at least 4 of the five following criteria ('major signs'): lip/oral mucous membrane changes (present in 90% of the cases), polymorphous rash (present in 70-90%), bilateral not exudative bulbar conjunctival injection (present in 75-90%), peripheral extremity changes (present in 68-98%) and cervical lymphadenopathy (present in 25-75%) (figure 1). According to the last guidelines the diagnosis can be accepted at day 4 if fever and at least 4 criteria are present. A number of symptoms and signs are not part of the criteria but support the diagnosis, including: irritability, diarrhea, cough, early perineal desquamation, reactivation at BCG (Bacillus Calmette-Guerin) inoculation site, orange-brown chromonychia, joint pain, arthritis, aseptic meningitis, anterior uveitis, cotton wool retinal exudate and cardiac findings such as tachycardia, gallop sounds, myocardial dysfunction, pericardial effusion and coronary artery dilatation. Supporting laboratory findings are increased CRP (C-reactive protein), leukocytosis, hypo-albuminemia, abnormal liver tests, sterile pyuria, hyponatremia and thrombocytosis (³ 450000/µl after 7 days).

The natural course of the disease has 3 stages: an acute febrile stage lasting +/- 12 days, a subacute stage associated with the potential development of coronary artery aneurysms lasting +/- 2 weeks, and a convalescent stage lasting +/- 6 weeks.

The most feared complication and the most determinative for the long-term evolution is the development of coronary artery aneurysms (CAA). CAA develop in 20% of the untreated children with KD. This risk is reduced 5-fold if high-dose intravenous immunoglobulin (IVIG) is administered within 10 days of fever onset [3]. Timely diagnosis is therefore of paramount importance. Most pediatricians are probably sufficiently familiar with the signs and symptoms described above to make a prompt diagnosis in case of classical presentation. However, there are many difficult, misleading and atypical clinical presentations of KD. All these presentations share the risk of late diagnosis and increased development of CAA. In this article we intend to provide an overview of these less common presentations, and use clinical cases to illustrate the challenges faced by clinicians. The focus of this article is on clinical aspects; therapeutic aspects will not be discussed.

Figure 1: oral mucous membrane changes (A), polymorphous rash (B), bilateral not exudative bulbar conjunctival injection (C), peripheral extremity changes (D) and cervical lymphadenopathy (E).



Difficult presentations

Kawasaki disease shock syndrome

A 4-year-old boy was admitted in a regional hospital with high fever for 4 days, severe tonsillitis, cervical lymphadenitis (unilateral) and abdominal pain. Therapy with clarithromycin was started (because of suspected penicillin allergy).

*On day 5 he appeared more ill and complained of abdominal pain in the right fossa. At clinical examination there was tenderness and voluntary guarding. CT-scan (computerized tomography) of the abdomen was suggestive for acute appendicitis. Appendectomy was performed but the appendix did not appear inflamed. Blood examination showed: sodium 132 mEq/l, CRP (C-reactive protein) 130 mg/l, leukocytes 29.3*10E9/l with 25.64*10E9/l neutrophils.*

On day 6 fever and abdominal pain persisted and he developed profuse bloody diarrhea; piperacillin-tazobactam was started. All cultures, taken at this point, remained negative.

On day 7 he was transferred. At clinical examination he appeared ill. Weight 16.7 kg, height 107 cm, blood pressure 92/38 mm Hg. Hands and feet were swollen. He had a strawberry tongue. There was a bilateral conjunctivitis. Gallop rhythm was heard at heart auscultation. Echocardiography revealed dilatation (4 mm) and hyperechogenic aspect of the left anterior coronary artery and moderate myocardial dysfunction. The diagnosis of KD was thus made. IVIG (2 mg/kg) was given and acetylsalicylic (50 mg/kg/day) started.

On day 8 fever persisted. He still had abdominal pain and had developed dyspnea. His blood pressure was 76/40 mm Hg. X-ray of the chest showed pleural effusion and pneumonic infiltrates (figure 2). CT-scan of the abdomen revealed ascites (figure 3). The albumin concentration in blood was 1.6 g/dl. He was transferred to the pediatric intensive care unit.

On day 9 his general condition was better after receiving albumin infusion and diuretics. However, fever persisted. A second dose of IVIG (2 mg/kg) was given and methylprednisolone (2 mg/kg/day) was started. The fever subsides after 12-24 hours and is general condition began to improve. On day 11 desquamation of the skin of fingers and toes appeared.

Cardiac follow-up 4 years later shows a normal heart function and no coronary abnormalities.

Kawasaki disease shock syndrome (KDSS) is a severe presentation of KD and defined as sustained presence of any of the following conditions: systolic hypotension for age or a decrease in blood pressure ≥ 20% from baseline (not related to IVIG administration) or clinical signs of poor perfusion (prolonged capillary refill, tachycardia, cold extremities, oliguria, change in level of consciousness). The incidence is about 5%. All KDSS occur in the acute febrile stage of KD (10-12 days). Some patients present with KDSS, some develop it shortly after initial presentation.

Our case illustrates several of the features of KDSS that are described in the literature [4-6].

KDSS is a severe form of KD and is often associated with unusual presentations or complications of KD (45.6% of the patients in the study of Gamez-Gonzalez et al.). The majority presents with shock and gastro-intestinal symptoms including abdominal pain, vomiting, diarrhea, gastro-intestinal bleeding, acute abdomen, hepatitis and gall bladder hydrops, pancreatitis. But other atypical presentations are not rare: pulmonary symptoms (pneumonia, pleural effusion), retropharyngeal edema, neurologic alterations (aseptic meningitis, encephalopathy), renal involvement (proteinuria and nephrotic syndrome, renal failure), macrophage activation syndrome, disseminated intravascular coagulation, orchitis.

KDSS is a form of distributive shock with severe inflammation and capillary leakage. Inflammatory markers in blood are significantly elevated. Thrombocytopenia is frequent and a risk factor for more severe forms. Hyponatremia is frequent.

Half of the cases of KDSS is resistant to the first dose of IVIG.

Cardiac abnormalities are more frequent in KDSS and up to 65% develop CAA. Misdiagnosis as septic shock and particularly as toxic shock syndrome (TSS) is frequent. There are overlapping features between KDSS and TSS: fever, conjunctivitis, rash, subcutaneous edema, gastro-intestinal symptoms, renal and liver disorders. However, there are some differences: younger age, lower hemoglobin, higher platelet count, echocardiographic abnormalities (table 1) [7]. Gall bladder hydrops is also typical for KD.

Neonatal Kawasaki disease

Neonatal disease is a very rare form of KD (0,02% of all patients with KD) that often presents as incomplete disease and with atypical laboratory features in

Table 1: differences between KDSS and TSS (Lin et al.)

	KDSS	TSS
Age	36.8 +/- 41.1 months	113.3 +/- 56.6 months
Hemoglobin age adjusted Z-scores	-1.88 (95% CI -3.9 to 3.9)	0.89 (95%CI -6.4 to 10.3)
Median platelet count	312*10E9/l (116-518)	184.5*10E9/l (31-629)
Echocardiographic abnormalities	Typical coronary involvement and valvulitis	

Figure 2: case 1, X -ray of the chest: right sided pleural effusion; right suprahilar and infrahilar pneumonic infiltrates, retrocardial pneumonic infiltrate

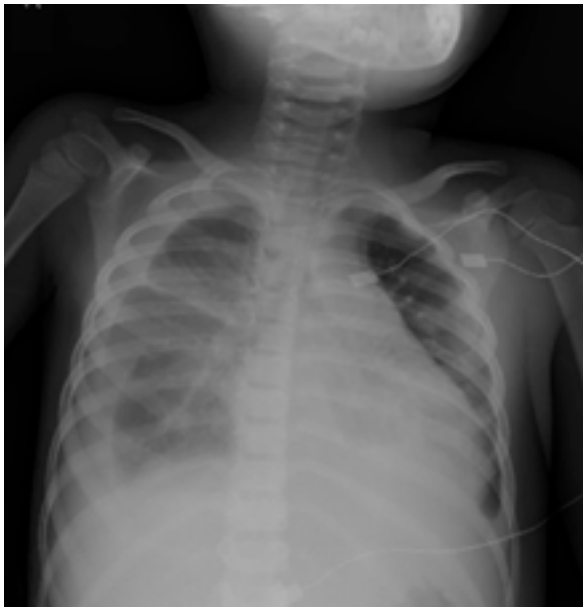
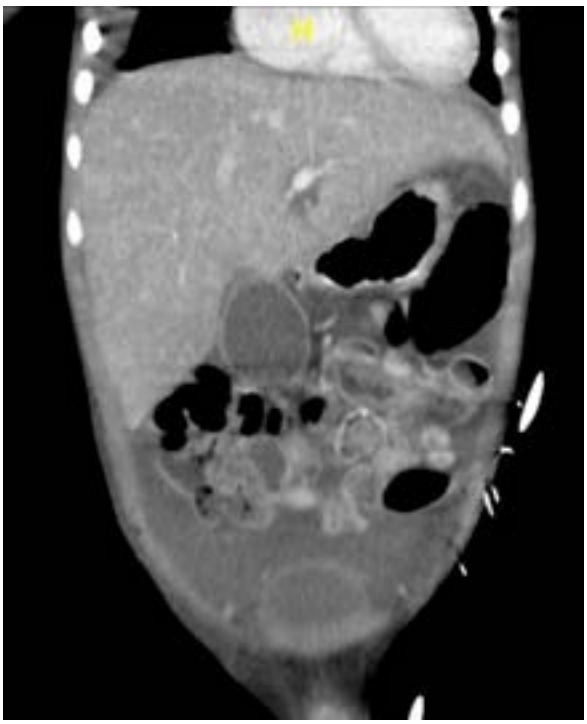


Figure 3: case 1: CT-scan of the abdomen revealing important ascites



the acute phase [8]. 16 cases ≤ 28 days of age were described in the literature review by Altammar et al. 75% presented as incomplete disease. 3 presented within 5 days of life without prolonged fever but with CAA. Fever duration was less than 5 days in 47%. Rash was present in 81%, extremity changes in 81%, oral changes in 63%, conjunctivitis in 31%; none had lymphadenopathy. CRP was normal in the acute phase in 43% and 27% had thrombocytopenia. 56% had cardiac complications.

Although neonatal KD is rare, the frequency and consequences of the cardiac complications warrant to include it in the extensive differential diagnosis of febrile illness in neonates and to consider it in febrile neonates who fail to respond to antibiotics.

Incomplete Kawasaki disease

Incomplete KD is defined as prolonged fever of at least 5 days but less than 4 major clinical signs, and the presence of laboratory features or echocardiographic findings compatible with KD [2,9,10]. About 75% have fever and 3 major signs, 25% have fever and 2 signs. Data on the frequency of occurrence of incomplete KD vary in the literature from 6.8% to 76% of all KD cases, depending on age and inclusion criteria. On average it can be estimated that an incomplete form occurs in about 1 out of 5 cases. Incomplete KD occurs at all ages but infants < 12 months and older children > 9 years are more likely to present with incomplete forms.

Complete and incomplete forms differ only in the number of clinical signs at presentation but the laboratory and coronary findings are similar (figure 4). Most patients with incomplete KD present with conjunctival injection, polymorphous rash and lip/oral mucosa changes, but many lack extremity changes and cervical lymphadenopathy.

The main difficulty and worry concerning incomplete KD is the risk of misdiagnosis leading to potential delay in treatment and increased risk of developing CAA. A longer duration of time between symptom onset and diagnosis, a delay of administration of IVIG within 10 days after onset of fever and a significant increase in coronary artery disease have all been described. A high level of suspicion is needed and the diagnosis of incomplete KD should be considered strongly in every infant or child with unexplained fever, fewer than 4 of the major clinical signs and typical laboratory and echocardiographic findings. It has to be kept in mind that incomplete disease can also present as atypical disease, as described below.

Misleading presentations

Scattered presentation of major clinical signs

A 2-year old boy was seen with fever up to 39° C since a few hours and a truncal and abdominal rash. The retained diagnosis was urticaria.

*On day 3 he was presented again for fever, diarrhea, rash and conjunctivitis. At clinical examination an acute otitis media was diagnosed. Blood examination: CRP 83 mg/l; white blood cell count 17.1*10E9/l with 84.5% segmented neutrophils; thrombocytes 541*10E9/l; sedimentation rate 69 mm/hour.*

Fever and conjunctivitis persisted on day 4 and 5. The mother described that he was 'swollen' on day 5. However, a physician was not consulted.

*On day 6 he was seen again because of persistent fever. Clinical examination however was normal. Blood examination: CRP 113 mg/l; white blood cell count 12.4*10E9/l; thrombocytes 374*10E9/l; alanine aminotransferase 92 U/l. X-ray of the chest was normal.*

Fever persisted and on day 8 redness of the tongue and conjunctivitis again was observed by the mother.

On day 9 he presented in the emergency department with fever and redness of the tongue. Finally, the diagnosis of KD was made. IVIG and acetylsalicylic acid were given, but unfortunately at first echocardiography on day 10 coronary artery aneurysms were seen. After 4 years of follow-up there is still a limited dilatation of the left coronary artery.

A schematic representation of the clinical course is shown in figure 5.

Scattered presentation has been described in only 1 article from Denver, Colorado, by Anderson et al. [11]. Dispersion of symptoms and signs over time causes delay in diagnosis. Often another initial diagnosis is made and more than 1 visit is needed before correct diagnosis. Sometimes more time passes until the clinical criteria are met.

In addition, our case illustrates another causes of deceit. Clinical manifestations of KD can be short-lived or come and go and not all are manifest at any given time. This can lead to a delay in diagnosis. A detailed anamnesis and thorough clinical examination are of absolute importance.

Misleading skin presentations

A polymorphous rash is one of the cardinal signs of KD and is present in 70-90% of the patients. The rash is often maculopapular or scarlatiniform and involves the trunk and extremities, often with perineal accentuation [12]. Desquamating perineal erythema is characteristic for KD [13]. However, the rash is variable and can manifest in a misleading way. Psoriasiform, micropustular and

Figure 4: percentage of presenting clinical signs in complete and incomplete KD (Manlhiot et al. and Perrin et al.)

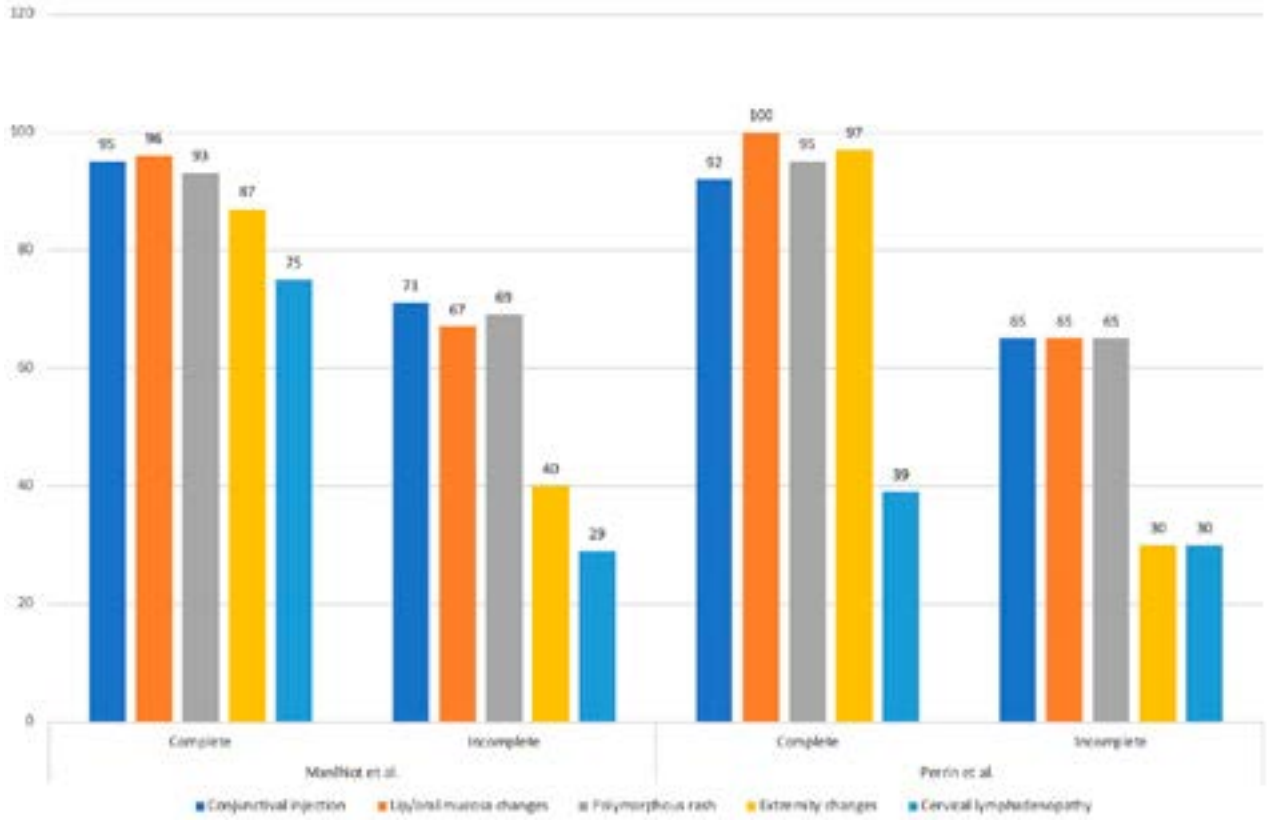
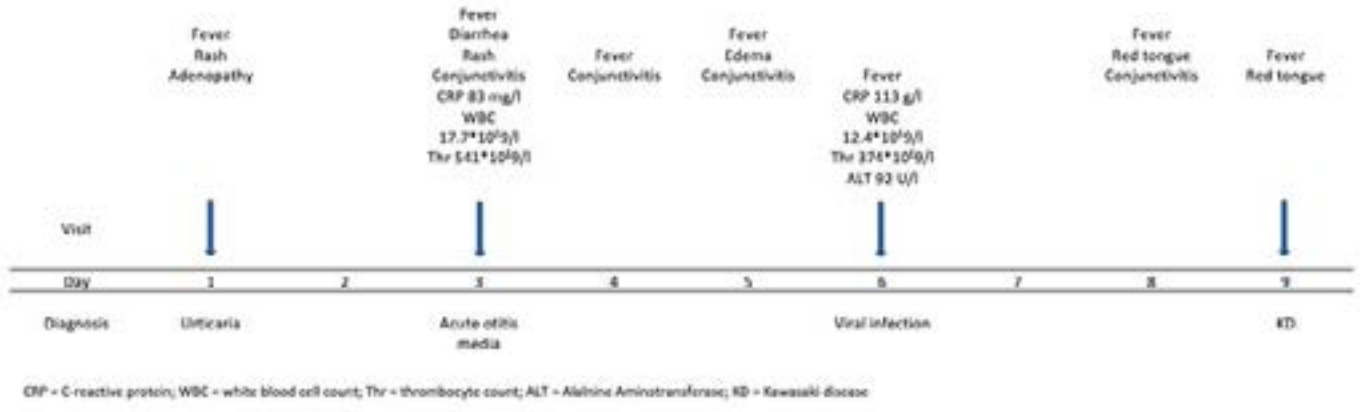


Figure 5: : schematic representation of the clinical course of case 2



acrodermatitis-like rash have been described [14,15]. Psoriasis has been described in at least 33 patients with KD, mostly in the subacute or convalescent stage, but 5 times in the acute phase, as psoriatic plaques or pustules [16].

A 5-year-old girl was referred with non-remitting high fever (up to 41°) and sore throat for 6 days. She was treated with amoxicillin. Since 1 day she had watery diarrhea and a diffuse rash.

At clinical examination there was a marked irritability, fever, edema of the hands, feet and eyelids and exanthema consisting of flat, red annular macules and patches on the arms, legs and trunk, some with concentric color changes suggesting erythema multiforme (figure 6). We had a high suspicion of KD but the differential diagnosis was erythema multiforme (EM). On day 7 she had red, swollen and cracked lips and conjunctivitis. Meanwhile we found reports of KD exanthema presenting as EM in the literature [17,18]. IVIG (2 g/kg) and acetylsalicylic acid were started. The fever subsided after 1 day. Echocardiography was normal. On day 16 there was peeling of the fingertips and toes.

The exanthema evolved in a special way to iris lesions on day 12 and erythema marginatum on day 14 (figures 7 and 8).

Although EM is less common in young children and usually has a much milder course than KD, the unusual exanthema may be confusing and cause delay in diagnosis.

Cellulitis like rash is another misleading skin presentation. Nonbacterial cellulitis is a rare presenting sign; axillary, inguinal and orbital cellulitis have been reported in the literature [19-21].

A 2-year-old boy developed fever, pain and redness under the left axilla 6 days after the beginning of chickenpox. At clinical examination there was also a scarlatiniform eruption on the legs. Blood examination revealed a CRP of 278 mg/l, hyponatremia of 128 mmol/l and a Streptococcus pyogenes bacteremia (the evolution of the most significative laboratory results is shown in figure 9). Antibiotherapy with intravenous penicillin and clindamycin was started. On day 2 the subaxillar region was swollen and painful. Ultrasonography revealed subcutaneous inflammation and embedded enlarged lymph nodes. As the fever and swelling persisted despite intravenous antibiotherapy he was transferred on day 5. Antibiotics were switched to vancomycin and piperacillin-tazobactam. Despite continued antibiotherapy, there was persisting high fever until day 13 and from day 13 to 17 intermittent fever spikes and normal temperature. The axillar swelling remained unchanged (figure 10). Ultrasonography of the chest wall remained unchanged; there were no signs of fasciitis. Ultrasonography of the liver was done because of increased gamma-GT (gamma-glutamyl-transpeptidase) and revealed cholecystitis. On day 13 peeling of the fingertips was observed. Echocardiography was normal. Because of persisting fever and incomplete but suggestive signs of KD, and after much hesitation, IVIG were given on day 17. Day 18 was the last day with fever. The axillar swelling started to decrease on day 19.

This case is certainly open to discussion, but we think that we initially missed the diagnosis of KD. Varicella and streptococcal infection have both been associated with KD and do not exclude the disease [22-24]. Although a number of classical signs are missing, or have been overlooked, there are arguments for (incomplete) KD: persisting fever under antibiotherapy and fall of fever after IVIG, the cellulitis and its non-evolutive course, the scarlatiniform rash limited to the legs, severe inflammatory markers, thrombocytosis, hyponatremia, involvement of the gall bladder, peeling of the fingertips.

Figure 6: case 3, day 6, maculae and patches some with concentric color changes

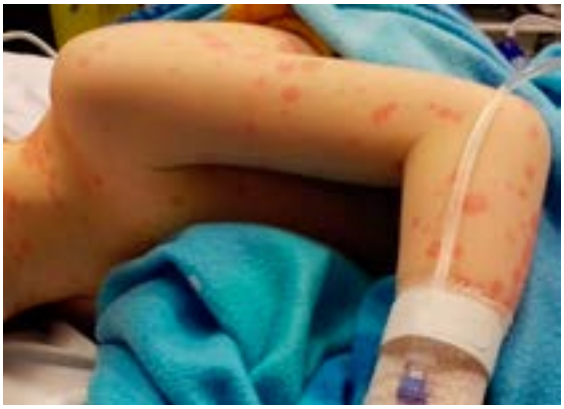


Figure 7: case 3, day 12, iris lesions

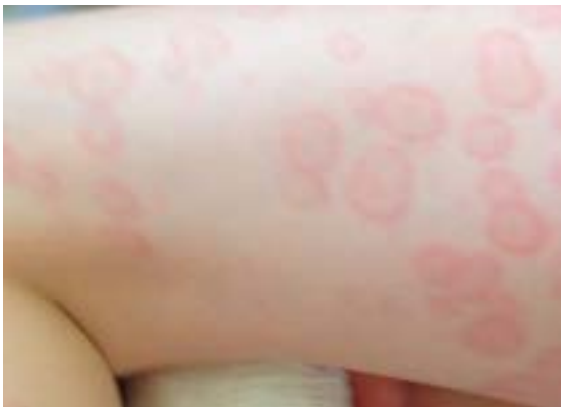


Figure 8: case 3, day 14, erythema marginatum

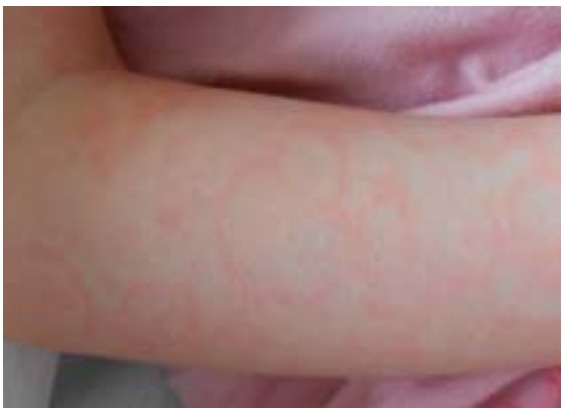
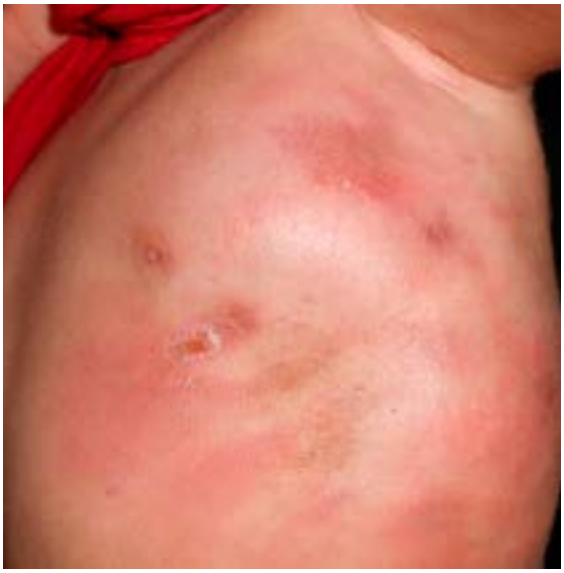


Figure 9: case 4, most significative laboratory results

	Day 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 16
Hb (g/l)	10		88,3		8			7,8			7,2	10,3	11,8			9,8
WBC (*10E9/l)	14,3		14,8		18,9			20,9			21,3	26,1	34			36,9
Thr (*10E9/l)	593		541		266			485			770	925	1145			1002
Sed (mm/hr)											100					135
CRP (mg/l)	27,8		25,5		25,7			64,2			44,7	43,2	47,7			40,3
Na (mmol/l)	128		129		136											
AST (U/l)	100		53		80			79			84	92	71			74
ALT (U/l)	75		55		54			82			83	88	83			85
yGT (U/l)	18		44		54			301			402	441	422			345
alb (g/l)			15,8					20			21	22				27

Hb = hemoglobin; WBC = white blood cell count; Thr = thrombocyte count; Sed = sedimentation rate; CRP = C-reactive protein; Na = natrium (sodium); AST = aspartate aminotransferase
ALT = alanine aminotransferase; yGT = gamma-glutamyl transpeptidase; alb = albumin

Figure 10: case 4, axillar cellulitis



Kawasaki disease presenting without fever

Presentation of KD without fever is very rare and a real conundrum. We have found 9 cases in the literature [25-28]. All cases were younger than 3 years. 2 children had 4 major signs, 2 had 3, 4 had only 2 signs, and 1 child was asymptomatic at presentation (only a new heart murmur was detected for which echocardiography was performed and a coronary artery aneurism was diagnosed). All cases developed CAA. It is curious that the guideline of the American Heart Association describes fever as an indispensable sign while the Japanese guideline gives equal weight to fever and the other major symptoms [28].

Atypical (unusual) presentations

Atypical KD is defined as classic or incomplete disease with evidence of other organ involvement and unusual symptoms for KD. The incidence of atypical presentation has been estimated around 3.5% of the KD cases [29]. As described above, KDSS is often associated with an atypical presentation. Persistent fever notwithstanding treatment is a common feature of all atypical forms and a clue to KD. Moreover, all patients develop major signs of KD, in a complete or incomplete way.

Atypical gastro-intestinal presentations include cholestatic jaundice, gall bladder hydrops, hepatitis, pancreatitis, intestinal pseudo-obstruction, bowel edema, hemorrhagic duodenitis, severe colitis, intussusception, appendicular vasculitis or histologically confirmed appendicitis [30-39]. In case 1 we have described a 4-years-old boy with KDSS presenting as appendicitis. In a recent review intestinal pseudo-obstruction was the most frequent form occurring in 65% of the children with gastro-intestinal involvement [40]. A recent retrospective review study in Italy demonstrated that presenting gastro-intestinal features are associated with higher risk of delayed treatment, IVIG resistance and the development of CAA [41].

Atypical respiratory presentations involving upper or lower airways have been described.

Retropharyngeal inflammation is the most frequently described upper respiratory tract presentation in the literature. Patients present with high fever, neck pain, torticollis, drooling. Computed tomography or magnetic resonance imaging show low density areas or edema and inflammation. Both clinically and with imaging, the presentation is initially indistinguishable from retropharyngeal cellulitis [42,43]. However, there is no improvement with antibiotics. Moreover, in cases where surgery has been performed no abscess could be found. All cases improve only after treatment with IVIG. As these children might be treated by ear-nose-throat specialists, less familiar with KD than pediatricians, KD mimicking retropharyngeal abscess could be an important pitfall for misdiagnosis.

Presentations with exudative tonsillitis and unilateral peritonsillar swelling mimicking peritonsillar abscess were also described [44,45].

An 8-month-old girl was admitted in the hospital with persistent high fever (40-41°) since 5 days, cough, wheezing and worsening respiratory distress. There was no response to antibiotic therapy (amoxicillin-clavulanate). Clinical examination: tachypnea and dyspnea, oxygen saturation 90%. X-ray of the chest: upper right lobe pneumonia. Blood examination: CRP 64 mg/l, hemoglobin 8.2 g/dl, normal white blood cell count, normal thrombocyte count. Urine examination: pyuria. Blood culture and urine culture remained negative. Despite antibiotic switch to cefotaxime intravenously there was no change in fever and clinical condition. It was noticed that she was markedly irritable. On day 8 she had red lips and tongue and cervical lymphadenopathy. On day 9 the lips were crackled and there was indurated edema of the hands and feet. KD was highly suspected. IVIG (2 g/kg) were given. 24 hours later there was no fever and her general condition cleared up. Echocardiography on day 11 showed no coronary abnormalities. On day 13 peeling of the fingertips and toes was seen; the thrombocyte count was 983000; X-ray of the chest showed disappearance of the infiltrate.

KD presenting as non-resolving pneumonia has been described in a few case reports [46-50]. Pleural effusion is a rare but possible pathology at presentation or during the acute phase of the disease [51,52]. Pulmonary involvement is perhaps less rare than generally thought. Umezawa et al. retrospectively reviewed 129 children with KD who had a chest X-ray in the acute phase of the disease; abnormal X-ray findings were found in 19 (14.7 %). Observed abnormalities were reticuloglandular pattern in 89.5 % of these 19 children, peribronchial cuffing in 21.1 %, pleural effusion in 15.8 %, atelectasis in 10.5 % and air trapping in 5.3 % [53].

Atypical neurological presentations: central nervous system involvement is rare in KD, apart from aseptic (lymphocytic) meningitis. Neurological complications have generally been described during the subacute stage especially cranial nerve pathology such as facial nerve palsy, abducens palsy or sensorineural hearing loss. Nevertheless, facial palsy, vertical gaze palsy, subdural effusion and stroke have been described during the acute febrile stage [54-57].

Atypical kidney and urinary tract presentations: sterile pyuria is not uncommon in KD; incidences from 29,5 to 79,8 % are reported in the literature [58-60]. Fever and (sterile) pyuria, without any other sign of KD have been described as sole initial presentation [61]. Pyuria often consists of mononuclear cells and originates in the urethra, bladder or kidney. But pyuria in KD is not always sterile. In a cohort study of 285 children with KD, 10 (3,5 %) had a culture-

proven bacterial urinary tract infection (8 with pyuria, 2 without) [59]. Thus, finding a urinary tract infection does not exclude KD. Suspicion is warranted in children with persisting fever despite treatment with antibiotics.

Although uncommon, acute kidney injury (AKI), defined as a serum creatinine level ³ 1,5 times the upper limit for age, has been reported in KD. In a recent literature review 39 children who developed AKI with KD were identified [62]. Prerenal as well as renal mechanisms of AKI have been described. Hypovolemia by gastro-intestinal losses and acute heart failure causing prerenal AKI were reported. Described renal causes include tubulo-interstitial nephritis, hemolytic uremic syndrome, acute nephritic syndrome, nephrotic syndrome, intrinsic AKI associated with KDSS and immune complex mediated nephropathy.

Other rare presentations or complications: Macrophage activation syndrome (MAS) has been described at presentation as well as a complication of KD [63-66]. The diagnosis is complicated by a significant overlap between KD and MAS. Laboratory testing is crucial for the diagnosis of MAS showing peripheral blood cytopenia, hypertriglyceridemia, hypofibrinogenemia, increased ferritin, elevated soluble CD25 (soluble IL-2 receptor alpha) and hemophagocytosis in bone marrow.

- Coombs positive hemolytic anemia has been described at presentation of KD [67]. More frequently reported is hemolysis as complication of IVIG treatment [68].
- There are 2 reports of simultaneous occurrence of Henoch-Schönlein vasculitis and KD [69,70].
- KD has been described in children with neuroblastoma in a few publications and it is hypothesized that this might be a paraneoplastic phenomenon [71-73].

Conclusion

The diagnosis of Kawasaki disease is essentially clinical and is classically based on well-defined criteria. However, the clinical presentation can be difficult, misleading or atypical; this increases the risk of late diagnosis and complications. Apart from incomplete disease (1/5 cases) and Kawasaki disease shock syndrome (1/20 cases), these presentations are rare and diagnosis can be unclear and difficult. A high index of suspicion is needed when fever persists despite therapy. Additional clinical signs and laboratory findings may support the diagnosis. But the most important is echocardiographic examination. The presence of coronary artery abnormalities, myocardial dysfunction or pericardial effusion are acceptable to confirm the diagnosis. However, a normal echocardiogram, particularly early in the disease, does not exclude the diagnosis of Kawasaki disease. In any case, if echocardiography cannot be performed or is negative, treatment with high-dose intravenous immunoglobulin should not be delayed.

This article gives a fairly complete overview of these less common forms (7 reviews, 15 studies and 51 case reports have been included in the references) and aims to increase the clinical index of suspicion for unusual forms.

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NIEUW: PAMPERS® AQUA PURE BABYDOEKJES

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

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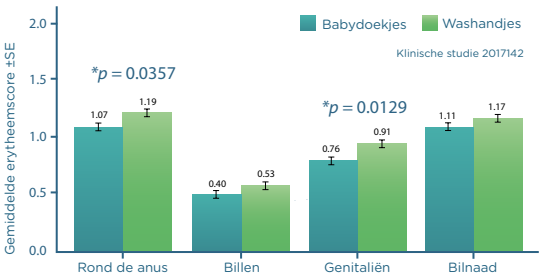
Gemiddelde erytheemscore per meetplaats



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European Society for Pediatric Dermatology

Goedgekeurd door ESPD

The effect of a rehabilitation program on BMI and pulmonary function in youngsters with cystic fibrosis.

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Key words

rehabilitation, cystic fibrosis, nutrition therapy, exercise, physical education and training

Abstract

Introduction: Cystic fibrosis (CF) is a chronic disease leading to progressive pulmonary function deterioration and malnutrition. A good nutritional status measured as body mass index (BMI), is strongly associated with pulmonary function. Nutritional and respiratory treatments are used to increase longevity. Treatments are, however, time-consuming and often difficult to combine with daily life routines. In an effort to intensify treatment, residential interventions at the rehabilitation center "Zeepreventorium, De Haan" are often used to improve pulmonary function and nutritional status.

Objectives and methods: This pilot study evaluates the impact of a 4-week residential rehabilitation program on BMI and pulmonary function in young adult CF patients, comparing patients with and without malnutrition (BMI<18,5). Patients were included after informed consent and received respiratory physiotherapy and supervised physical activity. Physical activity was measured using a SenseWear armband. Caloric and macronutrient intake were calculated based on a weighed intake diary. Patients received pulmonary function testing and were weighed and measured on admission and before discharge.

Results:

Seventeen patients (12/5 male/female, 26 (21-24) years old) were included. The number of patients with BMI < 18,5 kg/m2 reduced from 7 (41%) to 4 (23.5%). There was a significant increase in BMI (median 19,3 (18,4- 21,2) kg/m2 to 20,2 (18,4-21,2) kg/m2, p< 0,001). Pulmonary function also improved: FEV1 + 1 (-2-15) % predicted (p 0,032); FVC + 4,2 (± 7,1) % predicted (p 0,027).

Conclusion:

The short rehabilitation program consisting of respiratory and nutritional therapy as well as physical exercise significantly increased weight and BMI and improved pulmonary function.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis

transmembrane conductance regulator (CFTR) gene[1]. CF affects a variety of organs, including lungs, pancreas, intestine and hepatobiliary tract[1]. Although vastly improved in the last decades, CF patients still have a significantly lower life expectancy compared to healthy peers[2]. Main survival determining factors are, low forced expiratory volume in one second (FEV1), chronic *Pseudomonas Aeruginosa* colonization and nutritional status[3].

A good nutritional status defined as a body mass index (BMI) ≥ 23 kg/m^2 or ≥ 22 kg/m^2 for respectively male and female patients, is associated with a better longevity[1]. A high caloric diet associated with pancreatic enzyme replacement therapy (PERT) and fat-soluble vitamins are the corner stones of nutritional therapy in CF[1,4].

In an attempt to maintain the pulmonary function, patients are treated with regular physiotherapy and inhalation therapy several times a day[5]. Oral, intravenous or inhaled antibiotics are often necessary to treat pulmonary exacerbations or chronic infections. These treatments are time consuming and adherence is an issue as in many chronic diseases[6]. Finally, CF patients are also advised to be physically active, which can be a challenge when facing declining pulmonary function[7]. Treatments in hospital setting are often unavoidable, however they cannot give the complete treatment as described above.

Rehabilitation centers like "Zeepreventorium, De Haan" combine a homey atmosphere with intensified respiratory and nutritional therapy but also aim at improving physical condition with daily supervised physical activity. The aim of this pilot study is to assess the impact of a 4-week residential rehabilitation program on BMI and pulmonary function in young adult CF patients and to evaluate response differences according to nutritional status.

Materials and methods

Participants:

The present study is an interventional, one sample study with a pre-post study design in adult CF patients entering a rehabilitation program in "Zeepreventorium, De Haan", a medical rehabilitation center for children and young adults with chronic illnesses.

On admission CF patients are separated into groups according to colonization and are either separated in space (Pseudomonas Aeruginosa positive or negative) or time (Achromobacter Xylosoxidans positive or negative) in order to prevent new colonization. Inclusion criteria were: adult patients (>18 years) with genetically proven CF diagnosis admitted for a minimum of 4 weeks with the purpose of improving lung function and/or body mass between November 2016 and November 2017. Exclusion criteria were: absence from the rehabilitation center for more than 2 consecutive days during the stay and use of anabolic steroids.

Measurements:

On admission, a Teen/Adult Cystic Fibrosis Questionnaire-Revised (CFQ-R) was used to assess quality of life. A SenseWear Pro3 Armband (SWA) was used to measure exercise intensity during 5 days in the first week of admission. This accelerometer has a good agreement with indirect calorimetry for physical activity in adult CF patients[8]. Obtained results were number of steps, total energy expenditure (TEE), activity intensity expressed as metabolic equivalent of task (MET) and duration of different activity levels.

On admission and after 4 weeks of rehabilitation anthropometric measurements and pulmonary function were measured by the same operator. Patients were weighed with a digital scale (minimal difference 0.1 kg) and measured using a wall-mounted stadiometer (Harpenden) (minimal difference 1 mm). BMI (kg/m^2) was calculated. Patients were classified as malnourished if their BMI was ≤18,5 kg/m^2.

Static and dynamic spirometry was performed, to measure FEV1 and forced vital capacity (FVC) (Bodybox 5500 ®, Hypair compact ®, Medisoft). FEV1 is expressed as absolute value (liters) and as % of reference, FVC is expressed as % of reference. Zapletal references were used for patients below and ERS references for patients above 20 years old. The protocol used for pulmonary function testing was based on the European Respiratory Society guidelines[9].

The rehabilitation intervention:

During the residential rehabilitation program, a multidisciplinary team, consisting of a pneumologist, dietician, psychologist, a social worker and several physiotherapists, guided the patients. The rehabilitation was focused on weekdays. During the weekend most patients went home with the exception of the first weekend.

Patients received autogenic drainage therapy and aerosol treatment 2-3 times/day with help of trained physiotherapists (1 - 1.5 h/session). They had daily 1-hour lasting physical training sessions consisting of swimming and fitness training. Intensity of training was adjusted to capabilities and oxygen need during exercise.

A dietary plan was made, aiming at the theoretical energy needs calculated using the Schofield formula. During rehabilitation, caloric and macronutrient intake was calculated based upon weighed nutrition intake by a dietician of 2 days/week. Pancreatic enzyme replacement therapy (PERT) (Creon®) was given to all pancreatic insufficient patients based upon patients' habits and adjusted to current guidelines[1] and/or eventual abdominal complaints. There were 4 patients with cystic fibrosis related diabetes (CFRD), all treated with insulin. They received the same dietary adjustments as non-diabetic patients and their insulin dose was adjusted accordingly.

Statistics and ethics:

Data were analyzed using SPSS statistics 25. Results were described as median with interquartile range between brackets. Differences were analyzed using non-parametric Wilcoxon Rank or Mann-Whitney U test or Chi-square in case of categorical results. The level of significance was $p < 0.05$.

The study was approved by the Ethics Committee of the Ghent University Hospital (code: B670201734695).

Results

Clinical status on admission:

Nineteen out of 46 available residents met the inclusion criteria. Reasons for exclusion were short stay (< 4 weeks) (n=26) and steroid use (n=1). Nineteen adults (14 males, 5 females) agreed to participate after informed consent. Of them 2 male patients were excluded due to rehabilitation interruption (hospitalization (n=1), stop rehabilitation (n=1)). Four patients (24%) experienced pulmonary exacerbation during admission, which was defined as pulmonary symptoms needing antibiotic treatment and/or associated with decreased lung function, but continued the program.

All clinical parameters on admission are described in table 1. The median age of participants was 26 (21-34) years, FEV1 49 (33-65)% predicted and median BMI 19.3 (18.4-21.2) kg/m^2. Seven patients (41%) were malnourished (BMI<18.5 kg/m^2) at start of the program. Malnourished patients were comparable with well-nourished patients on most clinical items. They had of course a significantly lower weight and BMI, as this was the selection criterium, but also a poorer pulmonary function (FEV1% predicted (p 0.043)) and were more frequently colonized (p 0.044). Patients with Achromobacter colonization had a significantly lower BMI than non-colonized patients (p 0.016). The difference in BMI between Pseudomonas colonized and non-colonized patients was not significant.

Quality of life and physical activity:

The quality of life measured by the CFQ-R scored lower than the healthy population on every item but there were no differences in quality of life according to nutritional status (data not shown).

Results of the SWA worn by patients in the first 5 days of admission are shown in table 2. Malnourished patients were significantly less active resulting in a significantly lower TEE (p 0.043), less moderate intensity physical activity (3-6 MET) (p 0.043) and fewer steps per day (p 0.014).

Dietary intervention:

The actual caloric intake during rehabilitation was significantly lower than theoretical energy needs calculated according to Schofield but higher than the measured TEE (table 2). The median fat intake, expressed as % of total energy intake (EN%) was 29 EN% (27-31), and median protein intake was 17 EN% (15-18). The malnourished subgroup had no significant difference in calculated energy needs nor actual caloric intake compared to the well-nourished group. They had, however, a significantly lower fat intake (p 0.033) which was compensated by a higher carbohydrate intake (p 0.007). All patients with CFRD (n=4) were in the well-nourished group. Carbohydrate intake between patients with and without CFRD was not significantly different (p 0.66).

Malnourished patients had a higher energy excess when energy intake was compared with SWA measured energy expenditure.

Effect of the rehabilitation program:

The effect of the rehabilitation program on pulmonary function and nutritional status is summarized in table 3. The rehabilitation program resulted in a significant increase of 2.2 (±1.6) kg body mass (p 0.0001) and of 0.7 (±0.5) kg/m^2 BMI points (p 0.0001) (figure 1). The number of malnourished patients reduced from 7 (41%) to 4 (23.5%). BMI increased significantly in both the malnutrition and non-malnutrition group.

Pulmonary function improved after 4 weeks of rehabilitation (FEV1 + 1 (-2-15) % predicted (p 0.032); FVC + 4.2 (± 7.1) % predicted (p 0.027)). Pulmonary function did not improve in the malnutrition group. In the non-malnutrition group only FVC% predicted significantly increased.

Discussion

This pilot study evaluates the effect of a short rehabilitation program - including intensive respiratory therapy, physical exercise training and a high caloric diet- on pulmonary function and nutritional status in young adult CF patients. Patients with and without malnutrition, defined as a BMI below 18.5 kg/m^2, were compared to evaluate differences in response to the rehabilitation intervention.

The study population was different from the general adult CF population reported in the Belgian CF registry since there was a male predominance (70%) and patients had a worse nutritional status and pulmonary function although pseudomonas colonization was comparable[10]. CF has an important impact on quality of life[11, 12]. In contrast to the literature there was no significant difference in quality of life according to nutritional status[12]. Since the CFQ-R was only performed on admission we have no idea about the impact of the rehabilitation program on quality of life.

The intensive rehabilitation program reduced the number of malnourished patients from 7 (41%) to 4 (24%). A significant improvement in nutritional status (BMI) and pulmonary function (FEV1% predicted, FVC% predicted) was observed as a result of the program. The small subgroups analysis, however, only reached significance for the BMI. There was no improvement of pulmonary function in the malnutrition group. In contrast, there was numerical improvement of FEV1 (absolute value and % predicted) and a significant improvement of FVC% predicted in the non-malnutrition group. Possibly significance was not reached in this group because the spread for pulmonary function was too large. Three of the 7 malnourished patients (43%) experienced pulmonary exacerbation during rehabilitation which could have influenced the lack of improvement in pulmonary function in this group.

There was a large energetic deficit when theoretical energy needs, calculated according to the Schofield equation, were compared with the actual intake. Since there was significant gain in BMI despite increased physical activity, the caloric intake had to be sufficient. The Schofield equation has been shown to overestimate REE compared to indirect calorimetry in underweight females[13]. When comparing the SWA measured TEE with the actual registered intake, there was an energy excess making weight gain possible. As could be expected malnourished patients were less physically active compared to their well-nourished peers. This inactivity, which is probably a result of a worsening pulmonary function, can contribute to muscle mass loss.

The dietary intake was very close to the advised intake for patients with CF although fat intake was lower than the recommended 35-40 EN%[1]. Protein has been recently recognized as an important nutrient in CF to maintain fat free (muscle) mass[14,15]. The absolute protein intake in this study was 2.2 g/kg body weight, which is way above the 0.996 g/kg body weight recommended for chronic inflammation[16] and in contrast to the study of White et al. where 72% of adult patients didn't comply with the guidelines concerning protein intake[17]. There was a significantly lower carbohydrate intake in well-nourished patients compared to malnourished patients. Since all the patients with CFRD (n=4) were well-nourished this could influence the carbohydrate intake of this

group. However, carbohydrate intake was not significantly different between patients with and without diabetes. It cannot be excluded that gastro-intestinal digestive problems influenced the lower fat and higher carbohydrate intake in the malnourished group.

This small pilot study has several limitations. There might be an important selection bias as patients seeking residential support may experience more difficulties adhering to therapy in the home situation. The patients included were generally in a worse condition compared to the adult CF patients in the registry[10]. The effect of the rehabilitation program might be different in male and female patients and as the majority of our patients were male this may influence the results. The absence of a control population further weakens the study.

Future research should include larger patient groups and evaluate the duration of the intervention effect once the patient returns home. Research into the type of weight gain being fat mass or fat free mass is also necessary.

In conclusion, pulmonary function and nutritional status improved significantly after a short rehabilitation program consisting of respiratory and nutritional therapy associated with physical exercise in young adult CF patients.

Figure 1: Effect of the rehabilitation program on BMI

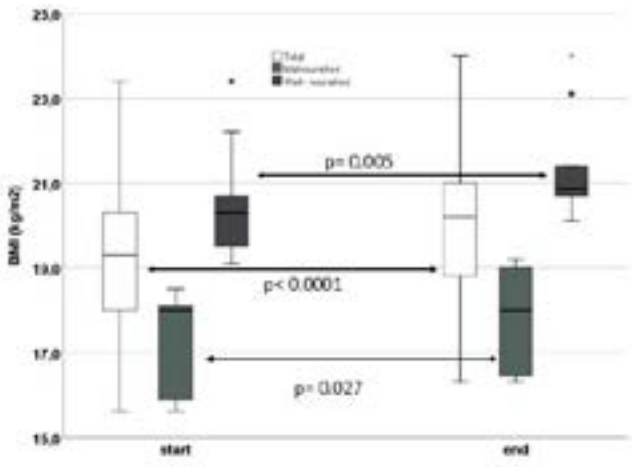

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Table 1: Patient characteristics on admission
Results are given as median (interquartile range) or number and % of population.
Significant differences are in bold.

		All patients (n= 17)	Malnutrition (n= 7)	Non-malnutrition (n= 10)	p-value
Age (yrs)		26 (21-24)	21 (19-36)	28.4 (23.2-34)	0.536
Sex	Male	12 (71%)	5 (71%)	7 (70%)	1
Pancreatic insufficiency		15 (88%)	6 (86%)	9 (90%)	1
Cystic fibrosis related diabetes		4 (24%)	0 (0%)	4 (40%)	0.103
Colonization	*Pseudomonas* +*	7 (41%)	3 (43%)	4 (40%)	**0.044**
	Achromobacter +*	5 (29%)	4 (57%)	1 (10%)	
Nutritional status					
- **BMI (kg/m^2)**		19.3 (18.4-21.2)	18 (15.7-18.2)	20.3 (19.4-21)	**<0.0001**
- **Height (m)**		1.74 (1.62-1.77)	1.71 (1.58-1.76)	1.75 (1.63-1.78)	0.669
- **Body weight (kg)**		56,9 (45.7-62.6)	44.4 (43.6-56.2)	61.2 (54.8-68)	**0.023**
Pulmonary function					
- **FEV1% predicted**		49 (24-76)	36 (29-47)	53.5 (47.2-71)	**0.043**
- **FVC% predicted**		65 (61.5-80.5)	65 (47-80)	73 (61.8-82)	0.364
Oxygen need during night or day		2 (12%)	1 (14%)	1 (10%)	1
Tube feeding at night		3 (18%)	2 (29%)	1 (10%)	0.537
Pulmonary exacerbation		4 (24%)	3 (43%)	1 (10%)	0.25

Abbreviations: BMI: body mass index, FEV1% predicted: forced expiratory volume in 1 second as % of reference, FVC% predicted: forced vital capacity as % of reference
* Clarification: *The Pseudomonas* positive patients mentioned are *Achromobacter* negative. *Achromobacter* positive patients could either be Pseudomonas positive or negative but these results are not shown.

Table 2: Results of dietary intake and physical activity/day measured by SWA
Results are given as median (interquartile range). Significant differences are in bold.

	All patients (n= 17)	Malnutrition (n= 7)	Non-malnutrition (n= 10)	p-value
Schofield theoretical E need	3192 (2751-3403)	3157 (2315-3192)	3344 (2847-3548)	0.07
Dietary intervention				
- **Energy intake (Kcal)**	2775 (2258-3470)	2597 (2396-3599)	2828 (2179-3454)	0.813
- **Fat (EN%)**	29 (27-31)	28 (25-29)	30 (28-35)	**0.033**
- **Carbohydrate (EN%)**	52 (50-54)	54 (52-58)	50 (47-53)	**0.007**
- **Protein (EN%)**	17 (15-18)	17 (13-18)	17 (16-19)	0.669
- **Protein (g/kg body weight)**	2.2 (1.7-2.7)	2.3 (1.8-2.8)	2.1 (1.5-2.5)	0.536
SWA				
- TEE	2527 (1921-3002)	2307 (1669-2527)	2830 (2267-3174)	**0.043**
- Moderate intensity PA	1:57 (1:16-2:23)	1:20 (0:34-2:00)	1:59 (1:51-2:54)	**0.043**
- Number of steps	6745 (4344-8543)	4206 (3475-7431)	8243 (6260-9405)	**0.014**
Energy difference intake				
Vs Schofield	-362 (-582- -79)	-180 (-560- 308)	-433 (-750- -155)	0.161
Vs SWA	472 (-43- 580)	543 (289- 1071)	291 (-381- 502)	**0.043**

Abbreviations: E: energy, EN%: Energy%, SWA: SenseWear armband, TEE = total energy expenditure, PA: physical activity.

Table 3: BMI, body composition and lung function on admission and at end of program
Results are given as median (interquartile range). Significant differences are in bold.

		Admission	End of program	p-value**
BMI (Kg/m^2)	All patients (17)	19.3 (18.4- 21.2)	20.2 (18.4-21.2)	**<0.0001**
	Malnutrition (7)	18 (15.7-18.2)	18 (16.4-19.2)	**0.027**
	Non-malnutrition (10)	20.3 (19.4-21)	20.9 (20.6-21.8)	**0.005**
	p-value*	**<0.0001**	**0.001**	
FEV1% predicted	All patients (17)	49 (24-76)	55 (35.5-68)	**0.032**
	Malnutrition (7)	36 (29-47)	36 (28-51)	0.141
	Non-malnutrition (10)	53.5 (47.2-71)	60.5 (54.5-74.5)	0.122
	p-value*	**0.043**	0.05	
FEV1 (L)	All patients (17)	2.02 (1.15-2.38)	2.11 (1.2-2.69)	0.097
	Malnutrition (7)	1.19 (1.13-2.02)	1.21 (1.16-2.2)	0.204
	Non-malnutrition (10)	2.12 (1.73-2.61)	2.29 (1.83-2.76)	0.283
FVC% predicted	All patients (17)	65 (61.5-80.5)	78 (63.5-85.5)	**0.028**
	Malnutrition (7)	65 (47-80)	64 (44-83)	0.446
	Non-malnutrition (10)	73 (61,8-82)	80 (70.8-88)	**0.041**
	p-value*	0.364	0.098	

*Significance of differences between malnourished and non-malnourished, **Significance of differences before and after program expressed as p-value.
Abbreviations: BMI: body mass index, FEV1% predicted: forced expiratory volume in 1 second as % of reference, FEV1: forced expiratory volume in 1 second in liters, FVC% predicted: forced vital capacity as % of reference

DÉNOMINATION DU MÉDICAMENT: HEMANGIOL 3,75 mg/ml, solution buvable. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** 1 ml de solution contient 4,28 mg de chlorhydrate de propranolol correspondant à 3,75 mg de propranolol base. Liste des excipients : Hydroxyéthylcellulose, Saccharine sodique, Arôme fraise (contient du propylène glycol), Arôme vanille (contient du propylène glycol), Acide citrique monohydraté, Eau purifiée. Excipient à effet notoire : 1 ml de solution contient Propylène glycol 2,60 mg. **FORME PHARMACEUTIQUE :** Solution buvable. Solution buvable limpide, incolore à légèrement jaune, avec une odeur fruitée. **INDICATIONS THERAPEUTIQUES :** HEMANGIOL est indiqué dans le traitement des hémangiomes infantiles prolifératifs nécessitant un traitement systémique : Hémangiomes entrainant un risque vital ou fonctionnel, Hémangiomes ulcérés douloureux et/ou ne répondant pas à des soins simples, Hémangiomes avec un risque de cicatrices permanentes ou de défiguration. Le traitement doit être instauré chez les enfants âgés de 5 semaines à 5 mois (voir rubrique 4.2 du RCP complet). **POSOLOGIE ET MODE D'ADMINISTRATION :** Le traitement doit être instauré par un médecin expérimenté dans le diagnostic, le traitement et la prise en charge des hémangiomes infantiles, dans un environnement clinique contrôlé dans lequel des installations adéquates pour la prise en charge des réactions indésirables, y compris celles nécessitant des mesures d'urgence, sont disponibles. Posologie : La posologie est exprimée en propranolol base. La dose initiale recommandée est de 1 mg/kg/jour, répartie en deux prises séparées de 0,5 mg/kg. Il est recommandé d'augmenter la dose jusqu'à la dose thérapeutique, sous surveillance médicale, de la manière suivante : 1 mg/kg/jour pendant 1 semaine, puis 2 mg/kg/jour pendant 1 semaine, puis 3 mg/kg/jour en dose d'entretien. La dose thérapeutique est de 3 mg/kg/jour, administrée en 2 prises séparées de 1,5 mg/kg, le matin et en fin d'après-midi, avec un intervalle d'au moins 9 heures entre deux prises. HEMANGIOL doit être donné pendant ou juste après un repas pour éviter le risque d'hypoglycémie. Si l'enfant ne mange pas ou vomit, il est recommandé de ne pas administrer la dose. Si l'enfant recrache une dose ou ne prend pas tout le médicament, il convient de ne pas lui administrer une autre dose et d'attendre la dose suivante prévue. Au cours de la phase de titration, chaque augmentation posologique doit être réalisée sous surveillance médicale dans les mêmes conditions que pour l'administration de la dose initiale. Après la phase de titration, la dose sera réajustée par le médecin en fonction de l'évolution du poids de l'enfant. Une surveillance clinique de l'état de l'enfant et un réajustement de la posologie doivent être effectués au moins une fois par mois. Durée du traitement : HEMANGIOL doit être administré pendant une période de 6 mois. L'arrêt du traitement ne nécessite pas de diminution progressive de la dose. Chez la minorité de patients qui présentent une rechute des symptômes après l'arrêt du traitement, celui-ci peut être réintroduit dans les mêmes conditions avec une réponse satisfaisante. Populations pédiatriques : En l'absence de données d'efficacité clinique et de sécurité, HEMANGIOL ne doit pas être utilisé chez le nourrisson âgé de moins de 5 semaines. Il n'y a pas de données d'efficacité et de sécurité dans les essais cliniques menés avec HEMANGIOL permettant de recommander l'instauration d'un traitement par HEMANGIOL chez le nourrisson et l'enfant âgé de plus de 5 mois. Enfants insuffisants hépatiques ou rénaux : En l'absence de données, l'administration du produit n'est pas recommandée chez l'enfant insuffisant hépatique ou rénal (voir rubrique 4.4 du RCP complet). Mode d'administration : Voie orale. HEMANGIOL doit être administré directement dans la bouche de l'enfant à l'aide de la seringue pour administration orale graduée en mg de propranolol base fournie avec le flacon de solution buvable (voir les instructions d'utilisation à la rubrique 3 de la notice). Le flacon ne doit pas être agité avant utilisation. Si nécessaire, le médicament peut être dilué dans une petite quantité de lait pour bébé ou de jus de pomme et/ou d'orange adapté à l'âge de l'enfant. Le produit ne doit pas être versé dans un biberon plein. Le mélange peut être effectué avec une cuillérée à café (environ 5 ml) de lait pour les enfants pesant jusqu'à 5 kg ou avec une cuillerée à soupe (environ 15 ml) de lait ou de jus de fruit pour les enfants pesant plus de 5 kg et administré dans un biberon. Le mélange doit être utilisé dans un délai de 2 heures. HEMANGIOL et le repas doivent être donnés par la même personne afin d'éviter le risque d'hypoglycémie. Si plusieurs personnes sont impliquées, une bonne communication est essentielle pour garantir la sécurité de l'enfant.**CONTRE-INDICATIONS :** Prématuré n'ayant pas atteint l'âge corrigé de 5 semaines (l'âge corrigé étant calculé en soustrayant le nombre de semaines de prématurité de l'âge réel) • Nouveau-né allaité par sa mère traitée par des médicaments contre-indiqués avec le propranolol • Hypersensibilité à la substance active ou à l'un des excipients • Asthme ou antécédent de bronchospasme • Blocs auriculo-ventriculaires des second et troisième degrés • Maladie du sinus (y compris bloc sino-auriculaire) • Bradycardie au-dessous des limites suivantes : Age : Fréquence cardiaque (battements/min) – 0-3 mois :100 – 3-6 mois : 90 – 6-12 mois : 80 • Hypotension artérielle au-dessous des limites suivantes : Age : Pression artérielle (mm Hg) – 0-3 mois: 65/45 – 3-6 mois : 70/50 – 6-12 mois : 80/55• Choc cardiogénique • Insuffisance cardiaque non contrôlée par un traitement • Angor de Prinzmetal • Troubles artériels périphériques sévères (syndrome de Raynaud) • Enfants prédisposés à l'hypoglycémie • Phéochromocytome. **EFFETS INDESIRABLES :** Résumé du profil de tolérance : Dans les essais cliniques conduits dans les hémangiomes infantiles prolifératifs, les effets indésirables les plus fréquemment rapportés chez les enfants traités par HEMANGIOL ont été des troubles du sommeil (16,7%), des infections respiratoires majorées telles que bronchite et bronchiolite associées à une toux et une fièvre, des diarrhées (16,5%) et des vomissements (11,5%). Globalement, les effets indésirables rapportés au cours du programme d'autorisation temporaire d'utilisation et dans la littérature ont été des hypoglycémies (et les événements associés tels que des crises convulsives hypoglycémiques) et des infections respiratoires majorées associées à une détresse respiratoire. Liste tabulée des effets indésirables : Le tableau suivant présente les effets indésirables rapportés, quelles que soient la dose et la durée du traitement, dans trois études cliniques conduites chez 435 patients traités par HEMANGIOL à la dose de 1 mg/kg/jour ou de 3 mg/kg/jour sur une durée maximale de traitement de 6 mois. La fréquence des effets indésirables est définie en utilisant la convention suivante : très fréquent (≥ 1/10) ; fréquent (≥ 1/100 à < 1/10) ; peu fréquent (≥ 1/1000 à < 1/100) ; rare (≥ 1/10 000 à < 1/1000) ; très rare (< 1/10 000) ; fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Compte tenu de la taille de la base de données des essais cliniques, les catégories Rare et Très rare ne sont pas représentées. Au sein de chaque classe de systèmes d'organes, les effets indésirables sont présentés par ordre décroissant de gravité. **Infections et infestations :** Très fréquent : Bronchite. Fréquent : Bronchiolite. **Troubles du métabolisme et de la nutrition :** Fréquent : Diminution de l'appétit. **Affections psychiatriques :** Très fréquent : Troubles du sommeil. Fréquent : Agitation, Cauchemars, Irritabilité. **Affections du système nerveux :** Fréquent : Somnolence. Fréquence indéterminée : Crise convulsive hypoglycémique. **Affections cardiaques :** Peu fréquent : Bloc AV. Fréquence indéterminée : Bradycardie. **Affections vasculaires :** Fréquent : Extrémités froides. Fréquence indéterminée : Hypotension artérielle, Vasoconstriction, Syndrome de Raynaud. **Affections respiratoires, thoraciques et médiastinales :** Fréquent : Bronchospasme. **Affections gastro-intestinales :** Très fréquent : Diarrhées, Vomissements. Fréquent : Constipation, Douleur abdominale. **Affections de la peau et du tissu sous-cutané :** Fréquent : Erythème, Erythème fessier. Peu fréquent : Urticaire, Alopécie. Fréquence indéterminée : Dermatite psoriasiforme. **Investigations :** Fréquent : Diminution de la pression artérielle. Peu fréquent : Diminution de la glycémie, Diminution de la fréquence cardiaque, Neutropénie. Fréquence indéterminée : Agranulocytose, Hyperkaliémie. Description d'effets indésirables sélectionnés : Concernant les infections des voies respiratoires inférieures telles que la bronchite ou la bronchiolite, une aggravation des symptômes (y compris de bronchospasme) a été observée chez des patients traités par HEMANGIOL en raison de l'effet bronchoconstricteur du propranolol. Ces effets ont dans de rares cas conduit à l'arrêt définitif du traitement (voir rubrique 4.4 du RCP complet). Les troubles du sommeil recouvrent l'insomnie, un sommeil de mauvaise qualité et l'hypersomnie. Les autres affections du système nerveux central ont principalement été observées en début de traitement. Des diarrhées ont été fréquemment rapportées sans être systématiquement associées à une maladie gastro-intestinale infectieuse. La survenue de diarrhées semble dose-dépendante entre 1 et 3 mg/kg/jour. Aucun cas n'a été d'intensité sévère et n'a conduit à l'arrêt du traitement. Les événements cardiovasculaires rapportés au cours des études cliniques ont été asymptomatiques. Lors des 4 heures de surveillance cardiovasculaire réalisée pendant les jours de titration, une diminution de la fréquence cardiaque (d'environ 7 bpm) et de la pression artérielle systolique (< 3 mm Hg) a été observée après l'administration du médicament. Un cas de bloc cardiaque auriculo-ventriculaire du second degré chez un patient avec des troubles de la conduction sous-jacents a entraîné l'arrêt définitif du traitement. Des cas isolés de bradycardie symptomatique et d'hypotension artérielle ont été rapportés dans la littérature. Les baisses de la glycémie observées au cours des études cliniques ont été asymptomatiques. Toutefois, plusieurs cas d'hypoglycémie associée à une crise convulsive hypoglycémique ont été rapportés au cours du programme d'autorisation temporaire d'utilisation et dans la littérature, notamment en cas de jeûne lors d'une maladie concomitante (voir rubrique 4.4 du RCP complet). Le traitement concomitant par corticoïdes systémiques peut majorer le risque d'hypoglycémie (voir rubrique 4.5 du RCP complet). Une hyperkaliémie a été rapportée dans la littérature chez quelques patients avec un hémangiome ulcéré étendu (voir rubrique 4.4 du RCP complet). Déclaration des effets indésirables suspectés: La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration. Belgique : Agence fédérale des médicaments et des produits de santé, Division Vigilance, EUROSTATION II, Place Victor Horta, 40/ 40, B-1060 Bruxelles, Boîte Postale 97 B-1000 Bruxelles Madou, Site internet: www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be, Luxembourg : Direction de la Santé – Division de la Pharmacie et des Médicaments, Allée Marconi – Villa Louvigny, L-2120 Luxembourg, Fax : +352 2479 5615, E-mail : pharmacovigilance@ms.etat.lu, Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ :** Pierre Fabre Dermatologie 45 place Abel Gance F- 92100 Boulogne. **NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ :** EU/1/14/919/001. **DATE DE MISE À JOUR DU TEXTE :** 01/2019. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne du médicament http://www.ema.europa.eu.). **MODE DE DELIVRANCE :** Médicament soumis à prescription médicale.

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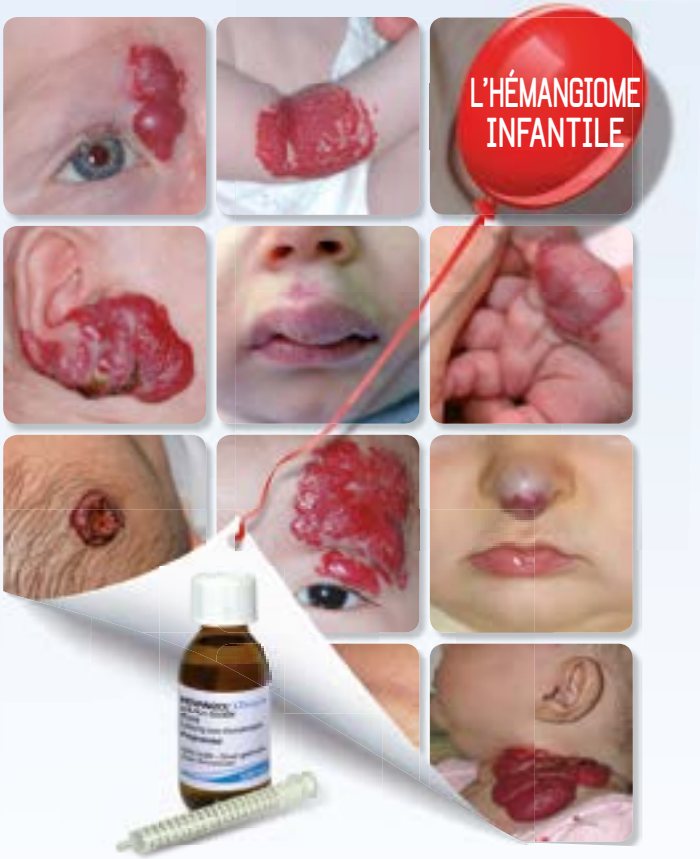

La seule et unique solution pédiatrique orale approuvée pour l'hémangiome infantile[2]

20190206 - 08/2019

Pierre Fabre
DERMATOLOGIE

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

Differences in empathy between Flemish paediatricians and surgeons

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Key words

physician empathy, surgeon, paediatrician, Jefferson Scale of Physician Empathy

Abstract

Background Physician empathy is a strong driver for patient satisfaction. It was previously suggested that some specialists are more empathic than others. The aim of this study is to challenge the dogma that surgeons are less empathic than paediatricians.

Methods We sent out an online survey based on the Jefferson Scale of Physician Empathy (JSE). The intended test groups comprised 40 Flemish physicians, 20 surgeons and 20 paediatricians

Results Seventeen surgeons and twenty paediatricians responded to the survey. The paediatricians scored higher on the JSE than surgeons. The odds ratio of male paediatricians scoring higher on the JSE than male surgeons was 1.61 (p=0.013), whereas female paediatricians scored higher than female surgeons (OR=1.81, p=0.003).

Conclusion The findings of this study suggest that females or paediatricians still score higher on the empathy scale than males or surgeons. The difference in empathy between different specialties and genders is, however, smaller than in previous older studies.

Introduction

Physician empathy is a strong driver for patient satisfaction [1,2]professional, and empathy data were collected during 2013-2015 from Cleveland Clinic Health System physicians prior to participation in mandatory communication skills training. Empathy was assessed using the Jefferson Scale of Empathy. Data were also collected for seven measures (six provider communication items and overall provider rating. Indeed, empathic care is becoming the cornerstone of health care, in each medical specialization. In the last couple of years, attention to communication skills and the importance of the doctor-patient relationship in medical studies has increased. The traditional paternalistic model has changed into a system where patients become partners of their doctors in decision-making of their own healthcare management[3] . The CanMEDS framework was introduced in 1996, with 'the communicator' as one of the seven roles, which focusses mainly on the interaction between physicians and their patients, including patients' families[4] . The implementation of this framework in medicine studies has led to an increased focus on empathy and communication competencies.

Despite the fact that empathic skills are required in all types of clinical specialties in order to establish a proper relationship with their patients, it was previously suggested that some specialists (e.g. paediatricians) are more empathic than others (e.g. surgeons)[1,5–8]its measurement properties, and group differences in empathy scores. Method: A revised version of the Jefferson Scale of Physician Empathy (with 20 Likert-type items. According to some researchers[9] ,a surgeon is classically stereotyped as a "big, bold, bullish, and a beer swilling rugby fan. Prefers to cut and run, rather than communicate with patients", and a paediatrician as "cute and fluffy, with a permanent smile and a small koala attached to a stethoscope at all times". Moreover, it has been reported in several previous studies that women are more empathic than man[1,7,8]professional, and empathy data were collected during 2013-2015 from Cleveland Clinic Health System physicians prior to participation in mandatory communication skills training. Empathy was assessed using the Jefferson Scale of Empathy. Data were also collected for seven measures (six provider communication items and overall provider rating . The validity of this statement at present remains to be elucidated since meanwhile the focus on communication skills during medical school has increased with the implementation of the CanMEDS roll 'communicator' and early contacts with patients. Also, the male/female ratio is changing over time with more women choosing specialties that were traditionally 'male bastions'.

A person's empathic capacity can be examined by checking his or her ability to imagine or experience the emotions of others[5]. Different methods have been proposed to measure dispositional empathy, which is considered as a person's stable character trait. These include observations in real life scenarios (patient or observer based), questionnaires associated with specific empathy scales ('Jefferson Scale of Physician Empathy')[5,6,10,11], by the identification of bodily maps of human emotion[12] or by facial emotion expression tests[13]. The latter three have the advantage of being available as ready-to-use tests that are not demanding in terms of time and effort.

The aim of this study is to challenge the dogma that surgeons are less empathic than paediatricians. To address this research question, a validated test based on the Jefferson Scale of Physician Empathy (JSE) was used.

Methods

Participants

For this prospective cohort study, volunteers who are actively working in the surgical and paediatric professions (at the UZ Leuven or in regional centres) were recruited.

The intended test groups comprised 20 surgeons (10 males – 10 females) and 20 paediatricians (10 males – 10 females). Group sizes were based on a power calculation where a 10% difference is detected between the two groups (power 80%, alpha 5%). As dispositional empathy has been shown to change during the lifespan, we tested subjects within a 10-year life span (24-34yr) in order to minimize the effects of age[14]. Physicians in other specialties and those who were not competent in understanding Dutch and English were not included.

Empathy scoring system

The JSE, which includes 20 Likert-type items answered on a seven-point scale (1= 'strongly disagree', 7= 'strongly agree')[5,6,10,11]. The additional demographic data that was collected includes specialty, gender, age and years of practice. We encoded all of the data in order to obtain anonymized data sets. We used the Dutch translation of the JSE.

Procedure

After approval by the Research Ethics Committee UZ/KU Leuven (MP006037), we sent out the empathic survey containing the JSE to 40 physicians. The participating physicians received a number, allocated by the principal investigator of this study, to guarantee anonymization. After regular follow-up reminders, and 6 more surveys sent out (a total of 46 surveys), we received a total of 37 completed surveys, representing an 80% response rate.

Statistical analysis

The Shapiro-Wilk test was used to evaluate the normal distribution of the cohorts. The unpaired (two sample) t-test and the Mann Whitney U test were used when appropriate. The JSE Likert-scale data were statistically analysed using ordinal regression. A p-value below 0.05 was considered statistically significant.

Results

This study achieved a final response rate of 80%, which is above the 75% response rate critical for statistical significance[15] .

Gender, age and years of practice

The empathy scores obtained with the JSE were compared between men and woman, using ordinal regression. The female physicians scored higher on the JSE than male physicians. The odds ratio of the female physicians scoring higher on the Likert scale than male physicians was 1.45 (p=0.007; Table 2). No significant difference in age nor years of practice between both groups was found (p=0.6; p=0.6; Table 1).

Specialty comparisons

The empathy scores obtained with the JSE were compared between surgeons and paediatricians using ordinal regression. The paediatricians scored higher on the JSE than surgeons (Table 1). The odds ratio of male paediatricians scoring higher on the Likert scale than male surgeons was 1.61 (p=0.013; Table 3). The odds ratio of the female paediatricians scoring higher on the Likert scale than female surgeons was 1.81 (p= 0.003; Table 4).

Discussion

In this study surgeons were compared, with regard to empathy, with paediatricians to examine if the 'old' stereotypes still stand. Age and gender are significant factors in relation to empathy, for this reason we ensured that the age of the participants had a narrow distribution and that the gender could be studied by inclusion of both in each cohort. The physicians that were included in this study have a median age of 31 years old and median years of practice of 6. Because of their significant number of years of practice, these physicians can be regarded as representative examples of their discipline. As empathy is age related[16] , nor the age nor the years of experience could be significantly different between the test groups, which was not the case in our study.

We used the JSE, as it is the most validated test to differentiate empathy between the test groups. The empathy scores obtained with the JSE were significantly different between gender and specialty. The odds ratio of male paediatricians scoring higher on the Likert scale than male surgeons was 1.61 (p=0.013; Table 3). The odds ratio of the female paediatricians scoring higher on the Likert scale than female surgeons was 1.81 (p= 0.003; Table 4). The highest score on the JSE in our study was achieved by a female paediatrician, with a score of 127 and the lowest score by a male surgeon with only a JSE of 93 out of 140. These data suggest that being female and being a paediatrician are both associated with statistically higher scores on the JSE.

Our results are in line with those reported in other studies, where gender and specialty were both statistically significant predictors of empathy[1,5,7,8]professional, and empathy data were collected during 2013-2015 from Cleveland Clinic Health System physicians prior to participation in mandatory communication skills training. Empathy was assessed using the Jefferson Scale of Empathy. Data were also collected for seven measures (six provider communication items and overall provider rating . The first three studies[1,5,6]professional, and empathy data were collected during 2013-2015 from Cleveland Clinic Health System physicians prior to participation in mandatory communication skills training. Empathy was assessed using the Jefferson Scale of Empathy. Data were also collected for seven measures (six provider communication items and overall provider rating also used the JSE to differentiate between gender and specialty. The most recent study[1] included 847 physicians, with median years of practice of 15 and a median age of 49 years old. This is significantly higher than the

Table 1: Median of age, years of practice, the Jefferson Scale of Physician Empathy

	Nr	Age,y median (IQR)	Yop[a] median (IQR)	JSE[b] mean (SD)
Female	18	31.5 (5)	6.5 (3)	115.67 (7.51)
Male	19	31 (3)	6 (3)	111.84 (8.36)
Female surgeons	8	31 (4)	6 (2)	112 (8.64)
Female paediatricians	10	31.5 (7)	7 (4)	118.6 (5.21)
Male surgeons	9	31 (5)	6 (5)	108.56 (9.37)
Male paediatricians	10	32 (4)	7 (3)	114.8 (6.41)

[a] Years of practice
[b] Jefferson scale of physician empathy (maximum score =140)

Table 2: Ordinal regression outcomes between male and female physicians

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Female	.371	.137	7.365	1	.007	.103	.639
Male	0	.	.	0	.	.	.

Odds ratio = $e^{0.371} = 1.45$

Table 3: . Ordinal regression outcomes between male paediatricians and surgeons

	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Male Surgeons	-,476	,191	6,207	1	,013	-,851	-,102
Male Paediatricians	0	.	.	0	.	.	.

Odds ratio = $e^{.476} = 1.61$

Table 4: . Ordinal regression outcomes between female paediatricians and surgeons

	Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Female Surgeons	-,596	,199	8,981	1	,003	-,987	-,206
Female Paediatricians	0	.	.	0	.	.	.

Odds ratio = $e^{.596} = 1.81$

median years of practice (6yrs) and the median age (31yrs) of our included physicians. Thirty-six orthopaedic surgeons were included in the other study with a mean score on the JSE of 115.3, and 20 thoracic surgeons with a mean score of 119.3. Thus, the mean JSE score of the surgeons in total was 116.7, which is higher than the average score on the JSE of 110.2 of our surgeons included (men and women). Fifty-seven paediatricians were included with an average score of 121.6 on the JSE, which is also higher than the 116.7 in our study. Even though the difference between surgeons and paediatricians in this previous study of 4.9 points on the JSE is less than the 6.5 points difference in our study, it is statistically more significant because of the larger group size. The difference between male and female in the previous study was 4.9 points on the JSE, which is comparable, and yet again statistically more significant, to the 3.8 points difference in our study. The highest score on the JSE in the previous study was obtained by the psychiatrists (n=22), with a score of 122.6 on the JSE, and the lowest score by the radiologists (n=68), with a JSE score of 110.7.

A study conducted by the researchers who developed the JSE[5] only found a small, insignificant difference between males and females. They included 78 paediatricians with a mean score of 121.3 on the empathy scale. The surgeons they included (n=122), had a mean score of 117.9. The difference between those groups is 3.4 points on the JSE, which again is smaller than the difference in our study between paediatricians and surgeons. A limitation of this previous study is that age nor years of practice of the included physicians is mentioned. The highest score was obtained by psychiatrists (127) and the lowest by anaesthesiologists (116.1).

A third study[7], compared the JSE of 853 medical students. They differentiated the medical students based on their specialisation preference. The mean JSE score of all the medical students was 109.6. Female (n=470) students obtained a mean score of 111 and male students (n=351) a mean score of 107. Overall these score are much lower than those of the practicing physicians in the other studies. Medical students that were interested in specializing paediatrics scored 112.8, which was the highest mean score of all the specialism preferences. Medical students interested in surgery scored a mean of 105.2 on the empathy scale, which was, with internal medicine, the lowest mean score on the JSE. The overall lower JSE score might be caused by the fact that these medical students have not yet finished their medical study yet, and have no experience in practice, which make the questions on the JSE less relatable.

The difference between surgeons and paediatricians in our study is smaller compared to these previous studies[1,5,7] . This can be explained by the smaller group sizes or the younger age (24-34yr) of the physicians included in our study.

Despite the statistically significant differences between surgeons and paediatricians, one can challenge the old stereotypes of surgeons and paediatricians. Even though a direct comparison between the specialists of the older and younger generation cannot be performed, it seems that the differences between the specialties are not very large. At present, physicians are expected to be empathic in all medical specialties, therefore the gap in empathy between gender and specialty may be becoming smaller.

Limitations

Several limitations were present in our study. First, response bias could have affected the results. The participation of this study has been on voluntary basis. As mentioned above, this study achieved a response rate of 80%. However, it is remarkable that the response rate of the paediatricians (100%), is considerably higher than the response rate of the surgeons (65%). The physicians that did not participate, were 7 male surgeons and 2 female surgeons. The fact that these surgeons chose not to participate can already cause a selection bias in the surgeon cohort, therefore the surgeon group's outcome may be overestimated in this study. Second, the sample size in this study was rather small.

Conclusion.

There is still a difference in empathy between males and females and also between paediatricians and surgeons in Flanders. Yet for the latter the difference may be smaller than before.

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Publieksprijs België	86,52€

Bexsero: het eerste vaccin tegen meningokokken van serogroep B.

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

BEXSERO

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

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL** Bexsero suspensie voor injectie in voorgevulde spuit Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd) - EU/1/12/812/001 Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09 **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING** Een dosis (0,5 ml) bevat: Recombinant ***Neisseria meningitidis*** groep B NHBAfusieeiwit [1, 2, 3] 50 microgram Recombinant ***Neisseria meningitidis*** groep B NadAeiwit [1, 2, 3] 50 microgram Recombinant ***Neisseria meningitidis*** groep B fHbpfusieeiwit [1, 2, 3] 50 microgram Buitenmembraanvesikels (BMV) van ***Neisseria meningitidis*** groep Bstam NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat 2 25 microgram [1] Geproduceerd in ***E. coli*** cellen door recombinantDNAtechnologie [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit) **THERAPEUTISCHE INDICATIES** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door ***Neisseria meningitidis*** groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **DOSERING EN WIJZE VAN TOEDIENING** Dosering **Tabel 1. Samenvatting van de dosering**

Leeftijd bij eerste dosis	Primaire immunisatie	Intervallen tussen primaire doses	Booster
Zuigelingen van 2 tot en met 5 maanden [a]	Drie doses, elk van 0,5 ml	Niet minder dan 1 maand	Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis [b, c]
Zuigelingen van 3 tot en met 5 maanden	Twee doses, elk van 0,5 ml	Niet minder dan 2 maanden	
Zuigelingen van 6 tot en met 11 maanden	Twee doses, elk van 0,5 ml	Niet minder dan 2 maanden	Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis [c]
Kinderen van 12 tot en met 23 maanden	Twee doses, elk van 0,5 ml	Niet minder dan 2 maanden	Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis [c]
Kinderen van 2 tot en met 10 jaar	Twee doses, elk van 0,5 ml	Niet minder dan 1 maand	Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen [d]
Adolescenten (11 jaar of ouder) en volwassenen*			

[a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld [d] Zie rubriek 5.1 van de volledige SPK. * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **CONTRAINDICATIES** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **BIJZONDERE WAARSCHUWINGEN EN VOORZORGEN BIJ GEBRUIK** Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen. Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Personen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van personen met complementdeficiëntie, asplenie of miltdisfuncties. Personen met familiale complementdeficiënties (bijvoorbeeld C3- of C5-deficiënties) en personen die behandelingen ondergaan die de terminale complementactivatie remmen (bijvoorbeeld eculizumab) hebben een hoger risico op een invasieve ziekte veroorzaakt door ***Neisseria meningitidis*** groep B, zelfs als deze personen antilichamen ontwikkelen na vaccinatie met Bexsero. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. **BIJWERKINGEN** Overzicht van het veiligheidsprofiel De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en ***Haemophilus influenzae*** type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥1/10) Vaak: (≥1/100, <1/10) Soms: (≥1/1.000, <1/100) Zelden: (≥1/10.000, <1/1.000) Zeer zelden: (<1/10.000) Niet bekend: (kan met de beschikbare gegevens niet worden bepaald) De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar)** Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Voedings en stofwisselingsstoornissen Zeer vaak: eetstoornissen Zenuwstelselaandoeningen Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn Soms: insulten (inclusief febriele insulten) Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen Soms: bleekheid (zelden na booster) Zelden: ziekte van Kawasaki Maagdarmstelselaandoeningen Zeer vaak: diarree, braken (soms na booster) Huid en onderhuidaandoeningen Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster) Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar) Soms: eczeem Zelden: urticaria Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: koorts (≥38°C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid Soms: koorts (≥40°C) Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) **Adolescenten (van 11 jaar en ouder) en volwassenen** Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Zenuwstelselaandoeningen Zeer vaak: hoofdpijn Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen Zeer vaak: misselijkheid Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: myalgie, artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem. **België** Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie EUROSTATION II Victor Hortaplein, 40/40 B-1060 Brussel Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **Luxemburg** Direction de la Santé – Division de la Pharmacie et des Médicaments Villa Louvigny – Allée Marconi L-2120 Luxembourg Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië **DATUM VAN DE GOEDKEURING VAN DE TEKST** 03/2019 (v09) **AFLEVERINGSWIJZE** Op medisch voorschrift.

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Pulmonary embolism : about two pediatric observations

L'embolie pulmonaire : à propos de deux observations pédiatriques

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Abstract

Pulmonary embolism is a rare and underestimated pathology within the paediatric population. The diagnosis is often delayed in children and teenagers, potentially increasing paediatric morbidity and mortality. Specific paediatric risk factors may be detected. Diagnostic, treatment and follow-up guidelines only exist for adults but are currently applied to children. The purpose of this article is to discuss clinical signs, assessment and paediatric management. Further studies will be required in order to establish standard paediatric guidelines.

Résumé

L'embolie pulmonaire (EP) est une pathologie rare et sous-estimée en pédiatrie. Le diagnostic est souvent retardé chez les enfants et adolescents ce qui augmente potentiellement la mortalité et la morbidité pédiatrique. Des facteurs de risque pédiatriques peuvent être dépistés. Des guidelines pour le diagnostic, la prise en charge et le suivi des EP existent en médecine adulte mais sont actuellement extrapolés aux enfants. Le but de cet article est de discuter des signes cliniques, du bilan et de la prise en charge spécifiquement pédiatrique. Des études ultérieures sont nécessaires pour parvenir à établir des guidelines pédiatriques reproductibles.

Observations

Une adolescente de 14 ans se présente en urgence pour dyspnée d'effort, palpitations depuis 1 mois et douleur thoracique rétrosternale respiro-dépendante. Notion de malaises pré-syncopaux et douleur croissante de la cuisse gauche depuis 7 jours. Œdème du mollet depuis 48 heures. Placée sous contraception orale (ethinylestradiol 0,02 mg/desogestrel 0,15 mg 1x/jour) depuis 3 semaines. A l'examen clinique d'admission, la température est à 37,2°C, la fréquence cardiaque à 90/min, la fréquence respiratoire à 16/min, la tension artérielle à 110/68, la saturation en O2 à l'air libre est à 94 %. L'examen relève une douleur à la palpation profonde du mollet gauche, une signe de Homans négatif, une augmentation du diamètre de la cuisse gauche de 3 cm, une circulation veineuse superficielle collatérale visible.

La suite de la prise en charge est basée sur la haute probabilité clinique d'embolie pulmonaire (EP). Le Wells score évalué à 3 témoigne d'une probabilité clinique intermédiaire d'EP. L'électrocardiogramme (ECG) montre des signes de surcharge de V1 à V3. La biologie objective des D-Dimères à 3570 ng/ml (dosées au vue de la probabilité intermédiaire). L'angio-scanner thoracique montre une EP bilatérale centrale (à la limite entre les bronches segmentaires et les bronches souches). L'échodoppler du membre inférieur gauche montre une thrombose veineuse profonde (TVP) de la veine iliaque gauche à la veine poplitée. La patiente sera placée sous anticoagulation par enoxaparine, paracetamol, tramadol et bas de contention. Après la phase aigüe, les facteurs de risque et les comorbidités sont évaluées par une échocardiographie normale hormis une hypertension artérielle pulmonaire (HTAP) avec une pression artérielle pulmonaire (PAP) systolique évaluée à 20 mmHg. Un bilan d'hémostase met en évidence un facteur V de Leiden, s'ajoutant au facteur de risque de la contraception orale. L'enoxaparine sera remplacée par du acenocoumarol pour une durée de 6 mois. La contraception orale est remplacée par le désogestrel. Il a été suggéré de remplacer la contraception hormonale par des contraceptifs non hormonaux (préservatifs, …).

Observation n°2

Une adolescente de 14 ans sans antécédents probants se présentant pour toux avec dyspnée d'effort depuis deux mois. Le médecin traitant débute le bilan par une échographie cardiaque objectivant des signes compatibles avec une EP. On notera une contraception par pilule depuis 3 mois. A l'examen clinique, la fréquence cardiaque à 112/min, la fréquence respiratoire à 19/min, la tension artérielle à 124/72, la saturation en O2 à l'air libre est à 100 %. L'examen clinique de départ est sans aucune particularité. La biologie met en évidence des D-Dimères à 2820 ng/ml, l'ECG montre des troubles de conduction intraventriculaire. L'échocardiographie montre une surcharge droite avec une dilatation du ventricule droit (VD), un mouvement paradoxal du septum, une HTAP modérée avec PAP systolique évaluée à 45mmHg. L'échodoppler des membres inférieurs (MI) est normale. L'angioscanner thoracique confirme une embolie pulmonaire plurifocale et bilatérale atteignant les niveaux centraux jusqu'en sous-segmentaire. Le bilan d'hémostase se révèle normal. La scintigraphie pulmonaire de ventilation-perfusion confirme de nombreux déficits segmentaires et sous-segmentaires bilatéraux. Cette jeune fille est placée sous héparine de bas poids moléculaire (HBPM) tinzaparine Sodique durant 4 jours relayé par acenocoumarol durant 6 mois.

Discussion

Notre connaissance de l'EP pédiatrique reste fragmentaire car cette pathologie semble rare mais sous-évaluée en pédiatrie. Malgré des symptômes parfois typiques, le diagnostic est souvent retardé. Il est dès lors possible que la mortalité et la morbidité des EP sous-diagnostiquées soient sous-estimées[1]. Les guidelines pédiatriques font défaut et les pratiques des adultes sont extrapolées aux enfants.

A Incidences et mortalité

L'EP pédiatrique est rare. L'incidence reste inconnue au vue de nombre probable de diagnostics non posés[2]. Certaines études ont observé une augmentation significative du taux d'EP pédiatrique ces dernières années probablement à cause du recours massif à la contraception orale, du taux majoré d'obésité et de la sensibilité affinée des examens radiologiques[3,4]. Certains auteurs parlent d'un possible surdiagnostic pédiatrique basé sur la difficulté d'interprétation de l' imagerie[3].

Son incidence est approximativement de 0,14 à 0,9/100.000 dans la population générale et de 8,6 à 57/100.000 chez les enfants hospitalisés[1,3]. Elle augmente secondairement à la prolongation de la durée de vie des enfants sévèrement malades et à l'utilisation de cathéters (KT) centraux[1]. On peut noter un premier pic d'EP chez les nourrissons (0-1 an) puis un second pic à l'adolescence [1,5,3].

B Symptomatologie

Les symptômes pédiatriques sont peu spécifiques et parfois absents. Comparativement aux adultes, la latence de diagnostic d'EP est plus longue avec un temps moyen supplémentaire évalué à 7 jours dans certaines études[1].

Les signes cliniques typiques sont : dyspnée (90 %) comme signe cardinal[2,6]; douleur thoracique unilatérale, majorée à l'inspiration profonde; angoisse ou sensation d'oppression thoracique (60 %); tachycardie (90 %); quintes de toux sèche; hémoptysie (10 %) retardées (24-36H)[12]. Malheureusement ces signes typiques ne s'observent qu'en cas d'EP massive, les petites EP provoquent des symptômes respiratoire vagues pouvant mimer d'autres maladies pulmonaires[2].

L'examen évaluera l'état hémodynamique du patient ainsi que d'éventuels signes de choc. L'auscultation pulmonaire est normale. La température peut être élevée en cas d'infarctus pulmonaire. L'auscultation cardiaque met en évidence des signes de cœur pulmonaire aigu. Les signes périphériques de surcharge (hépatomégalie, turgescence de jugulaires, reflux hépato-jugulaire,…) et les signes de thrombophlébite doivent être scrupuleusement recherchés. L'absence de TVP n'exclut néanmoins en rien le diagnostic.

C Examens complémentaires

La RX Thorax est souvent normale (88 %)[2] . Elle pourrait montrer des atélectasies (18 %) [2], un épanchement pleural (23 %) [2], une surélévation d'une coupole diaphragmatique, une image d'infarctus pulmonaire (17 %), une image d'amputation d'une artère pulmonaire ou d'hyperclareté pulmonaire, une cardiomégalie (27 %)[2]. Elle permet d'exclure une pneumopathie infectieuse, un pneumothorax, un œdème pulmonaire aigu (OAP).

L'*ECG* montre des anomalies électriques peu spécifiques : tachycardie (90 %), anomalie du segment ST ou de l'onde T, des signes de cœur pulmonaire aigu à savoir déviation axiale droite, bloc de branche droit, onde P pulmonaire, inversion de l'onde T en V1 à V3. Ces anomalies sont peu fiables en pédiatrie[12].

L'échocardiographie confirme le retentissement sur le cœur droit : dilatation des cavités cardiaques droites, hypokinésie du VD, insuffisance tricuspidienne, mouvement paradoxal du septum interventriculaire. Elle met en évidence une HTAP. Elle permet d'éliminer d'autres diagnostics. Une échographie cardiaque transoesophagienne permet de mettre en évidence des thrombi au sein des cavités cardiaques droites ou dans l'artère pulmonaire. La normalité d'une échocardiographie n'exclut pas une EP.

L'échodoppler des membres inférieurs met en évidence une thrombose veineuse profonde des MI (Figure 1). Sa spécificité est de 94 %, sa sensibilité de 97 %[2] . Sa normalité n'exclut pas une EP [6]. Certains auteurs affirment que la découverte d'une TVP implique de ne pas devoir rechercher l'EP car le traitement des TVP et EP est identique [2] mais ceci reste controversé.

La biologie est utilisée surtout chez les adultes pour le dosage des D-Dimères (N<500 ug/l permettant d'exclure avec quasi-certitude une EP). Le taux des D-Dimères n'a cependant aucune valeur prédictive significative en pédiatrie[3]. Certains auteurs recommandent de screener chaque enfant présentant une EP pour la thrombophilie[1].

L'angioscanner spiralé thoracique (angio TDM) est l'examen de référence du diagnostic. Des critères diagnostics standards sont établis pour les EP aigüe vs chroniques[2]. Il n'existe pas de données équivalentes en pédiatrie mais sa position de choix dans l'EP pédiatrique vient de sa disponibilité, sa rapidité d'exécution, sa haute résolution spatiale et sa capacité d'image en 2D/3D[2,7]. L'embole pulmonaire se visualise sous forme d'une lacune centrale ou marginale intraluminale occupant totalement ou partiellement la section du vaisseau (Figures 2-3). Sa normalité n'exclut pas le diagnostic d'EP. Il est non invasif mais ignore les microemboles périphériques, expose aux radiations[1]. De nouvelles techniques de scanner arrivent pour minimiser ces désavantages[2].

La scintigraphie pulmonaire de perfusion et ventilation a historiquement été un examen de référence avec une spécificité de 100 %[2]. Sa normalité exclut le diagnostic d'EP. Une scintigraphie V/P (ventilation/perfusion) positive peut par ailleurs se voir dans des cas de pneumonie, drépanocytose, sténose artérielle et embolie gazeuse/graisseuse/corps étranger[1]. Certains auteurs, comme Victoria et al. ont décrit une faible sensibilité avec beaucoup de faux positifs[1,8,2].

L'angiographie pulmonaire est le gold standard du diagnostic d'EP mais est invasive, expose à des radiations et inclut la mise en place d'un KT placé dans l'artère pulmonaire. Elle est très rarement en pédiatrie[12] sauf dans les unités de cardiologies pédiatriques.

L'imagerie par résonnance magnétique (IRM) ou angio-résonnance magnétique pulmonaire est attractive vu l'absence de radiation et l'utilisation d'un produit de contraste plus sûr. Elle est utilisée chez les adultes quand l'angioscanner est contre indiqué. La nécessité de sédation chez les jeunes enfants reste un frein à sa réalisation[2] d'autant qu'elle n'a pas encore été étudiée dans cette population[1].

Figure 1: Echo MI cas 2 : thrombose de la veine fémorale superficielle gauche

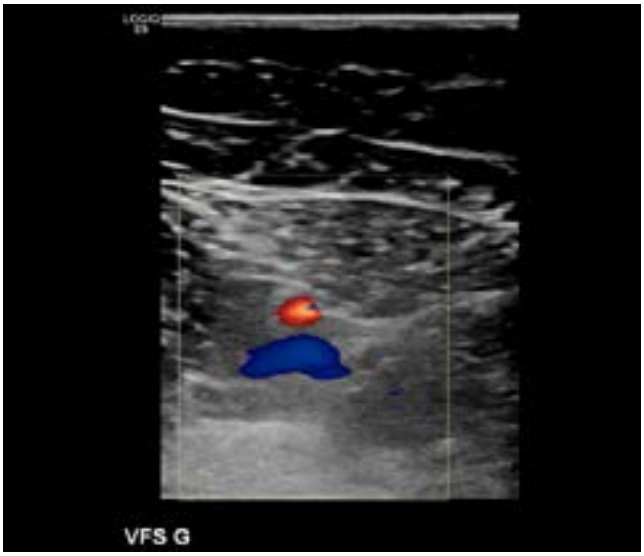


Figure 2: Angio TDM cas 1 : thrombus moulé dans l'artère pulmonaire commune droite et l'artère pulmonaire de la pyramide basale gauche

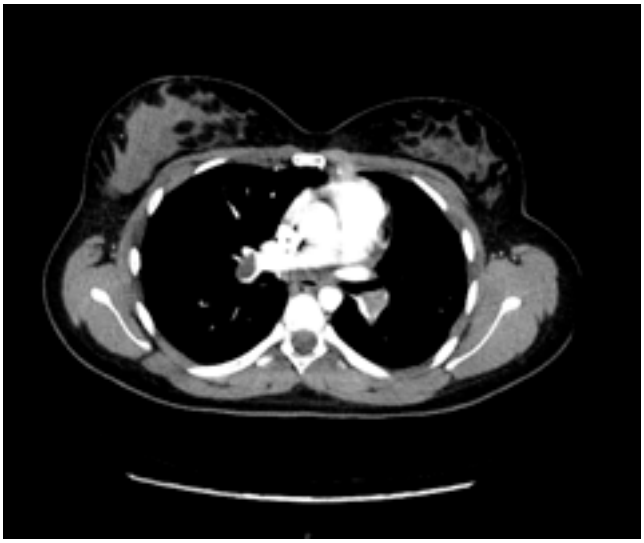
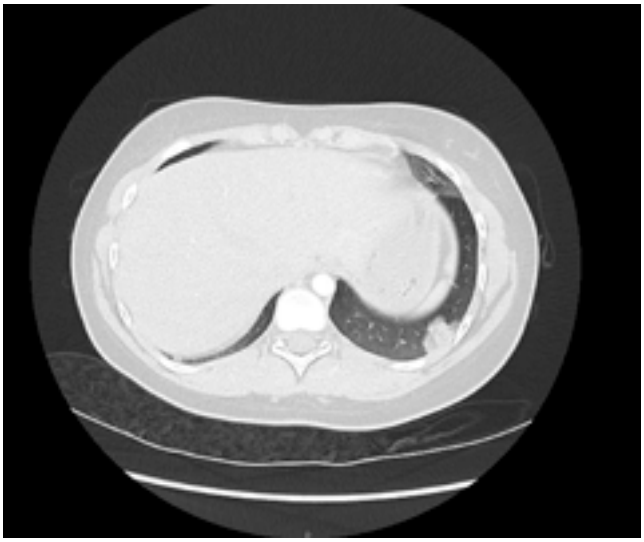


Figure 3: Angio TDM fenêtre parenchymateuse : zone de densification à base pleurale : infarctus latéro-basal gauche



D Facteurs de risque

Les scores prédictifs utilisés par les adultes (Wells -Tableau I) n'ont pas été validés en pédiatrie[1,9]. Certains auteurs décrivent l'identification des facteurs de risque dans 96-97 % des cas pédiatriques [2,7], surtout chez le nourrissons et le petit enfant[2].

En période néonatale, on retrouve le sepsis (staphylocoques Aureus) , la déshydratation et l'asphyxie péri-natale[2]. Chez les plus grands, on identifie l'immobilité, les KT veineux centraux, les chirurgies récente, les antécédents de TVP, une contraception orale (risque prépondérant)[3] . Les diagnostics sous-jacents sont les cardiopathies congénitales, les troubles de la coagulation, les maladies malignes hématologiques, le syndrome néphrotique, les malformations des MI, le Lupus érythémateux Systémique, la colite ulcérative, le purpura thrombocytopénique immun, les traumatismes …

Les scores prédictifs positifs d'EP en pédiatrie sont focalisés sur le risque de TVP chez les hospitalisés[10]. Le développement de facteurs prédictifs positifs ciblés en pédiatrie diminuera le risque de surdiagnostic et adaptera l'imagerie chez les patients à haut risque[3].

Score prédictif de Wells (tableau 1)

Symptômes de TVP	3 points
Autre diagnostic moins probable pour expliquer la maladie	3 points
Tachycardie avec pouls > 100	1,5 points
Immobilisation (> ou = 3 jours) ou chirurgie au cours des 4 semaines précédentes	1,5 points
Antécédents de TVP ou d'embolie pulmonaire	1,5 points
Hémoptysie	1 points
Malignité	1 points

Score > 6: Forte probabilité
Score >= 2 et <= 6: Probabilité moyenne
Score < 2: Faible probabilité

Facteurs de risque (triade de Virchow) (tableau 2)

1-Dommages de l'endothélium :	2- Variation du flux :	3-Thrombophilie Acquise :	4- Thrombophilie secondaire
-cathéter veineux central	-cardiopathie congénitale	- syndrome néphrotique	-déficit en anticoagulant, protéine C/S, antithromin III
-inflammation (LED, Crohn, …)	-causes anatomiques locales (Fontan, post-chir, anomalie congénitales artérielles)	-cancer	-Factor V Leiden, variant gène prothombin, …
-infection systémique	-nutrition parentérale	-médications	-homocystéine élevée
-Ac antiphospholipides		-grossesse ou traitement hormonal	
		-Ac antiphospholipides	

E Diagnostic différentiel

Face à une symptomatologie à prédominance respiratoire, les diagnostics à exclure sont la pneumonie, le pneumothorax, la pleurésie, l'état de mal asthmatique, l'œdème pulmonaire, le syndrome de Tietze, la ribcontusion, ...

F Traitement

Il n'existe pas d'algorithme de traitement de l'EP en pédiatrie. Les recommandations de prise en charge sont extrapolées des adultes mais doivent être adaptées aux spécificités pharmacologiques et étiologiques pédiatriques. Cependant, certains centres proposent la prise en charge suivante :

Les thérapies anticoagulant reste le traitement initial le plus utilisé en pédiatrie chez des patients stables hémodynamiquement[2] . La durée varie entre 3 et 12 mois.

Les thrombolytiques permettent une fibrinolyse rapide des thrombi mais provoquent un risque d'hémorragie. Ils sont réservés aux patients instables à haut risque d'EP mais doivent être évités chez les enfants à risque de saignement. Certains auteurs parlent d'un taux de résolution complète de 55-65 % contre 5-20 % de résolution incomplète[2,6].

Les thrombolyses mécaniques sont rares en pédiatrie et réservées aux récidivistes malgré un traitement anticoagulant bien conduit ou après embolectomie chirurgicale.

L'embolectomie chirurgicale est exceptionnellement réalisée lors des EP gravissimes avec état de choc, en cas de contre-indication aux thrombolytiques ou d'échec du traitement thrombolytique.

Les nouvelles thérapies prometteuses telle que la thrombolyse écho-assistée n'ont pas été étudiées en pédiatrie [1].

Pronostic et follow-up

Le pronostic dépend de la rapidité du diagnostic et du traitement. La majorité des patients survivent en pédiatrie[8,2]. Seuls les patients se présentant en choc cardiovasculaire ont un mauvais pronostic. Les séquelles à long terme sont la récidive, les complications des anticoagulants, l'hypertension pulmonaire et la défaillance cardiaque droite[2,11].

Le follow-up est important afin d'évaluer le résultat des traitements mais aussi pour évaluer les potentielles complications à long terme (HTAP ou EP chronique).

Après un épisode aigu, certains auteurs recommandent de réaliser d'emblée un bilan de thrombophilie (facteur V de Leiden, Prot S, Prot C , …) chez le patient et parfois au sein de la famille[1].

Conclusion

L'embolie pulmonaire est une entité pédiatrique rare mais potentiellement fatale. Les symptômes pédiatriques sont peu spécifiques et entraînent un retard de diagnostic alors que le traitement anticoagulant doit être débuté rapidement. Les facteurs de risque associés doivent être recherchés et sont présents dans plus de 95 % des cas d'EP pédiatrique. L'imagerie joue un rôle primordial dans le diagnostic définitif de l'EP. Des études complémentaires évaluant l'efficacité de score de probabilité, les outils diagnostics les plus adéquats, la place de l'IRM, les séquelles à long termes en pédiatrie, … doivent être réalisées. La contraception orale doit être considérée comme un réel facteur de risque de thrombose veineuse profonde et dès lors préférentiellement évitée après un épisode aigu. Un bilan de thrombophilie doit être réalisé après tout épisode initial d'EP en pédiatrie.

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Innovation in monitoring and treatment of nephropathic cystinosis

PhD thesis presented on 20th September 2019 at Promotiezaal, Universiteitshallen KU Leuven, Leuven, Belgium

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Introduction

Cystinosis is a rare, autosomal recessive lysosomal storage disorder caused by bi-allelic mutations in the gene *CTNS* which encodes a cystine proton cotransporter, *cystinosin*, located in the lysosomal membrane[1]. Due to the loss of function of this transporter, cystine, a di-amino acid consisting of two cysteine molecules, accumulates in the lysosomes followed by cystine crystal formation which is the pathognomonic hallmark of the disease [2]. Cystinosis mainly affects the kidney, more specifically the cells of the renal proximal tubule which is the most metabolically active part of the nephron, involved in reabsorbing many of solutes that are freely filtered through the glomerulus[3,4]autosomal recessive inherited lysosomal storage disease. It is the most frequent and potentially treatable cause of the inherited renal Fanconi syndrome. If left untreated, renal function rapidly deteriorates towards end-stage renal disease by the end of the first decade of life. Due to its rarity and non-specific presentation, the entity is often not promptly recognized resulting in delayed diagnosis. Two major milestones in cystinosis management, cystine-depleting therapy with cysteamine and renal allograft transplantation, have had a considerable impact on the natural history and prognosis of cystinosis patients. However, due to its significant side effects and a strict 6-hourly dosing regimen, non-adherence to the immediate release of cysteamine bitartrate formulation (Cystagon®. Later, the disease also affects the podocytes [4]. Clinically, the disease therefore is characterized by a general proximal tubular dysfunction, the renal Fanconi syndrome, leading to failure to thrive, polyuria and polydipsia. Chronic kidney disease develops, which gradually evolves towards end-stage renal disease if the disease is left untreated. Since the transporter, *cystinosin*, is present in all cells of the body, many other organs apart from the kidney, can also get affected, including mainly the eyes, endocrine system (primary hypothyroidism, diabetes mellitus, primary hypogonadism in males), muscles (peripheral myopathy, swallowing dysfunction) and central nervous system (cerebrovascular events, stroke-like episodes, idiopathic intracranial hypertension). Depending on the age and severity of the disease, three different phenotypes have been described: the most common and severe infantile phenotype (90%) presenting in the first year of life, a juvenile phenotype presenting in adolescence or early adulthood with a mild renal Fanconi syndrome (5%), and a rare ocular phenotype affecting exclusively the eye (5%).

Fortunately, a highly specific, disease-modifying treatment is available. Cysteamine is an aminothiol which is able to cleave the disulphide bond of cystine, enabling the lysosome to be depleted of cystine. Since its widespread availability, cysteamine has shown to improve the life expectancy of cystinosis patients by postponing the onset of end-stage renal disease, improving growth, and decreasing the incidence of extra-renal complications [5–8]. However, cysteamine has significant side-effects (halithosis, gastro-intestinal complaints), has to be taken frequently (most common formulation, short-acting cysteamine bitartrate, q6h) and to ensure effectivity, regular drug monitoring is necessary [9]. The current only available modality for monitoring cysteamine treatment, concerns an assay in which the cystine level in white blood cells (WBC) is assessed. However, this WBC cystine assay suffers important practical and technical limitations, and has a limited availability even in high resource countries, hampering further potential improvements in outcome of cysteamine-treated cystinosis patients [10]. Therefore, alternative or additional modalities for monitoring of cystine-depleting therapy would be highly valued in the clinical management of cystinosis.

Nevertheless, cysteamine treatment has significantly improved the life expectancy of cystinosis patients, allowing them to survive into adulthood. This changing spectrum of patients has, in part, changed the face of the disease while some clinical manifestations come to the fore. Some specific dermatological manifestations observed in cystinosis are more pronounced in the (young) adult cystinosis population. Also, specific issues related to adult life, including the wish for having children, has become a relevant topic for the adult cystinosis patient population. The infertility in male cystinosis patients which recently has been appointed to an azoospermia of yet unknown origin, has turned this topic into a real concern for the cystinosis patient community [11,12]male cystinosis patients treated with cysteamine. Cystinosis is an autosomal recessive disease leading to intralysosomal cystine accumulation. Worldwide, a few female cystinosis patients have given birth. However, no male cystinosis patients are known to have induced pregnancy. Adequate cysteamine treatment might improve male fertility. Patients.

Furthermore, despite the progress that has been realized in the management of cystinosis due to the advent of renal replacement therapy and cysteamine treatment, a cure for cystinosis is lacking. Hematopoietic stem cell transplantation has been an alluring approach for providing this cure in cystinosis, given the recent promising data in the cystinosis mouse model [13–15]. However, it remains uncertain whether this future treatment strategy will be sufficient to provide a real cure for the kidney disease and all extra-renal complications.

In this thesis, we aimed to address these challenges faced in the management of cystinosis.

1. Innovation in monitoring of nephropathic cystinosis

1.1 Enhanced intrinsic skin aging in nephropathic cystinosis as evidenced by HD-OCT in nephropathic cystinosis

We utilized the currently most advanced non-invasive optical imaging technology available in clinical practice (HD-OCT) to identify distinctive cutaneous features of cystinosis in a quantitative manner. We demonstrated that signs of an enhanced intrinsic skin aging are present in cystinosis patients, which are apparent from adolescent to young adult age, prior to kidney transplantation [16]. Moreover, in cystinosis patients whom the *CTNS* gene is absent due to a large deletion (hom 57kb del), significant thinning of the epidermis predicts the presence of (other) extra-renal complications, which suggests that in these patients, the degree of skin involvement reflects the overall disease severity [16].

Hereby, for the first time, we could demonstrate in a quantitative manner the involvement of the skin in the phenotype of cystinosis.

1.2 Chitotriosidase as a novel biomarker for therapeutic monitoring of nephropathic cystinosis

We aimed to explore the potential of biomarkers of macrophage activation in blood plasma to serve as an alternative or additional modality for the monitoring cystine-depleting therapy. In a 2-year longitudinal international multicentric study, in which 61 nephropathic cystinosis patients were recruited, we demonstrated that plasma chitotriosidase enzyme activity, an enzyme secreted by macrophages upon exposure and engulfment of cystine crystals, significantly correlates with white blood cell cystine levels in cystinosis patients. In a multivariate regression analysis correcting for age, gender, genetic background (hom 57kb del) and other markers of macrophage activation, chitotriosidase was a significant and independent predictor of white blood cell cystine levels in cystinosis patients of all ages. Additionally, we could establish a cut-off value for chitotriosidase enzyme activity (150 nmol/ml plasma/h) distinguishing good versus poor therapeutic control with cysteamine treatment (in terms of WBC cystine levels < or 2 nmol ½ cystine/mg protein respectively), that harbors a high negative predictive value for ruling out patients with a poor compliance (NPV 83%). Importantly, we were able to demonstrate that chitotriosidase does not merely reflect the inflammation related to chronic kidney disease (CKD): in a multivariate regression analysis, both the estimated glomerular filtration rate (eGFR) and WBC cystine levels were identified as both independent and significant predictors of chitotriosidase enzyme activity.

Furthermore, chitotriosidase enzyme activity levels were superior to WBC cystine levels in predicting the presence of multiple extra-renal complications in the subgroup of patients having at least one extra-renal complication. A cut-off value for chitotriosidase enzyme activity at 250 nmol/ml plasma/h showed a high positive predictive value (PPV 86%) for identifying patients with multiple extra-renal complications.

In conclusion, our data suggest that plasma chitotriosidase enzyme activity reflects the whole-body tissue cystine burden, and could serve as an additional modality for monitoring long-term adherence to cysteamine treatment. A large-scale, multicentric international prospective study is underway to validate and corroborate our findings.

2. Innovation in treatment of nephropathic cystinosis

2.1 Allogeneic hematopoietic stem cell transplantation transfers wild-type cystinosin to nonhematological epithelial cells in nephropathic cystinosis: first human report

We described the first case of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in a 16-year old cystinosis patient that suffered from substantial side effects and toxicity of cysteamine treatment [17]. We demonstrated clinically a significant reduction of polyuria, the appearance of expression of wild-type cystinosin at messenger RNA (mRNA) level in the liver and kidney, and the expression of wild-type cystinosin-LKG protein, a specific isoform of cystinosin, at various locations at the mucosa of the gastro-intestinal tract in the weeks-months following the allo-HSCT [17]. However, following the need for a second HSC donation, a severe and refractory chronic graft-versus-host disease developed, kidney function deteriorated due to drug toxicity ending in the need for dialysis, and the patient finally succumbed to a multidrug resistant Pseudomonas infection.

Despite convincing evidence in support of the proposed mechanism of the group of Stephanie Cherqui of transfer of *cystinosin* mRNA or protein from the graft hematopoietic stem cells to epithelial cells of various organs, the limited therapeutic effect on the renal and extra-renal complications, significant morbidity and mournful outcome of the patient should encourage to reflection and careful reconsideration of the concept of HSCT [18–20]we previously showed that HSC transplantation could correct cystinosis, a multisystemic lysosomal storage disease, caused by a defective lysosomal membrane cystine transporter, cystinosin (CTNS gene. Therefore, we proposed that other innovative strategies for the treatment of cystinosis, and the kidney phenotype in specific, need to be explored.

2.2 Kidney progenitor cells are present in urine of cystinosis patients and can be genetically rescued via ex-vivo gene therapy

We described for the first time the presence of kidney progenitor cells (Cys-uKPCs), expressing a panel of genes reminiscent of early nephrogenesis (*CITED1*, *NCAM1*, *VIM, PAX2*), showing clonogenic and self-renewal capacity, in the urine of nephropathic cystinosis patients. Upon quantification of these cells, none were demonstrated in healthy control subjects. Some of these Cys-uKPC clones show the potential to differentiate into a proximal tubular epithelial (PTEC)-like cell, expressing *ABCB1*, *CUBN*, and a highly specific marker for PTECs, *AQP1*. Other Cys-uKPC clones show the potential to differentiate into a podocyte-like cell, which express podocyte-specific markers nephrin, synaptopodin and podocalyxin. Using PTEC- and podocyte-specific assays (P-glycoprotein calcein assay; albumin endocytosis assay and calcium influx assays respectively), we could demonstrate functionality of these Cys-uKPC-derived PTECs and podocytes. Moreover, we demonstrated that, by delivering the *CTNS* gene using viral vector technology (lentiviral vector, LV), the main cellular hallmarks of cystinosis, comprising lysosomal cystine accumulation and the altered distribution of the LAMP1 lysosomal compartment, could be rescued towards the healthy phenotype. Urine-derived kidney progenitor cells offer many advantages in terms of the method of harvesting, the avoidance of the need for immortalization, cost-effectiveness and utility in future applications. Currently, these urine-derived kidney progenitor cells constitute a novel platform for studying disease biology, new drug development and future kidney bio-engineering. Obviously, the potential of these cells should be further explored *in vitro*, e.g. organoid formation, and in a cystinosis disease model *in vivo*.

2.3 Unravelling the mechanism of azoospermia in nephropathic cystinosis

Finally, we addressed one of the concerns of the young adult cystinosis patient population and one of the most universal human needs in life, the wish of having children.

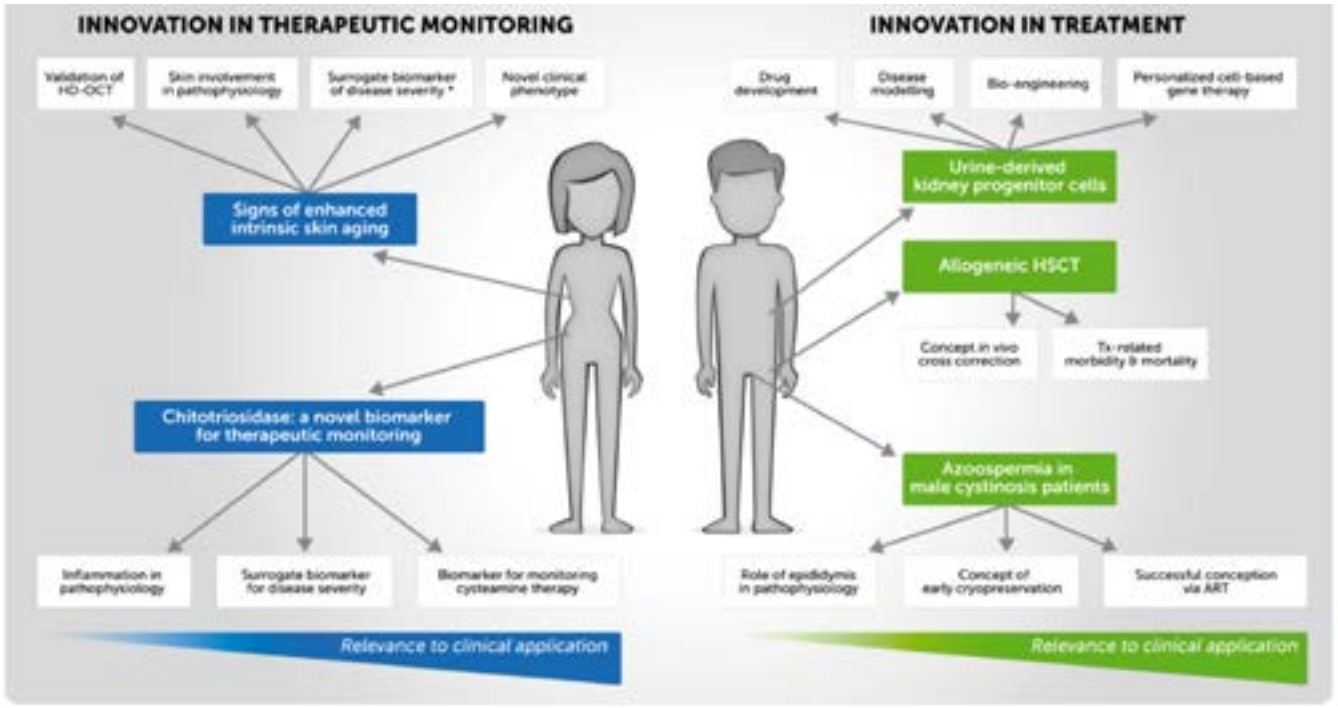
We described the first case of a successful conception induced by a male, infantile-type nephropathic cystinosis patient via retrieving viable sperm at the epididymal level via assisted reproductive techniques [21]. This case holds a promising message to the cystinosis patient community that fathering a child is feasible, if considered timely, and that despite an azoospermia, viable sperm can be retrieved at the epididymal level.

Furthermore, we aimed to further unravel the origin of the azoospermia observed in male cystinosis patients. Indeed, in male cystinosis patients, previous studies have suggested that, on top of an evolving primary hypogonadism with increasing age, the azoospermia can only be explained by additional pathogenic factors involved at, presumably, the epididymal level.

Therefore, we have initiated a multicentric study in which we aimed to further define the origin of azoospermia in cystinosis patients, via non-invasive means including scrotal ultrasound and the assessment of biomarkers of obstruction in seminal plasma. In this currently still ongoing project, we have found indications for an obstruction or malfunction from the epididymal level onwards via scrotal ultrasound (caput epididymis diameter) and examination of markers of obstruction on seminal plasma (neutral alpha glucosidase, NAG; extracellular matrix protein 1, ECM1). We proposed that cryopreservation could be a useful strategy to be considered at young adult age in order to preserve their fertility potential. If considered, techniques for harvesting sperm cells should be as minimally invasive as possible, aimed preferentially at the epididymal level.

In conclusion, in this thesis, we have addressed some of the important challenges faced in the current management of nephropathic cystinosis (**Figure 1**).

Figure 1: Overview of the main contributions of the work presented in this thesis to the cystinosis research field and their relevance to clinical application



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Faster growth comes with increased risks of severe bowel problems when using formula rather than donor breast milk in preterm or low birth weight infants

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Question

Does feeding preterm or low birth weight infants with formula rather than donor breast milk affect digestion, growth or the risk of severe bowel problems?

Context

In preterm and low birth weight infants, enteral feeding with the mother's own breast milk is rec-ommended. However, when a mother's own breast milk is not available or insufficient, infant feeds can be supplemented or replaced with formula or donor breast milk. Artificial formula is thought to have a more stable consistency and to contain more nutrients than donor breast milk, but could be harder to digest for the infants. Donor breast milk on the other hand may deliver some immunopro-tective and growth factors to the immature gut mucosa of the infants which might prevent necrotis-ing enterocolitis and serious gut infections. This donor breast milk is, however, expensive and is thought to sometimes lack the necessary nutrients for growth and development.

Criteria for study selection

The Cochrane review included trials comparing enteral feeding of formula versus donor breast milk in preterm (<37 weeks' gestation at birth) or low birth weight (<2500g) infants. The formula or donor breast milk could be a supplement to maternal breast milk or could form the sole diet. The main out-comes reported by the review were short-term and long-term growth, death and neurodevelopmen-tal outcomes including severe neurodevelopmental disability, neurodevelopmental scores in chil-dren of at least 12 months of age and cognitive and educational outcomes in children over 5 years old.

Summary of the results

The review included eleven randomized controlled trials and one quasi-randomised trial. The twelve trials with a total of 1879 infants were all conducted in neonatal units in Europe or North America. The donor breast milk was pasteurised in all but one trial. Four trials compared term formula to do-nor breast milk and eight trials compared nutrient-enriched preterm formula to donor breast milk. Five trials used breast milk from women who had delivered at term, one trial used preterm donor milk and another used a combination. Five trials did not specify the type of donor breast milk. Four trials, all performed after 2000, used donor breast milk with multinutrient fortifier.

Infants receiving formula had higher rates of weight gain (mean difference: 2.51 g/kg/day higher (95% CI^ 1.93-3.08); 1028 infants, 9 studies, moderate-certainty evidence), linear growth (mean differ-ence: 1.21 mm/week higher (95% CI 0.77-1.65); 820 infants, 8 studies, moderate-certainty evidence) and head growth (mean difference: 0.85 mm/week higher (95% CI 0.47-1.23); 894 infants, 8 studies, moderate-certainty evidence). The meta-analyses contained high levels of heterogeneity for the effect estimates and this lowered our confidence in the effect estimate. Post-hospital discharge growth was measured in only two trials but did not show differences in weight, length or head circumference at 9 months, 18 months or 7.5 to 8 years post-term. There is also no evidence of an effect on mortality (donor breast milk: 86 per 1000 vs formula: 94 per 1000 (95% CI: 69-128); 1527 infants, 7 studies, moderate-certainty evidence) or the prevalence of neurodevelopmental disability (donor breast milk: 73 per 1000 vs formula: 88 per 1000 (95% CI: 45-171); 400 infants, 2 studies, moderate-certainty evidence). The number of infants developing necrotising enterocolitis was higher when formula was used compared to donor breast milk (donor breast milk: 36 per 1000 vs formula: 67 per 1000 (95% CI: 44-102); 1675 infants,9 studies, moderate-certainty evidence).

Conclusion

Feeding preterm or low birth weight infants with formula compared to donor breast milk, either as a supplement to maternal breast milk or as the sole diet, probably increases short-term growth rates. However, it probably makes little or no difference to long-term growth, survival and neurodevelop-ment. Using formula compared to donor breast milk probably leads to an increase in infants with necrotising enterocolitis.

Implications for practice

The evidence shows that using formula compared with using donor breast milk leads to faster in-hospital growth in preterm and low birth weight infants, but is also associated with a near-doubling of the risk of developing necrotising enterocolitis. Only a few of the trials included in the review compared using formula with using nutrient-fortified donor breast milk. As the fortification of donor breast milk has become standard practice, this does limit the implications for practice from this re-view. The inclusion of several ongoing trials in future updates will generate more precise effect esti-mates and strengthen the applicability of the data for practice.

REFERENCE:

Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD002971.

DOI: 10.1002/14651858.CD002971.pub5.

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

^ **CI:** confidence interval

NOUVEAU: LINGETTES PAMPERS® AQUA PURE

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

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

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

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

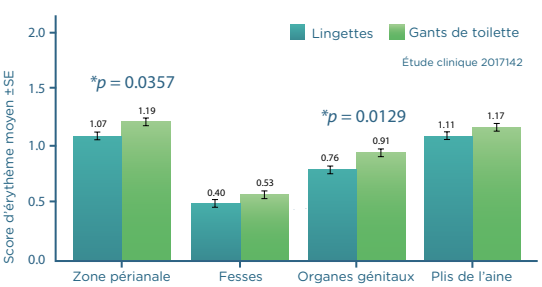
Une nouvelle étude clinique démontre que les lingettes Pampers® Aqua Pure sont au moins aussi douces qu'un gant de toilette imbibé d'eau

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

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

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

Score d'érythème moyen par site



Composants d'origine végétale qui ont été testés dermatologiquement

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

Effet tampon de pH

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

Les lingettes Pampers® Aqua Pure sont :

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

[1] Données internes de P&G

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Approuvées par ESPD

Slipped Capital Femoral Epiphysis: think about it!

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Introduction

Slipped Capital Femoral Epiphysis (SCFE) is characterized by the anterior displacement of the femoral neck in regard of the femoral head through the physeal plate. This displacement is usually chronic, stable, and progressive, but can also be acute and unstable, most of the time after a period of continuous evolution.
The general practitioner or the pediatrician is almost exclusively confronted with the stable and chronic presentation since the acute form is very painful, a fracture alike, and the patient is most of the time conducted immediately to an emergency service.
In most cases, the patients describe pain in the groin, often accentuated during exercise and partially relieved by rest. However, 15% of the patients have only isolated pain in the knee or the thigh.
Therefore, physicians should have a high degree of clinical suspicion as the delay in diagnosis can result in more critical deformity of the proximal femur, which worsens the prognosis.

Epidemiology

SCFE occurs in 1 per 1000 to 1 per 10000. Black people are more affected than Caucasians. Obesity is a predisposing factor. The mean age of presentation is 12 years in girls, and 13.5 years in boys, but slips have been reported in 9-year old children. The affection is bilateral in about 20% of the patients at presentation. In the case of unilateral presentation, the risk of developing a slip on the other side is estimated at 30%. This risk is higher as the child is young at the onset. In the case of an underlying disorder, the risk approaches 100%.
Underlying risk factors are renal osteodystrophy, hypothyroidism, growth hormone deficiency, and some genetic affections as the Down syndrome. In atypical presentations (younger than ten or older than 16 or in patients with a weight percentile < 10%), a complete diagnostic workout is mandatory.

Clinical presentation

The most common pattern of the chronic and stable SCFE is a vague pain in the groin in the obese adolescent. Most often, there is no trauma involved. About 15% present with anterointern thigh or knee pain. These cases can be easily missed at the initial visit.
The patient typically presents a limp on the affected side and can show an external rotation.
In a prone position, the affected leg turns externally. Upon passive flexion of the hip, the leg turns spontaneously in external rotation and abduction (Drehmann sign), which is an almost pathognomic sign of SCFE, providing there is already a significant deformity. Trying to turn the hip inwards usually causes discomfort.
When there is clinical suspicion of SCFE, an AP and a frog leg X-ray of the pelvis must be realized as soon as possible.

Radiology

On AP-view (Fig 1):
Widening and irregularity of the physis
Metaphyseal blanch sign of Steele (projection of the posterior epiphyseal edge)
Abnormal Klein's line: a line along the superior border of the neck intersects typically approximately 15-20% of the epiphysis
Coxa vara is seen in more advanced slips

On the frog-leg view (Fig 2):
Posterior slippage of the epiphysis is noted and the Southwick-angle drawn on both sides
If unilateral the Southwick angle is defined as the difference between both measurements
If bilateral, 12° (its normal value) has to be subtracted.
The Southwick angle can be used to classify the severity of slips as mild (less than 30 degrees), moderate (30-50 degrees), or severe (more than 50 degrees).
It is essential to realize that the Southwick-angle can be symmetric in the pre-slip phase of the disease.

Treatment

Once the diagnosis confirmed or highly suspected, further weight-bearing on the affected side is forbidden, and the patient must be referred immediately to a hospital with orthopediatric facilities and expertise. Every SCFE should be considered as an emergency to prevent the worsening of the deformity or transformation in an acute slip.
The following illustrative case underscores the importance of a quick diagnosis, followed by immediate operative stabilization.

Illustrative case

An X-ray of the pelvis was asked by her general practitioner for this twelve-year-old girl after she complained from hip pain for three weeks without trauma. Despite the presence of evident signs suggesting SCFE (positive Klein's sign,

Figure 1: Bilateral SCFE on AP view : Although the Klein's sign is negative (black line), the metaphyseal blanch sign of Steele (white arrow) and the blurring of the physis (black arrow) are clearly demonstrated.

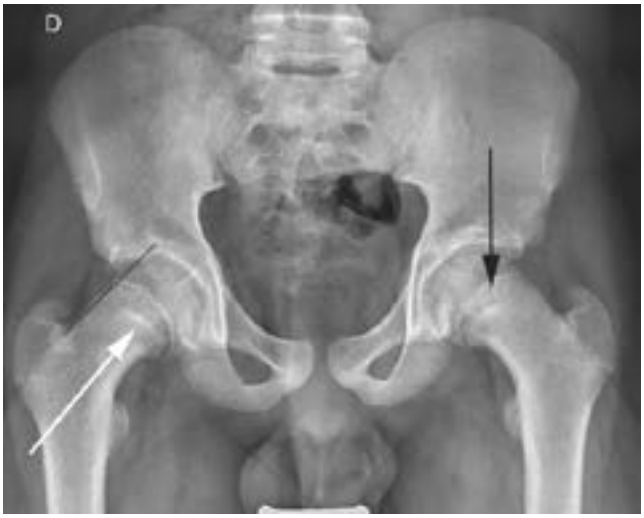
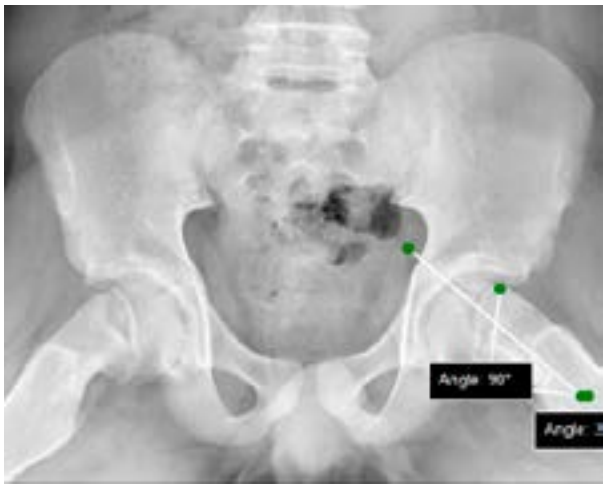


Figure 2: Bilateral SCGE on frogleg view : The Southwick angle (defined as the angle between the femoral neck axis and the line perpendicular to the epiphyseal basis). The normal value is 12° and has to be subtracted. In this example the left Southwick angle is 34°-12° = 22°, which is a mild slip.



widening, and irregularity of the physis), she was erroneously diagnosed as Perthes disease (Fig 3).
She was sent home with rest.
Ten days later, she was admitted to the hospital due to sudden augmentation of the pain followed by the inability of weight-bearing (Fig 4).
The x-ray showed an acute displacement of the left hip.
She was treated by gentle and partial reduction and fixation with a single screw, followed by non-weight bearing for six weeks.
Eight months later, she started to complain of hip pain on the right side. The physis is widened, but there is no slippage (Fig 5).
Edema on the metaphyseal side (T1 weighted magnetic resonance imaging, Fig 6) confirms the SCFE in the pre-slip stage, and consequently, the epiphysis is fixed in situ with a single screw.
Six months later, the physis is closing, and the right hip shows no deformity. The left hip shows a shortening of the neck and a persistent posterior deformity, putting this hip at risk for impingement and subsequent coxofemoral osteoarthritis at a young age. This could have been prevented with a correct diagnosis and prompt treatment after the first X-ray (Fig 7).

Conclusion

The aim of this communication is to raise the degree of suspicion concerning the SCFE among first-line caregivers because there is a growing body of evidence that the time between the onset of symptoms and treatment is strongly correlated with the outcome.

Figure 5: Illustrative case: Eigth months later, the patient complains of a a painful right hip. The X-ray shows some epiphyseal blurring, without significant displacement of the physis.

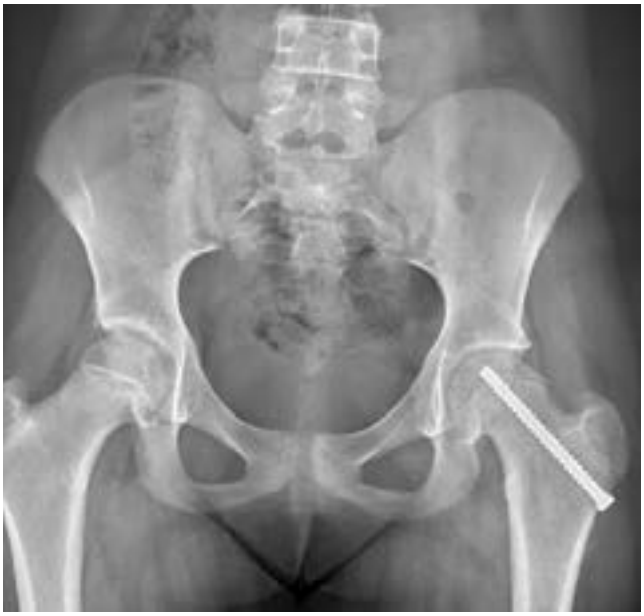


Figure 3: Illustrative case: The first X-ray, showing distinctive features of SCFE was labeled erroneously as Perthes' disease and treated with rest. No frogleg view was realized.

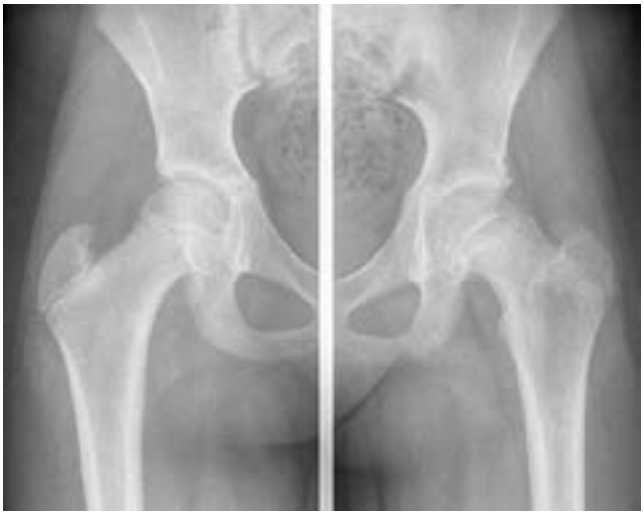


Figure 6: Illustrative case : A magnetic resonance study shows metaphyseal edema (hyposignal in T1 weighted image). An epiphysiodesis in situ was performed.

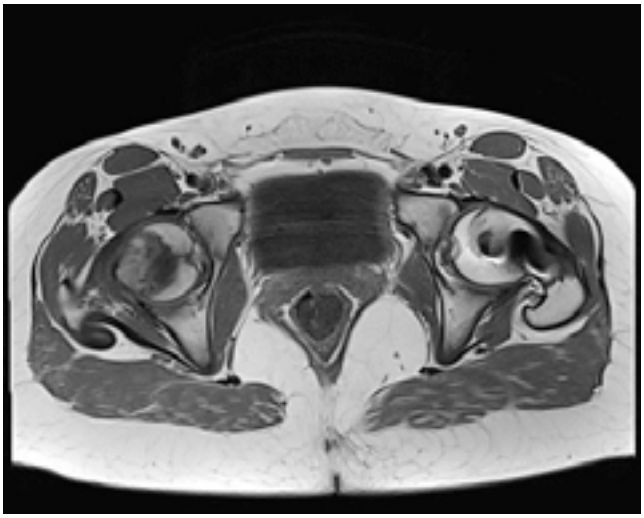


Figure 4: Illustrative case: Ten days after the initial x-ray, the patient was unable to walk. The X-ray shows a severe displaced and unstable epiphysiolysis.

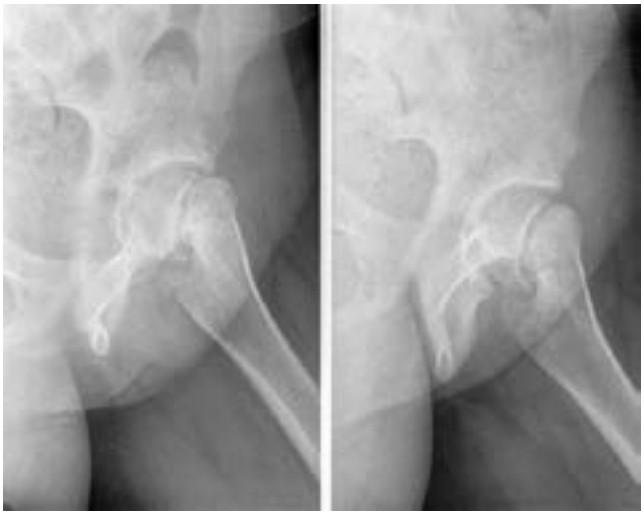
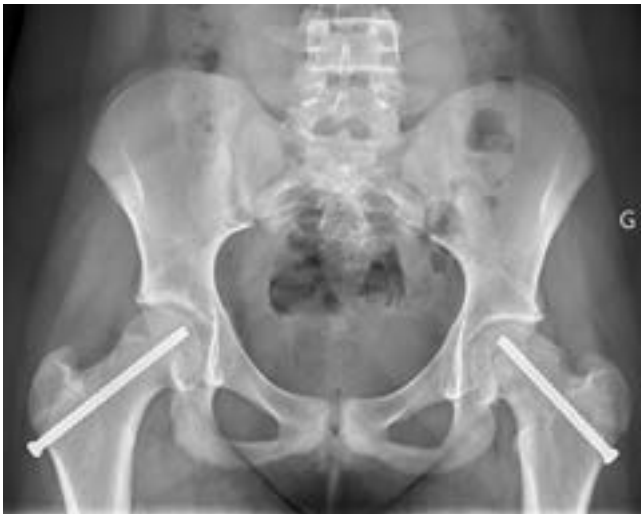


Figure 7: Illustrative case : Final outcome with a deformed left hip and an normal right hip. Early coxarthrosis is likely to develop at left.



NAAM VAN HET GENEESMIDDEL: HEMANGIOL 3,75 mg/ml. Drank **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING:** ml oplossing bevat 4,28 mg propranolol hydrochloride equivalent aan 3,75 mg propranololbase. Lijst van hulpstoffen: Hydroxyethylcellulose, Natriumsacharine, Aardbeienaroma (bevat propyleenglycol), Vanillearoma (bevat propyleenglycol), Citroenzuurmonohydraat, Gezuiverd water. Hulpstof met bekend effect: 1 ml oplossing bevat Propyleenglycol 2,60 mg. **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 (zie rubriek 4.2 van de volledige SKP). **DOSERING EN WIJZE 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. HEMANGIOL moet tijdens of onmiddellijk na een voeding worden gegeven om het risico op hypoglykemie te vermijden.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. Pediatrische patiënten: door de afwezigheid van klinische werkzaamheids en veiligheidsgegevens mag HEMANGIOL niet gebruikt worden bij zuigelingen 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 zuigelingen en 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 geneesmiddel aan kinderen jonger dan 1 jaar met een lever- of nierfunctiestoornis niet aanbevolen (zie rubriek 4.4 van de volledige SKP). Wijze van toediening: oraal gebruik. HEMANGIOL 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 gevulde 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: Hartslag (slagen/min) - 0-3 maanden: 100 - 3-6 maanden: 90- 6-12 maanden: 80 • Lage bloeddruk onder de volgende grenzen: Leeftijd: Bloeddruk (mmHg) - 0-3 maanden: 65/45 - 3-6 maanden: 70/50 - 6-12 maanden: 80/55 • Cardiogene shock • Hartfalen dat niet onder controle is met behandeling • 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 (16,7%), verergerde luchtweginfecties zoals bronchitis en bronchiolitis in combinatie met hoesten en koorts, diarree (16,5%) en braken (11,5%). 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: bronchits. Vaak: bronchiolitis. **Voedings- en stofwisselingsstoornissen:** Vaak: verminderde eetlust. Psychische stoornissen: Zeer vaak: slaapstoornissen. 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. **Maagdarmstelsel-aandoeningen:** Zeer vaak: diarree, braken. Vaak: obstipatie, abdominale pijn. **Huid- en onderhuidaandoeningen:** Vaak: erytheem, luierdermatitis. Soms: urticaria, alopecia. Niet gekend: psoriasiforme dermatitis. **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 (zie rubriek 4.4 van de volledige SKP). 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 (zie rubriek 4.4 van de volledige SKP).. Gelijktijdige behandeling met systemische corticosteroïden kan het risico op hypoglykemie verhogen (zie rubriek 4.5 van de volledige SKP).. In de literatuur werd bij enkele patiënten met groot geülcereerd hemangioom hyperkaliëmie gemeld (zie rubriek 4.4 van de volledige SKP). 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 Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie EUROSTATION II Victor Hortaplein, 40/ 40 B-1060 Brussel / Postbus 97 B-1000 Brussel Madou Website: 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 VAN HERZIENING VAN DE TEKST:** 01/2019. Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees geneesmiddelenbureau http://www.ema.europa.eu. **AFLEVERWIJZE:** geneesmiddel op medisch voorschrift.

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Pierre Fabre
DERMATOLOGIE

1. D.P. Krowchuk et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. Pediatrics Volume 143, number 1, january 2019: e20183475
2. Waarvoor systemische behandeling vereist is

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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 ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT** Bexsero suspension injectable en seringue préremplie Vaccin méningococcique groupe B (ADNr, composant, adsorbé) - EU/1/12/812/001 Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09 **COMPOSITION QUALITATIVE ET QUANTITATIVE** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de ***Neisseria meningitidis*** groupe B [1, 2, 3] 50 microgrammes Protéine recombinante NadA de ***Neisseria meningitidis*** groupe B [1, 2, 3] 50 microgrammes Protéine de fusion recombinante fHbp de ***Neisseria meningitidis*** groupe B [1, 2, 3] 50 microgrammes Vésicules de membrane externe (OMV) de ***Neisseria meningitidis groupe*** B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4 [2] 25 microgrammes [1] produite dans des cellules d'*E. coli* par la technique de l'ADN recombinant [2] adsorbée sur hydroxyde d'aluminium (0,5 mg Al^{3+}) [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H) **DONNÉES CLINIQUES 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	Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique [d]
Adolescents (à partir de 11 ans) et adultes*			

[a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne doit pas être administrée au-delà de l'âge de 24 mois. [c] Voir rubrique 5.1 du RCP complet. La nécessité et le moment d'administration d'une dose de rappel n'ont pas encore été déterminés. [d] Voir rubrique 5.1 du RCP complet. * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, sous-cutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **CONTRE-INDICATIONS** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **MISES EN GARDE SPÉCIALES ET PRÉCAUTIONS D'EMPLOI** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entraîner le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vaso-vagales (syncope), de l'hyperventilation ou des réactions en rapport avec le stress peuvent survenir lors de la vaccination comme réaction psychogène à l'injection avec une aiguille (voir rubrique « Effets indésirables »). Il est important que des mesures soient mises en place afin d'éviter toute blessure en cas d'évanouissement. Ce vaccin ne doit pas être administré aux patients ayant une thrombocytopénie ou tout autre trouble de la coagulation qui serait une contre-indication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination par Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation. Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles post-vaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique. Les personnes ayant des déficits hétréditaires du complément (par exemple les déficits en C3 ou C5) et les personnes recevant un traitement inhibiteur de l'activation de la fraction terminale du complément (par exemple, l'éculizumab) ont un risque accru de maladie invasive due à ***Neisseria meningitidis*** du groupe B, même après avoir développé des anticorps après vaccination par Bexsero. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. **EFFETS INDÉSIRABLES** Résumé du profil de sécurité La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6837 étaient des nourrissons et des enfants (de moins de 2 ans), 1051 étaient des enfants (entre 2 et 10 ans) et 2677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69% à 79 % des sujets lorsque Bexsero était co-administré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et ***Haemophilus influenzae*** de type b), contre 44% à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) Fréquent : (≥ 1/100 à < 1/10) Peu fréquent : (≥ 1/1 000 à < 1/100) Rare : (≥ 1/10 000 à < 1/1 000) Très rare : (< 1/10 000) Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles) Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans)** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Troubles du métabolisme et de la nutrition Très fréquent : troubles alimentaires Affections du système nerveux Très fréquent : somnolence, pleurs inhabituels, céphalée Peu fréquent : convulsions (y compris convulsions fébriles) Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire) Affections vasculaires Peu fréquent : pâleur (rare après le rappel) Rare : syndrome de Kawasaki Affections gastro-intestinales Très fréquent : diarrhée, vomissements (peu fréquents après le rappel) Affections de la peau et du tissu sous-cutané Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel) Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans) Peu fréquent : eczéma Rare : urticaire Affections musculo-squelettiques et systémiques Très fréquent : arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité Peu fréquent : fièvre (≥ 40 °C) Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois) **Adolescents (à partir de 11 ans) et adultes** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Affections du système nerveux Très fréquent : céphalée Fréquence indéterminée : syncope ou réaction vaso-vagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire) Affections gastro-intestinales Très fréquent : nausées Affections musculo-squelettiques et systémiques Très fréquent : myalgies, arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois) Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration. **Belgique** Agence fédérale des médicaments et des produits de santé Division Vigilance 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** 03/2019 (v09) **MODE DE DELIVRANCE** Sur prescription médicale.

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

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