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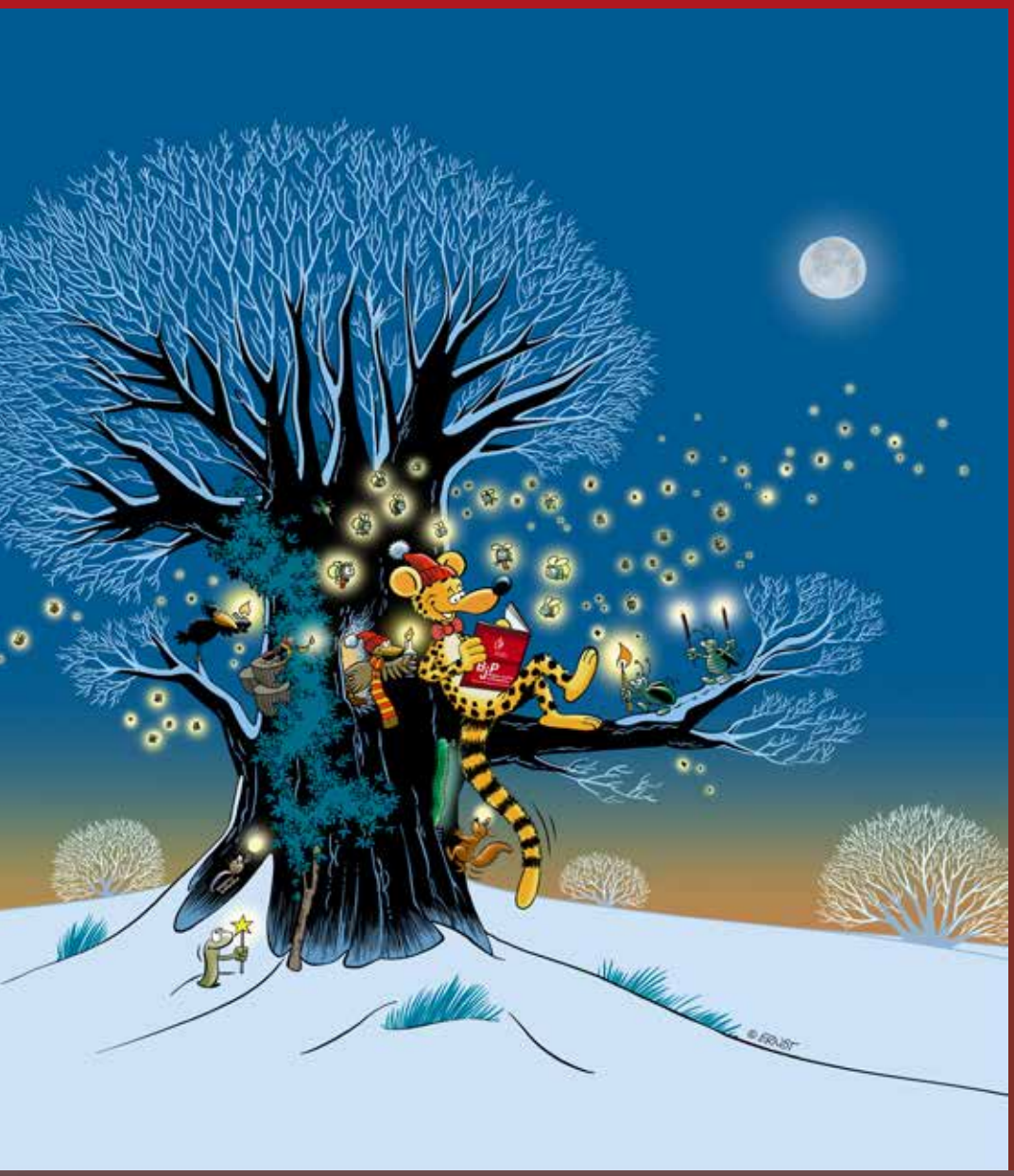

Research articles

Predictive factors for Cerebral Palsy: a cohort study

Acceptability of New RSV Preventive Tools to Parents and Healthcare Workers

General Knowledge about Sudden Infant Death Syndrome Prevention Measures among Flemish Mothers

Non-Invasive Ventilation and NIV-NAVA in Preterm Infants: a Prospective Observational Cohort Study

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Review article

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Case report

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Made in Belgium

Fear-Anxiety-Phobia of the Dentist: Development and Analysis of a Federating Instrument about the Different Material and Behavioral Techniques for Ideal Patient Management: Clinical Studies

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Tania Vanhée

Les soins pour **les peaux très sèches à atopiques de toute la famille(*)**

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Light and kindness on earth !

At this time of year, light assumes a particular significance in our lives, coinciding with the winter solstice. This period is characterised by the shortest days and longest nights, a phenomenon attributable to the tilt of the Earth's axis of rotation around the sun. At the end of December (on the 21st or 22nd to be precise), the northern hemisphere is at its furthest from the sun, resulting in a reduction in the amount of sunlight received.

As paediatricians, we all know the importance of light. It is a source of energy, a natural regulator and a fundamental element in the health, growth and development of living beings. Through photosynthesis, plants, algae and some bacteria use light to produce energy in the form of glucose, releasing oxygen in the process. This energy then feeds the herbivores and carnivores in the food chain. Increasingly widespread technological tools, such as photovoltaic panels, now make it possible to convert sunlight into electricity, which can then be modulated and distributed to support human activities. Light plays also a key role in regulating circadian rhythms, which influences sleep, wakefulness, digestion and many other physiological functions. Natural light promotes a gentle awakening while darkness prepares your body for rest. Many organisms depend on light to trigger growth or reproduction. The most illustrative examples are plants that flower only when the days are longer and some animals that hibernate to slow down their metabolism during winter. Light is essential for well-being and health. Notably, light serves in necessary to activate vitamin D, which is essential for the proper functioning of our bodies. It contributes to our mental and psychological development, as demonstrated by seasonal depression, which is more common in winter, and the benefits of light therapy.

Light also reminds us of the importance of balance and nuance. Light can present risks when used incorrectly or in excess. In contemporary societies, adults, young people and children alike are subject to the harmful effects of blue light, emitted by phone, computer and tablet screens. These devices have become an integral part of our daily, evening and night-time routines, and their use has been linked to a number of health concerns. These include eye strain, headaches, and disturbances in the production of melatonin that regulates sleep. Additionally, there is a growing concern over digital dependency and the stress that arises from the inability to disengage from devices and obtain sufficient rest. Excessive and repeated exposure to sunlight, particularly UV rays, causes skin irritation. In the longer term, this can lead to accelerated ageing of the skin, eye diseases such as cataracts, and an increased risk of skin cancer. Disproportionate artificial lighting in urban areas has also been shown to disrupt natural ecosystems. This has been observed with migratory birds and certain marine species such as sea turtles being disoriented by urban lights. Similarly, insects and plants experience disruption to their life and growth cycles when exposed to abnormal light level or timing.

Beyond these astronomical and biological considerations, light also has a symbolic dimension. Over the last few weeks, we have seen all kinds of lighting appear to guide and brighten up our long nights. These illuminations transform facades and buildings into magical canvases. Trees are adorned with little stars that glow in the dark. These lights narrate a collective story, the quest of humanity for warmth and sharing. These lights bring people together in squares, Christmas markets and homes. They warm the atmosphere, reminding us that even in the darkest of times, there is always a way forward.

In this spirit, the editorial board of *The Belgian Journal of Paediatrics* wishes you a Holiday season filled with radiance, sparkle and light. Through this editorial text and the cover drawing by our cartoonist Serge Ernst, we also hope that in 2025, each of us will be able to embody a little sources of light in our own way. In our families, in our teams or with our patients, may we incarnate these little fireflies, the squirrel with the headlamp, the blackbird with the candle or the lizard with the star. May we bring these little lights that comfort or reassure, may we be these invitations to hope or gratitude, may we turn our gaze with confidence on new horizons.

With all our affection and enthusiasm,

Christophe Chantrain and Marc Raes, Editors-in-chief

Uw vragen of commentaar
Vos questions ou commentaires

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VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

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Voor een **gemakkelijke spijsvertering** en een verminderde gastro-intestinale transittijd[4,5]

PREBIOTISCHE VEZELS scGOS:lcFOS (9:1)
Ondersteunt een gezonde darmmicrobiota door het aantal **nuttige bacteriën te verhogen** en **schadelijke bacteriën te verminderen**[6,7]

VERLAAGD LACTOSEGEHALTE**
Minder **flatulentie**, **krampen** en **kolieken**[8]

INGEDIKT MET AARDAPPEL- EN MAÏSZETMEEL
Significante daling van **milde regurgitatie**[9]

INGEDIKT MET JOHANNESBROODPITMEEL
Significante daling van regurgitatie[10,11]

ONZE UNIEKE **PREBIOTISCHE COMBINATIE** scGOS:lcFOS (9:1) EN **POSTBIOTICA**
Ondersteunt het **immuunsysteem** via de **darmmicrobiota**[6,12] Samenstelling en frequentie van de ontlasting benadert die van gezonde, **borstgevoede zuigelingen**[13]

HMO 3'GL
Rechtstreeks effect op **immuuncellen**[14]

CASEÏNE EN **WEI-EIWIT-VERHOUDING** 60:40
Uitvlokking van caseïne in de maag[15]

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Predictive factors for Cerebral Palsy: a cohort study

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Keywords

Cerebral Palsy, Magnesium sulphate, Neuroprotection, Prematurity, Periventricular leukomalacia.

Abstract

Objective

Antenatal administration of magnesium sulphate (MgSO4) is recommended worldwide for imminent preterm birth due to its proven protective effect on Cerebral Palsy (CP). The aim of this study was to identify predictive factors for (suspect) CP, for neonates born between 24 and 32 weeks' gestation, who are dismissed from the Neonatal Intensive Care Unit (NICU).

Methods

Cohort study of neonates born between 2012 and 2018 in Ghent University Hospital at a gestational age between 24 and 32 weeks. Predictive and risk factors for (suspect) CP described in literature were examined through modelling using generalized estimating equations.

Results

The study population consisted of 474 neonates, of which 293 were antenatally exposed to MgSO4. The composite outcome (suspect CP or CP) was present in 44 (9.3%) neonates. The final model consisted of the following variables: neuroprotection (odds ratio (OR): 0.38 (95% confidence interval (CI): 0.19, 0.75); p = 0.005), periventricular leukomalacia (OR: 2.41 (95%CI: 1.20, 4.82); p = 0.013), smoking (OR: 2.57 (95%CI: 1.21, 5.44); p = 0.014) and reason of preterm delivery (placental insufficiency versus SPL (OR: 0.34 (95%CI: 0.11, 1.08); p = 0.068), PPROM versus SPL (OR: 1, 23 (95%CI: 0.60, 2.52); p = 0.567) and other causes of preterm delivery versus SPL (OR: 0.70 (95%CI: 0.17, 2.99); p = 0.633)).

Conclusion

Neuroprotection is shown to be a protective factor. Periventricular leukomalacia and smoking are negatively associated with CP.

Introduction

Cerebral Palsy (CP) is described as a heterogeneous group of non-progressive motor disorders caused by chronic brain injury which occurs in the developing brain of the foetus or infant (1). Cerebral palsy is the main cause of disability at young age. The incidence amounts to 2 to 3 per 1000 live births worldwide; in Belgium it is estimated at 1.48 per 1000 live births (2). This number increases to 40 to 100 per 1000 live births when the neonate is born at less than 27 weeks or with a birth weight less than 1000 grams (3). Preterm birth is thus an important risk factor for CP. There are numerous other risk factors, both maternal and foetal, such as maternal smoking and periventricular leukomalacia (PVL) (4, 5). The consequences of CP not only affect the individual but also the family. Furthermore it has a high socio-economic burden (6, 7).

One of the preventive measures is prenatal administration magnesium sulphate (MgSO4) as a neuroprotective agent to mothers at risk of delivering preterm. Five randomized controlled trials (RCT) were performed evaluating the effect of MgSO4 on the occurrence of CP (8-12). Only one of these trials showed that the administration of MgSO4 results in a significant decrease of patients with mild or severe CP (relative risk (RR): 0.55 (95%CI: 0.32 - 0.95)) (11). Meta-analyses and an individual participant data meta-analysis, however, showed a significant reduction of CP in the MgSO4 group (13-18). As a result, several guidelines recommend the intravenous use of MgSO4 as neuroprotection for imminent preterm birth at less than 32 weeks' gestation (19, 20). Major maternal and foetal side effects are limited with the recommended MgSO4 dosing schemes (10, 13, 14, 21-23).

Considering the burden of disease and the absence of a cure, the prevention of CP is important. The aim of this study was to identify predictive factors for (suspect) CP, for neonates born between 24 and 32 weeks' gestation, discharged from the neonatal intensive care unit (NICU).

Methods

This study was performed in the context of the PRETURN-project at the Ghent University Hospital (PREdiction in preTerm birth meets caUsal infeReNce). In this project, one of the aims is to provide clinical risk predictions. Informed consent was obtained from the parents of included neonates. The approval of the Medical Ethics Committee of Ghent University Hospital was obtained on 22/10/2019 with following registration numbers: B670201941300 and B670201941301.

From 2012 until 2017, data were collected retrospectively from the patient records. Prospective data collection began in mid-2017. Data were collected and managed using REDCap® (Research Electronic Data Capture) (24, 25).

The primary outcome of this study was to identify predictive factors for (suspect) CP. These factors could be used for counselling parents

whose neonates are born before 32 weeks' gestation and are discharged from the NICU.

The diagnosis of CP is not based on a single diagnostic tool. It is recommended to use a combination of clinical history, neurological imaging and a standardized neurological examination to make an early and accurate diagnosis of CP (5). Based on the neurological examination, a distinction can be made between a normal result, suspect psychomotor problem, suspect CP and confirmed CP. The following neurological test results indicate suspect CP: hyperreflexia, problems with muscle coordination, muscle control, muscle tone, balance and posture (26, 27). For evaluation of motor development between birth and 10 months (corrected age), the Alberta Infant Motor Scale (AIMS) is used. To classify the various categories of CP, the Flemish Centres for Developmental Disorders use Flemish norms of the Bayley-III scales for cognition, gross motor skills, fine motor skills, language comprehension, and language expression. The assessment is conducted from 10 months (corrected age) to 36 months of age. The centre consistently collaborates with an experienced paediatric neurologist, who also reviews imaging, and a specialized physical therapist trained in Bobath therapy. At a post-term age of 4 months (corrected age), there may still be uncertainty, especially if the patient shows only hypertonia without pyramidal reflex or imaging abnormalities. In these cases, the term 'suspect CP' is used. From a post-term age of 10 months (corrected age), CP can definitively be diagnosed.

Participants

Neonates born between 2012 and 2018 in Ghent University Hospital (Belgium), were included in this study. Only neonates born at less than 32 weeks' gestation, discharged from the NICU, followed-up in the Centre for Developmental Disorders and without missing data of the composite outcome (CP or suspect CP) were included.

Instruments

Neonates born before 2015 were offered long term follow-up at the Centre for Developmental Disorders if they were born at less than 30 weeks and/or if their birth weight was less than 1250 grams. From the year 2015 onwards, follow-up was provided at a gestational age of less than 32 weeks and/or a birth weight of less than 1500 grams. Four follow-up appointments are scheduled at the corrected age of 4 months, the corrected age of 10 months, and at the age of 2 and 4 years old.

In Ghent University Hospital, MgSO4 has been given for imminent preterm delivery since 2014. However, neonates born before 2014 were also included in the dataset. The indication for MgSO4 before 2014 was preeclampsia. Both for neuroprotection and eclampsia prevention, a bolus of 4g MgSO4 followed by a maintenance dose of 1 g/h is administered intravenously. Neuroprotection is started when birth is expected within the following 24 hours at a gestational age less than 32 weeks.

Model and modelling strategy

Risk and protective factors for CP were identified by literature review and the evidence for the neuroprotective effect of MgSO4 was studied based on published RCT data (10-14). A search was performed via Pubmed and Embase with the following search terms: 'premature birth', 'parturition', 'prematurity', 'premature labor', 'neurodevelopmental disorders', 'motor dysfunction', 'cerebral palsy', 'infant mortality', 'neuroprotection', 'magnesium sulfate' and 'brain protection' (The literature search is detailed in the appendix).

The following factors associated with CP were identified in literature: neuroprotection with MgSO4, smoking, PVL, gestational age at birth, mode of delivery, reason for preterm delivery, intracerebral haemorrhage (ICH), birthweight, foetal growth restriction (FGR), antenatal administration of corticosteroids (ACS), gender and number of foetuses.

All statistical analyses were performed using IBM SPSS version 26. Generalized estimating equations were used to account for the non-independence of multiples. As a first step, a descriptive analysis of the database was performed (Table 1).

Table 1: Descriptive statistics.

Variable		Number	%
Gender	Male	262	55.3
Smoking	Never smoked or quit before/during pregnancy	404	85.2
	Smoking during pregnancy	65	13.7
	Missing values	5	1.1
Gestational age	24 weeks	18	3.8
	25 weeks	21	4.4
	26 weeks	38	8.0
	27 weeks	36	7.6
	28 weeks	67	14.1
	29 weeks	85	17.9
	30 weeks	91	19.2
	31 weeks	118	24.9
Reason preterm delivery	SPL	164	34.6
	PPROM	158	33.3
	Placental insufficiency (preeclampsia or FGR)	124	26.2
	Others	28	5.9
Birth weight	500 -1000 grams	144	30.4
	1001 – 1500 grams	211	44.5
	1501 – 2000 grams	108	22.8
	2001 – 2500 grams	11	2.3
Neuroprotection	Yes	293	61.8
FGR	Yes	61	12.9
CP or suspect CP	Yes	44	9.3

Results

Before combining multiple predictors, every variable identified as a risk or protective factor for CP was tested individually for an association with the composite outcome (suspect CP or CP) using univariate analysis. A significant association was observed for five out of the 12 factors described above: neuroprotection ($p < 0.001$), smoking ($p = 0.012$), PVL ($p = 0.017$), gestational age at birth ($p = 0.022$) and reason for preterm delivery ($p = 0.036$). In the next step, both forward and backward selection of variables, significantly associated in univariate analysis, were used ($\alpha = 0.05$). In the forward model the most significant variable was added first. For backward selection, the variable with the highest p-value was removed from the model in each step, to end with only significant variables (5 variables). For variables with multiple categories the lowest

Table 2: Overview of included predictors in the final model.

Predictor	B	95% Wald Confidence interval for B		Exp(B)	Standard Error	95% Wald Confidence interval for Exp (B)		P-value
		Lower	Upper			Lower	Upper	
Intercept	-2.090	-2.696	-1.485	0.124	0.309	0.068	0.227	< 0.001
Neuroprotection = yes	-0.973	-1.656	-0.290	0.378	0.349	0.191	0.748	0.005
Neuroprotection = no	0	.	.	1	.	.	.	.
PVL = yes	0.879	0.185	1.573	2.409	0.354	1.204	4.821	0.013
PVL = no	0	.	.	1	.	.	.	.
Smoking = Smoked during pregnancy	0.942	0.190	1.694	2.565	0.384	1.209	5.440	0.014
Smoking = Never smoked or quit before/during pregnancy	0	.	.	1	.	.	.	.
Reason for preterm delivery = placental insufficiency	-1.068	-2.217	0.080	0.344	0.586	0.109	1.084	0.068
Reason for preterm delivery = PPROM	0.209	-0.507	0.925	1.233	0.365	0.602	2.522	0.567
Reason for preterm delivery = others	-0.353	-1.801	1.094	0.702	0.739	0.165	2.987	0.633
Reason for preterm delivery = SPL	0	.	.	1	.	.	.	.

Table 3: Incidence of (suspect) CP according to gestational age. N (%).

	24	25	26	27	28	29	30	31	Total
CP or suspect CP = no	12 (66.7)	19 (90.5)	35 (92.1)	34 (94.4)	63 (94.0)	71 (83.5)	85 (93.4)	111 (94.1)	430 (90.7)
CP or suspect CP = yes	6 (33.3)	2 (9.5)	3 (7.9)	2 (5.6)	4 (6.0)	14 (16.5)	6 (6.6)	7 (5.9)	44 (9.3)
Total	**18**	**21**	**38**	**36**	**67**	**85**	**91**	**118**	**474**

p-value was used. Table 2 gives an overview of the included predictors in the final model. The variables retained after this stepwise method were tested for correlations via the chi-square test in crosstabs to prevent overfitting of the model. Multicollinearity was subsequently assessed by means of Variance Inflation Factor (VIF) to check for a linear relationship between the predictors. The resulting model with the lowest goodness of fit value was considered to contain the most important predictors for (suspect) CP. The composite outcome (suspect CP or CP) in this dataset is low (9.3%), hence odds ratio's (OR) can be interpreted as relative risk (RR) (28).

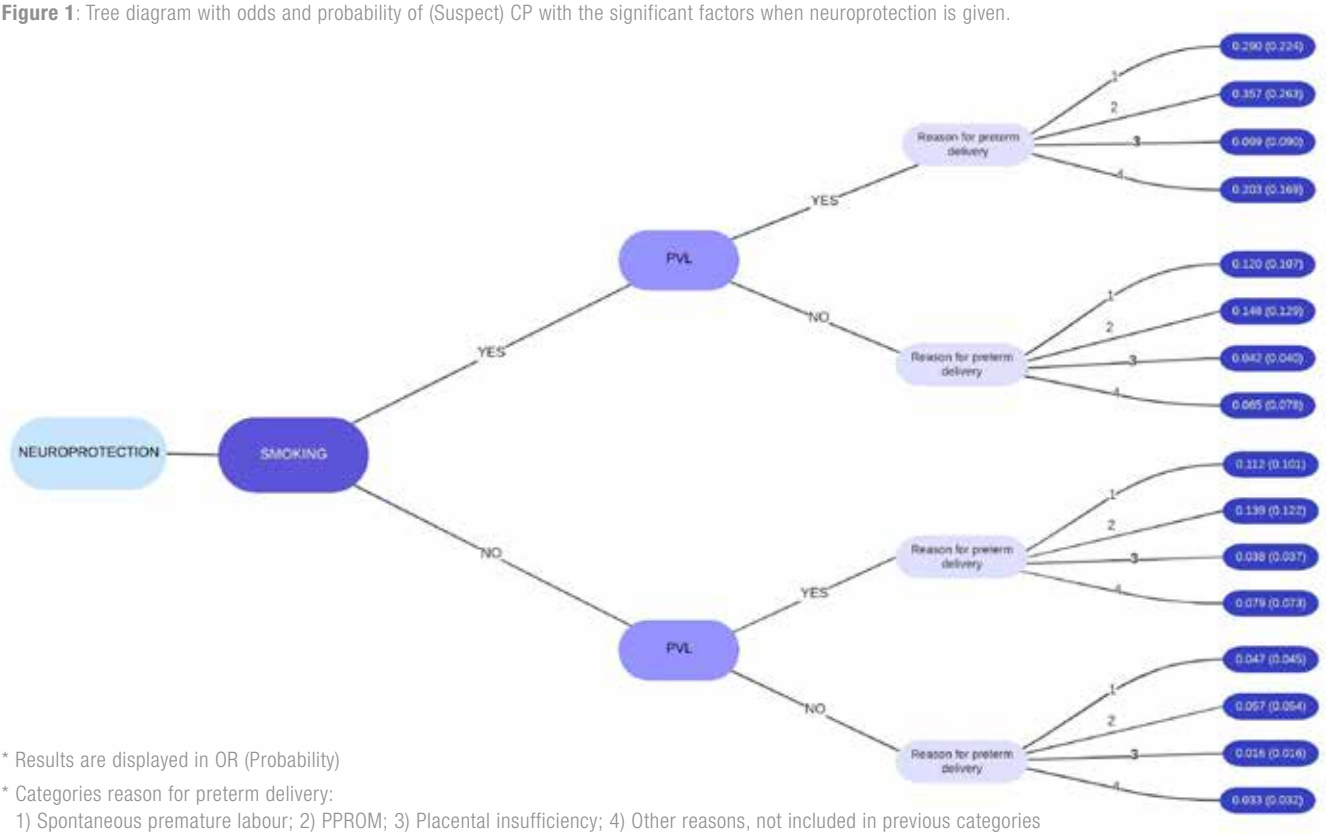
Of the initial dataset (1363 neonates born between 2012 and 2018), 848 neonates were born before 32 weeks' gestation. Of the 708 neonates discharged from the NICU (16.5 % neonatal mortality), only 474 presented for follow-up in the Centre for Developmental Disorders. There was no missing outcome data. Five missing values were found for the variable smoking, no missing values were observed in the other variables. Antenatal MgSO4 was given in 293 (61.8%) of cases. In the dataset, more males than females where under follow-up (resp. 55.3% versus 44.7%). There were 30.6% multiple births. Different reasons for preterm delivery were noted in the dataset: spontaneous premature labour (SPL), premature preterm rupture of membranes (PPROM), placental insufficiency and other not further specified reasons (respectively 34.6%, 33.3%, 26.2% and 5.9%). The composite outcome (suspect CP or CP) was present in 44 (9.3%) neonates. The incidence of (suspect) CP according to gestational age is presented in Table 3.

Antenatal neuroprotection was associated with a 62% lower risk of (suspect) CP (OR: 0.38 (95%CI: 0.19, 0.75); p = 0.005) adjusted for smoking, PVL and reason for preterm delivery.

Periventricular leukomalacia and smoking were associated with a higher risk of (suspect) CP (respectively (OR: 2.41 (95%CI: 1.20, 4.82); p = 0.013) and (OR: 2.57 (95%CI: 1.21, 5.44); p = 0.014)) irrespective of the other factors: administration of neuroprotection, aetiology of preterm delivery, PVL and smoking.

When gestational age was examined in relation to CP in an individual GEE model, a correlation was observed (p = 0.022 (95%CI: 0.718, 0.974)). However, when a GEE model with multiple variables was constructed, gestational age was no longer significantly correlated with CP (p = 0.295 (95%CI 0.764, 1.085)).

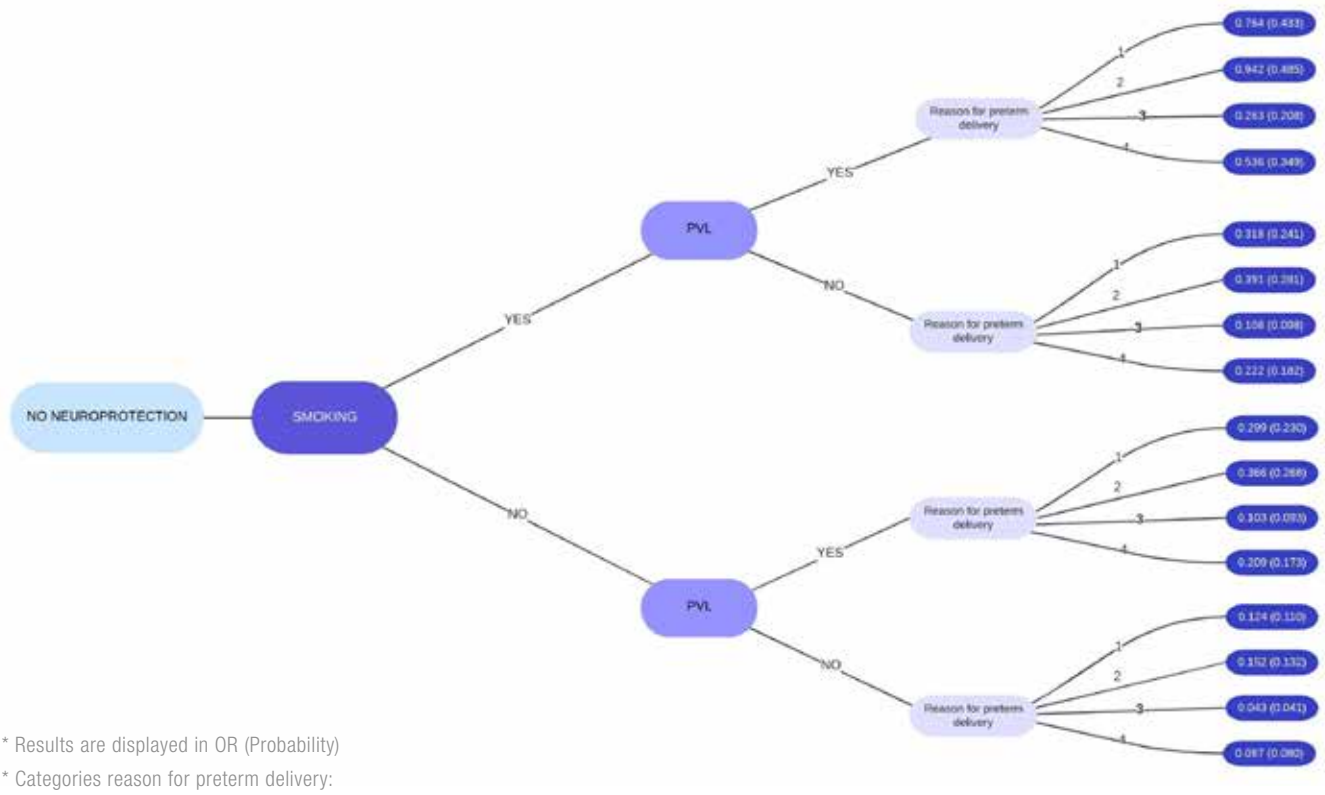
Figure 1: Tree diagram with odds and probability of (Suspect) CP with the significant factors when neuroprotection is given.



* Results are displayed in OR (Probability)

* Categories reason for preterm delivery:
1) Spontaneous premature labour; 2) PPROM; 3) Placental insufficiency; 4) Other reasons, not included in previous categories

Figure 2: Tree diagram with odds and probability of (Suspect) CP with the significant factors when neuroprotection is not given.



* Results are displayed in OR (Probability)

* Categories reason for preterm delivery:
1) Spontaneous premature labour; 2) PPROM; 3) Placental insufficiency; 4) Other reasons, not included in previous categories

Adjusted for smoking, PVL and neuroprotection, there is no obvious association between the reason of preterm delivery and (suspect) CP (placental insufficiency versus SPL (OR: 0.34 (95%CI: 0.11, 1.08); p = 0.068), PPROM versus SPL (OR: 1, 23 (95%CI: 0.60, 2.52); p = 0.567) and other causes of preterm delivery versus SPL (OR: 0.70 (95%CI: 0.17, 2.99); p = 0.633)).

Table 4 was composed to present the model in a practical way. It shows all possible combinations of the four predictors with their corresponding odds on the composite outcome. A tree diagram was also created to represent the model more practically (Figure 1 and 2).

Table 4: Possible combinations with probability and odds.

Neuro-protection	PVL	Smoking	Reason	N	CP (%)	Probability[1]	Odds[2]
0	0	0	1	40	0 (0)	0,110	0.124
0	0	0	2	47	4 (8.5)	0.132	0.152
0	0	0	3	14	1 (7.1)	0.041	0.043
0	0	0	4	13	3 (23.1)	0.080	0.087
1	0	0	1	63	7 (11.1)	0.045	0.047
1	0	0	2	58	4 (6.9)	0.054	0.057
1	0	0	3	73	1 (1.4)	0.016	0.016
1	0	0	4	6	0 (0)	0.032	0.033
0	1	0	1	12	2 (16.7)	0.230	0.299
0	1	0	2	14	7 (50)	0.268	0.366
0	1	0	3	3	0 (0)	0.093	0.103
0	1	0	4	4	0 (0)	0.173	0.209
0	0	1	1	11	6 (54.5)	0.241	0.318
0	0	1	2	8	1 (12.5)	0.281	0.391
0	0	1	3	5	1 (20)	0.098	0.108
0	0	1	4	4	0 (0)	0.182	0.222
1	0	1	1	6	0 (0)	0.107	0.120
1	0	1	2	11	0 (0)	0.129	0.148
1	0	1	3	7	0 (0)	0.040	0.042
1	0	1	4	0	0 (0)	0.078	0.085
0	1	1	1	1	0 (0)	0.433	0.764
0	1	1	2	2	2 (100)	0.485	0.942
0	1	1	3	2	1 (50)	0.208	0.263
0	1	1	4	1	0 (0)	0.349	0.536
1	1	0	1	26	2 (7.7)	0.101	0.112
1	1	0	2	14	1 (7.1)	0.122	0.139
1	1	0	3	17	0 (0)	0.037	0.038
1	1	0	4	0	0 (0)	0.073	0.079
1	1	1	1	3	0 (0)	0.224	0.290
1	1	1	2	2	1 (50)	0.263	0.357
1	1	1	3	2	0 (0)	0.090	0.099
1	1	1	4	0	0 (0)	0.169	0.203
.	.	Missing	.	5	0 (0)		

Discussion

The aim of this study was to identify predictive factors that could be used for counselling at the time of discharge from the NICU. Four factors were identified: neuroprotection with MgSO4, PVL, smoking and reason for preterm delivery. One of the categories within the variable reason for preterm delivery, namely placental insufficiency, is associated with PVL and smoking. When this variable was added in the combined GEE model, it gave a better fit, even though none of the categories in the variable were significantly correlated with CP. Furthermore, preeclampsia is included in the category placental insufficiency. Women suffering from preeclampsia also receive MgSO4, this is another reason why the variable reason for preterm delivery affects the goodness of fit of the model. The variable gestational age was not significantly correlated with CP in this study, contrary to evidence found in the literature. Gestational age is regarded as one of the most important risk factors for CP in literature. While a significant association was observed between gestational age and the composite outcome in the univariate analysis, this significant association disappeared in the multivariate analysis. A possible explanation for this phenomenon is that the variables PVL and reason for preterm delivery, which are correlated to the variable gestational age, are included in the final model. Therefore, the incorporation of gestational age as a predictor was not of added value.

Using these factors, a mean odds of developing CP can be calculated (Table 4). We present an example to illustrate the practical application of the prediction model. Consider a neonate whose mother received neuroprotection and smoked during pregnancy. The neonate did not develop PVL and was born preterm due to PPROM. In this case, the average odds of (suspected) CP would be 0.148. Table 4 represents all possible combinations with their respective odds of (suspected) CP. From this table, it is confirmed that the average odds of (suspected) CP are the lowest when neuroprotection is provided, the neonate does not develop PVL, the mother does not smoke, and the reason for preterm delivery is placental insufficiency (odds = 0.016). Conversely, the average odds of (suspected) CP are the highest when no neuroprotection is given, the neonate develops PVL, the mother smokes, and the reason for preterm delivery is PPROM (odds = 0.942).

Strengths and limitations

Data collection was conducted both retrospectively and prospectively, resulting in a higher quality study compared to conventional retrospective studies. A superior data collection can be obtained by solely using prospective studies.

The findings in this study correlated with the results found in literature. Furthermore, from a clinical perspective, these results can also be expected.

Only neonates with a known outcome were included in this study. Thus, neonates who were not further followed at the Centre for Developmental Disorders, regardless of the reason why, were not included. This could have resulted in an overestimation of the incidence of CP in the study population. The risk of selection bias should therefore be taken into account.

As mentioned earlier, CP is a heterogeneous group of disorders. Based on the identified factors, counselling can be provided regarding the presence or absence of CP. However, no statement can be made regarding the severity of the disorder.

In the RCTs and meta-analyses, different doses of MgSO4 are infused. Further investigations could focus on two topics. First, the ideal dose of MgSO4 as a neuroprotective agent. Secondly, the long-term effects of the administration of MgSO4 on the development of the children.

Conclusion

In this study, several predictive factors for (suspect) CP are identified in the specific population of extremely to very preterm neonates who are discharged from the NICU. Neuroprotection with MgSO4 is found to be a protective factor. Factors that are negatively associated with CP are PVL, smoking during pregnancy and reason for preterm delivery. Despite extensive research on this topic, this study contributes to raising awareness of potential contributing factors, thereby fostering discussion and encouraging further investigation. Additionally, the findings of this study corroborate existing hypotheses concerning the prevention of CP. This study demonstrates an association between

maternal smoking and the development of (suspected) cerebral palsy (CP). The influence of additional maternal health factors on the development of (suspected) CP warrants further investigation.

Conflicts of interest: All authors declare that they have no conflicts of interest.

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APPENDIX: SEARCH STRATEGY

A. PubMed

A search was conducted using the MeSH terms 'premature birth', 'parturition', 'neurodevelopmental disorders', 'cerebral palsy', 'infant mortality', 'neuroprotection', and 'magnesium sulfate'. An 'All fields' search was also performed to identify articles where these terms appeared only in the abstract or full text, rather than the title. On October 29, 2019, 152 articles were found. A second search on September 25, 2020, yielded 171 articles.

The search query was:

("premature birth"[MeSH] OR ("premature"[All Fields] AND "birth"[All Fields]) OR "premature birth"[All Fields] OR ("premature"[All Fields] AND ("parturition"[Mesh] OR "parturition"[All Fields] OR "birth"[All Fields]))) AND ("Neurodevelopmental Disorders"[Mesh] OR "Cerebral Palsy"[Mesh] OR "infant mortality"[Mesh] OR "Neurodevelopmental Disorders"[All Fields] OR "cerebral palsy"[All Fields] OR "infant mortality"[All Fields] OR ("cerebral"[All Fields] AND "palsy"[All Fields])) AND ("neuroprotection"[Mesh Terms] OR "neuroprotection"[All Fields] OR "magnesium sulfate"[Mesh] OR "magnesium sulfate"[All Fields])

B. Embase

A search was conducted using the PICO model with Emtree terms 'prematurity', 'premature labor', 'magnesium sulfate', 'neuroprotection', 'brain protection', 'cerebral palsy', 'infant mortality', and 'motor dysfunction'. On October 29, 2019, 700 articles were found. A second search on September 25, 2020, yielded 733 articles.

The search query was:

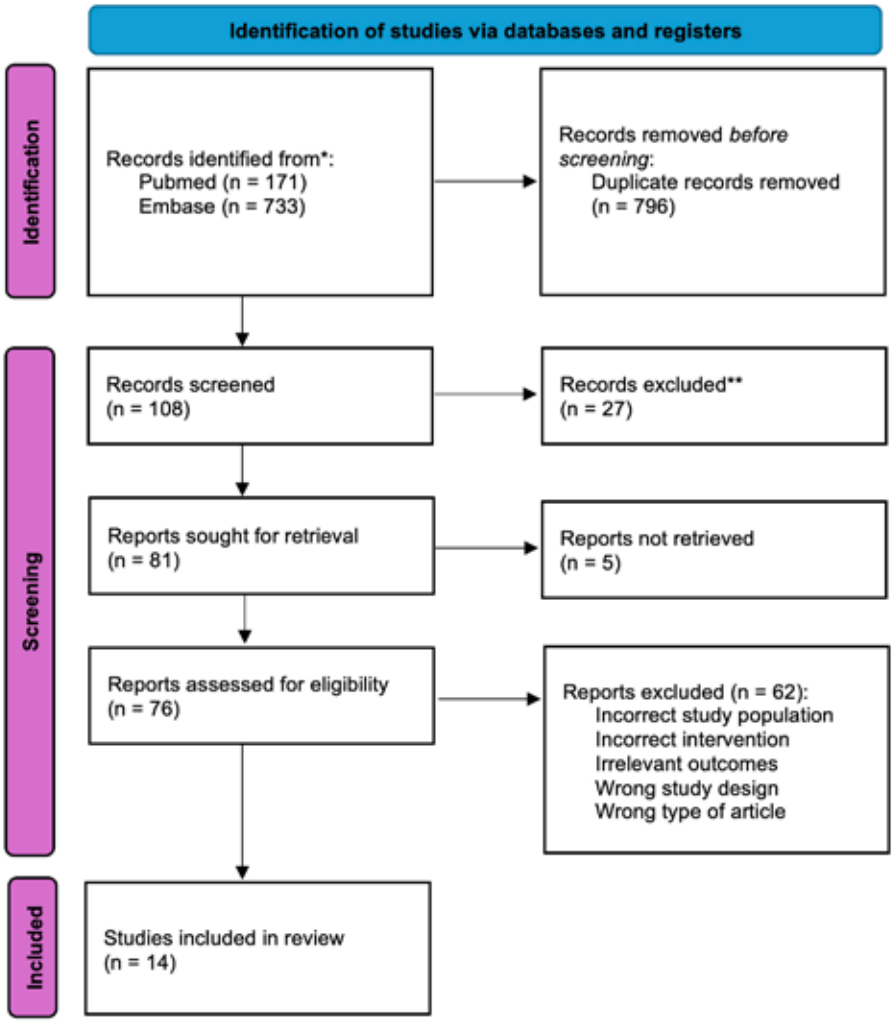
('prematurity'/exp OR 'prematurity' OR 'premature labor'/exp OR 'premature labor') AND ('magnesium sulfate'/exp OR 'magnesium sulfate' OR 'neuroprotection'/exp OR 'neuroprotection' OR 'brain protection'/exp OR 'brain protection') AND ('cerebral palsy'/exp OR 'cerebral palsy' OR 'infant mortality'/exp OR 'infant mortality' OR 'motor dysfunction'/exp OR 'motor dysfunction')

Inclusion and Exclusion Criteria

Using the above search strategy, a total of 904 articles were found. Randomized controlled trials (RCTs), meta-analyses, and reviews were included. Only studies with full text available were retained. Duplicates (n = 216) were removed using the EndNote software. Studies were initially screened based on the title and abstract, followed by full-text screening. Selection was based on the PICO model. Studies not involving the appropriate study population were excluded. Studies using a different neuroprotective agent (e.g., erythropoietin) or using MgSO4 for other purposes (e.g., tocolysis) were excluded. Studies that did not investigate CP outcomes were excluded.

This master's thesis aims to correlate findings from the PRETURN dataset with those from the literature. Only studies with the highest evidence levels, such as meta-analyses and RCTs, were used for comparison. Observational studies were not included. Articles were excluded if they were not in English, French, or Dutch. Due to evolving knowledge on MgSO4 as a neuroprotective agent, only studies published after 2000 were considered. Four additional articles were identified using the snowball method, resulting in a final selection of 14 articles (see PRISMA (Figure 1)).

PRISMA flowchart



Mieux boire. **Mieux vivre.**

Acceptability of New RSV Preventive Tools to Parents and Healthcare Workers

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Keywords

Vaccine, immunization, vaccine hesitancy, RSV, monoclonal antibodies, survey.

Abstract

In view of new RSV prevention strategies, we conducted a multicenter opinion survey among parents and antenatal caregivers in Brussels between August and November 2023. Awareness of RSV was initially low, but parental acceptance to universal RSV prevention increased up to 89% after additional information on RSV burden was provided. 86% of gynecologists and 66% of midwives considered RSV prevention necessary for all infants regardless of the presence of comorbidity. The Covid-19 pandemic reduced the confidence of 24% of parents in vaccination.

Introduction

Although it almost disappeared during the Covid-19 pandemic, respiratory syncytial virus (RSV) is now resurging in many countries, leading to a high burden of disease within the pediatric population (1, 2). After years of research, new anti-RSV preventive tools, i.e., a vaccine for pregnant women and extended half-life monoclonal antibodies, are entering the market and raising high expectations among the pediatric community (3).

Many valuable prevention strategies could be imagined using either tool, alone or in combination, in a year-round or seasonal program (4, 5). Whereas cost-effectiveness analysis is ongoing in many countries to guide their recommendations, we decided to investigate another key feature of prevention success: the acceptability of a new RSV preventive action to parents. Therefore, we conducted a multicenter opinion survey among parents in the cosmopolitan city of Brussels and further assessed the support that might be expected from their healthcare workers (HCWs) involved in antenatal cares – i.e., gynecologists and midwives- to promote RSV prevention beside pediatricians.

Methods

The study was conducted over a four-month period (August-November 2023) preceding the release of recommendations by the Belgian National Immunization Technical Advisory Group (BNITAG) on RSV prevention in children and the introduction of new anti-RSV preventive products in Belgium.

All mothers expecting a baby or having just delivered and their partners were invited to participate. Recruitment was done during out-patient prenatal visits and maternity ward stays in three hospitals of the Chirec network, located in distant neighborhoods of the Brussels and Walloon Brabant regions and gathering different socio-economic and ethnic populations.

Parents were invited to complete a multiple-choice questionnaire through an online platform, and, in the middle of the survey, to read some information about RSV disease and its new prevention tools. Login could be done via a QR code on a paper folder or on a social media. HCWs were recruited through hospital networks and invited to complete another specific questionnaire on the same platform. Questionnaires are displayed as Supplemental Digital Content 1 and 2[1].

Differences between groups were assessed by Chi-square test using GraphPad Prism Software; a two-tailed p-value of <0.05 was considered as statistically significant.

Data collection was strictly anonymous. The study has been approved by the Ethics Committee of the Chirec Network and was GDPR compliant.

Results

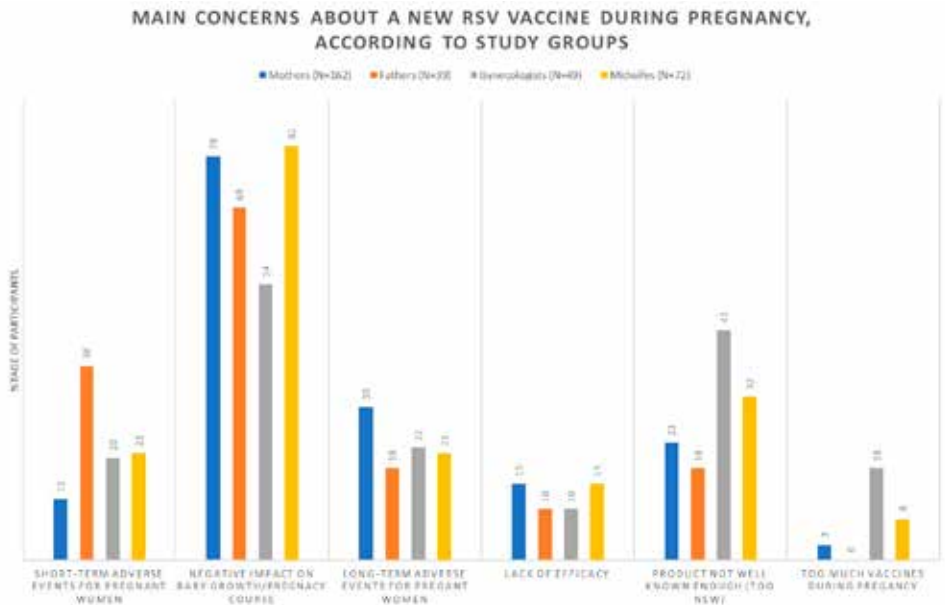
Two hundred and sixty-eight parents (223 women, 45 men) participated in the survey, 82% of whom completed the entire questionnaire. Ninety percent had already heard about bronchiolitis, but less than half knew that it was related to a virus called RSV. Nearly 40% remembered a relative who already suffered from bronchiolitis, and who had been hospitalized in half of the cases (20% of the total). Ninety-three percent of the participants already applied the Belgian national immunization program for their children or intended to do so.

Sixty-nine percent of the parents were at first glance in favor of adopting a new preventive measure against RSV for every otherwise healthy infant, while 6% would leave it to those with comorbidity and 25% were against or doubtful. After reading a short informative document about the RSV burden and the existence of new preventive tools, the proportion of parents in favor of universal prevention increased up to 89%, with 11% remaining against (5%) or hesitant (6%) ($X^2=17,5$; $p<0.001$). This trend was observed similarly among mothers and fathers.

When asked about a hypothetical preference between a maternal vaccine or an antibody administered to the baby, 36% chose the vaccine, 17% chose the antibodies and 35% answered it didn't matter as long as it will be included in the national immunization program or recommended by their HCWs. Parents' main theoretical concerns about a new maternal vaccine are illustrated in Figure 1. The possibility of co-administration with other antenatal vaccinations to avoid extra-visit was not deemed mandatory for 60% of parents. Finally, 40% of the cohort

1. Digital content can be accessed through the journal's website (https://www.belgjpaediatrics.com/index.php/bjp) or by searching the article in Google Scholar (https://scholar.google.com/).

Figure 2: Main concerns about a new RSV vaccine during pregnancy, according to study groups.



Choices were not mutually exclusive. Results are expressed as percentage of positive answer inside each subgroup.

declared that the COVID-19 pandemic had influenced their attitude towards vaccination, and this influence was considered negative for 24% of participants, more often among mothers than fathers (OR 3,39, 95%CI [1.14-10.07], p<0.05).

Furthermore, 128 HCWs (1/3 gynecologists and 2/3 midwives) participated to the opinion survey, of whom 90% declared to apply the BNITAG recommendations in their family environment. Ninety-eight percent were aware of bronchiolitis and 48% knew a close relative who suffered from RSV disease. Seventy-four percent of HCWs, of whom significantly more gynecologists than midwives (86% vs 66%, OR=2.74, 95%CI [1.13-6.68], p<0.05), considered RSV prevention as a need for every infant regardless of the presence of any comorbidity. However, 16% thought it should be limited to high-risk groups and 10% of the cohort considered it useless. Among HCWs in favor of prevention, 42% would prefer the principle of a maternal vaccine over monoclonal antibodies given to babies, whereas for 41% of them, there would be no preference if both are equally recommended. Only half of the cohort were aware of a new maternal RSV vaccine that will be soon in Europe and 80% would like to receive more information about vaccination during pregnancy. Forty-five percent of the cohort (65% of gynecologists, 31% of midwives (OR=4, 95%CI [1.86-8.59], p<0.001) agreed to prescribe a new RSV vaccine if advised by the BNITAG. However, a further 42% would only use it under certain conditions (8% possible co-administration with other vaccines, 10% reimbursement by authorities, 24% similar recommendations from other countries) whereas 12% declined the option. Figure 1 displays the main concerns of our cohort of HCWs regarding a hypothetical new RSV vaccine. Concerning the antenatal immunization program already implemented in our country, dTPa-, influenza- and Covid-19-vaccines were recommended by 91%, 56% and 36% of midwives, respectively, and by 98%, 94% and 80% of gynecologists, respectively, (X^2=103, p<0.001). Finally, while 31% of midwives reported that the Covid-19 pandemic had had a negative impact on their attitudes toward vaccination, the opposite was true for 38% of gynecologists, who reported a favorable impact.

Discussion

Despite its very high threat to infants worldwide, there has been so far no preventive measure available against RSV, except for passive immunization with palivizumab restricted to high-risk groups (1, 2). Since experts agree that every infant deserves protection against such a virus, regardless of the presence of any comorbidity, the two new anti-RSV preventive tools entering the market are in the spotlight (3, 5). Under the current knowledge, it remains difficult for experts to recommend one tool over another based on efficacy and safety data only (4, 5). We therefore investigated a cornerstone of prevention success: acceptability to parents of a new anti-RSV preventive measure, which seemed to us to be of paramount importance in our post-pandemic era of increasing vaccine hesitancy (6).

Fortunately, we showed that a preventive strategy against RSV seemed relatively well accepted by parents and caregivers, whatever the tool -vaccine or antibodies- chosen. Almost all parents knew about bronchiolitis and many recalled a serious case in their family; however, much fewer were aware that this condition is caused by a virus called RSV, which is potentially preventable through immunization. The importance of thorough information during immunization campaigns, describing not only the benefits/risks of the product itself but also the burden of the targeted disease, was supported by the impact that our informative document had on patients' opinion. A similar observation has been reported in a previous study assessing parental hesitancy regarding monoclonal antibodies in eight countries (7). However, in this study, "anti-vax" people (i.e., refusing their national immunization program) were excluded from enrollment, whereas we decided to retain vaccine hesitant subjects to better mirror the real setting in which prevention should be implemented. Moreover, even in a population with low rate of vaccine hesitancy, a proactive educational campaign preceding implementation of a new immunization program is of utmost importance. This concept has been highlighted by the successful approach of Galician colleagues, who already reported very high uptake after 3 weeks of a hospital-based nirsevimab administration program (8).

The belief of HCWs in the benefits of vaccination as well as the insertion of a new action in the regular national schedule have both been suggested as key factors to reinforce parental adherence (7). Our results confirmed these findings and also underlined the influence of similar recommendations from neighboring countries on HCWs' opinions. Conversely, co-administration with other vaccines to limit extra visits was not deemed necessary by either parents or HCWs. This observation was reassuring since this possibility of co-administration is often not available at the beginning of a vaccine program (due to lack of data) and since several other maternal vaccines are under development (9).

Furthermore, our results were in line with those from a previous pre-pandemic trial from the United Kingdom showing that vaccine hesitancy was significantly higher among midwives than gynecologists (10). Whether looking at the new RSV vaccine or the other vaccines recommended during pregnancy, our study confirmed that this difference remained after the COVID-19 pandemic, which for 31% of midwives was deemed as a source of loss in vaccine confidence. The reasons why midwives are more reluctant to adopt immunization programs have not been explored in this study but should be further investigated. In Belgium as in many other European countries, midwives play a key role in antenatal and postnatal care and their impact on patient adherence to vaccination recommendations has been reported (7, 10).

A major limitation of our study was that although it was conducted in three different socioeconomic neighborhoods, we could not ascertain the representativity of the general Belgian population through our study cohort. No question regarding educational/economic level was asked to avoid stigmatization and discouragement. Moreover, as participation was voluntary, we could not determine the participation rate among parents who received the folder or saw the call on social media. Finally, our survey was conducted only in the Brussels region, where the lowest compliance with the antenatal vaccination program has been registered compared to Flanders and Wallonia (11).

Conclusion

Our study was encouraging in that it showed an overall enthusiasm toward new preventive actions against RSV. We also highlighted how information about the targeted disease itself is crucial to ensure the success of vaccination campaigns by increasing parental awareness and, thereby, acceptance. Considering the rise of anti-vax waves in our post-pandemic era, new communication tools should be investigated to promote patient and HCWs adherence to immunization programs during pregnancy and early childhood.

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Statements and declarations

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Both authors have no conflict of interest to declare.

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▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden. Zie rubriek 4.8 voor het rapporteren van bijwerkingen. NAAM VAN HET GENEESMIDDEL Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit. Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit Elke voorgevulde spuit bevat 50 mg nirsevimab in 0,5 ml (100 mg/ml). Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit Elke voorgevulde spuit bevat 100 mg nirsevimab in 1 ml (100 mg/ml). Nirsevimab is een gehumaniseerd immunoglobuline G1 kappa (IgG1κ) monoklonaal antilichaam dat geproduceerd wordt uit ovariumcellen van de Chinese hamster (Chinese hamster ovary, CHO) met behulp van recombinant-DNA-technologie. FARMACEUTISCHE VORM Oplossing voor injectie (injectie).Heldere tot opalescente, kleurloze tot gele oplossing met een pH-waarde van 6,0. THERAPEUTISCHE INDICATIES Beyfortus is geïndiceerd voor de preventie van lagere-luchtwegaandoeningen veroorzaakt door het respiratoir syncytieel virus (RSV) bij pasgeborenen en zuigelingen tijdens hun eerste RSV-seizoen. Beyfortus dient te worden gebruikt in overeenstemming met officiële aanbevelingen. DOSERING EN WIJZE VAN TOEDIENING Dosering De aanbevolen dosering is een enkelvoudige dosis van 50 mg intramusculair toegediend voor zuigelingen met een lichaamsgewicht < 5 kg en een enkelvoudige dosis van 100 mg intramusculair toegediend voor zuigelingen met een lichaamsgewicht ≥ 5 kg. Beyfortus moet worden toegediend vóór het begin van het RSV seizoen, of vanaf de geboorte voor zuigelingen die tijdens het RSV seizoen zijn geboren. De dosering bij zuigelingen met een lichaamsgewicht van 1,0 kg tot < 1,6 kg is gebaseerd op extrapolatie. Hiervoor zijn geen klinische gegevens beschikbaar. Naar verwachting zal blootstelling bij zuigelingen van < 1 kg hogere blootstellingen opleveren dan bij zuigelingen die meer wegen. De voordelen en risico's van het gebruik van nirsevimab bij zuigelingen van <1 kg moeten zorgvuldig worden afgewogen. Er zijn beperkte gegevens beschikbaar over extreem premature zuigelingen (zwangerschapsduur < 29 weken) jonger dan 8 weken. Er zijn geen klinische gegevens beschikbaar over zuigelingen met een postmenstruele leeftijd (zwangerschapsduur bij geboorte plus chronologische leeftijd) van minder dan 32 weken (zie rubriek 5.1). Voor zuigelingen die een hartoperatie ondergaan met cardiopulmonale bypass, kan zodra de zuigeling stabiel is na de operatie een extra dosis toegediend worden om adequate nirsevimab-serumspiegels te garanderen. Als dit binnen 90 dagen na ontvangst van de eerste dosis Beyfortus plaatsvindt, dient de aanvullende dosis 50 mg of 100 mg te zijn, afhankelijk van het lichaamsgewicht. Als er meer dan 90 dagen zijn verstreken sinds de eerste dosis, kan de aanvullende dosis een enkelvoudige dosis van 50 mg zijn, ongeacht het lichaamsgewicht, om de rest van het RSV seizoen te dekken. Er zijn geen veiligheids- en werkzaamheidsgegevens beschikbaar over herhaalde dosering. De veiligheid en werkzaamheid van nirsevimab bij kinderen in de leeftijd van 2 tot 18 jaar zijn niet vastgesteld. Er zijn geen gegevens beschikbaar. Wijze van toediening Beyfortus is alleen voor intramusculaire injectie. Het wordt intramusculair toegediend, bij voorkeur in de anterolaterale zijde van de dij. De gluteale spieren mogen niet routinematig als injectieplaats worden gebruikt vanwege het risico op beschadiging van de ischiaszenuw. Instructies voor toediening Beyfortus is verkrijgbaar in een voorgevulde spuit van 50 mg en 100 mg. Controleer de etiketten op de doos en de voorgevulde spuit om er zeker van te zijn dat u de juiste dosis heeft (50 mg of 100 mg). Beyfortus 50 mg (50 mg/0,5 ml) voorgevulde spuit met een paarse zuigerstang. Beyfortus 100 mg (100 mg/1 ml) voorgevulde spuit met een lichtblauwe zuigerstang. Stap 1: Terwijl u de Luer-lock met één hand vasthoudt (vermijd het vasthouden van de zuigerstang of de cilinder), draait u het naaldkapje van de spuit los door deze met de andere hand tegen de klok in te draaien. Stap 2: Bevestig een Luer-lock-naald aan de voorgevulde spuit door de naald voorzichtig met de klok mee op de voorgevulde spuit te draaien totdat u lichte weerstand voelt. Stap 3: Houd de cilinder met één hand vast en trek met de andere hand voorzichtig de naaldbeschermer met een rechte beweging van de naald af. Houd de zuigerstang niet vast terwijl u de naaldbeschermer verwijdert, anders kan de rubberen stop bewegen. Raak de naald niet aan en laat deze niet met in contact komen met een oppervlak. Plaats de naaldbeschermer niet terug op de naald en haal de naald niet los van de spuit. Stap 4: Dien de volledige inhoud van de voorgevulde spuit toe als een intramusculaire injectie, bij voorkeur in de anterolaterale zijde van de dij. De gluteale spieren mogen niet routinematig als injectieplaats worden gebruikt vanwege het risico op beschadiging van de ischiaszenuw. CONTRA-INDICATIES Overgevoeligheid voor de werkzame stof of voor een van de in rubriek 6.1 vermelde hulpstoffen. BIJWERKINGEN Samenvatting van het veiligheidsprofiel De meest voorkomende bijwerking was rash (0,7%) die binnen 14 dagen na toediening optrad. Het merendeel van deze bijwerking was licht tot matig van intensiteit. Aanvullend werden pyrexie en injectieplaatsreacties binnen 7 dagen na toediening gemeld met een prevalentie van respectievelijk 0,5% en 0,3%. Injectieplaatsreacties waren niet ernstig. Lijst van bijwerkingen Hieronder staan de bijwerkingen die zijn gemeld bij 2.966 voldragen en premature zuigelingen (zwangerschapsduur, Gestational Age (GA) ≥ 29 weken) die nirsevimab kregen in klinische onderzoeken. De bijwerkingen die zijn gemeld in gecontroleerde klinische onderzoeken zijn ingedeeld volgens systeem/orgaanklasse (SOC) van MedDRA. Binnen elke SOC zijn voorkeurstermen gerangschikt op afnemende frequentie en vervolgens op afnemende ernst. De frequenties van optreden van bijwerkingen wordt gedefinieerd als: zeer vaak (≥ 1/10); vaak (≥ 1/100 tot < 1/10); soms (≥ 1/1.000 tot < 1/100); zelden (≥ 1/10.000 tot < 1/1.000); zeer zelden (< 1/10.000) en niet bekend (kan met de beschikbare gegevens niet worden bepaald). Huid- en onderhuidaandoeningen • Soms - Rasha a Rash is gedefinieerd door de volgende gegroepeerde voorkeurstermen: rash, maculo-papulaire rash, vlekkerige rash Algemene aandoeningen en toedieningsplaatsstoornissen • Soms – Injectieplaatsreactieb ; Pyrexie b Injectieplaatsreactie is gedefinieerd door de volgende gegroepeerde voorkeurstermen: injectieplaatsreactie, injectieplaatspijn, injectieplaatsverharding, injectieplaatsoedeem, zwelling van injectieplaats Zuigelingen met een verhoogd risico op ernstige RSV-ziekte De veiligheid is ook onderzocht in MEDLEY bij 918 zuigelingen met een verhoogd risico op ernstige RSV ziekte, onder wie 196 extreem premature zuigelingen (GA < 29 weken) en 306 zuigelingen met chronische longziekte van prematuriteit of hemodynamisch significante aangeboren hartziekte die hun eerste RSV seizoen ingingen, die nirsevimab (614) of palivizumab (304) kregen. Het veiligheidsprofiel was vergelijkbaar met het vergelijkende geneesmiddel palivizumab en consistent met het veiligheidsprofiel bij voldragen en premature zuigelingen GA ≥ 29 weken (D5290C00003 en MELODY). Immunogeniciteit Zoals met alle therapeutische eiwitten, is er potentieel voor immunogeniciteit. Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via: België: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – Afdeling Vigilantie – Postbus 97 – 1000 Brussel Madou – Website: www.eenbijwerkingmelden.be – e-mail: adr@fagg.be HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly, Frankrijk NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN EU/1/22/1689/001 - 50 mg, 1 voorgevulde spuit voor eenmalig gebruik EU/1/22/1689/002 - 50 mg, 1 voorgevulde spuit voor eenmalig gebruik met naalden EU/1/22/1689/003 - 50 mg, 5 voorgevulde spuiten voor eenmalig gebruik EU/1/22/1689/004 - 100 mg, 1 voorgevulde spuit voor eenmalig gebruik EU/1/22/1689/005 - 100 mg, 1 voorgevulde spuit voor eenmalig gebruik met naalden EU/1/22/1689/006 - 100 mg, 5 voorgevulde spuiten voor eenmalig gebruik DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING Datum van eerste verlening van de vergunning: 31 oktober 2022 DATUM VAN HERZIENING VAN DE TEKST Goedkeuringsdatum: 11/2023 Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau http://www.ema.europa.eu

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1. Beyfortus SKP, nov 2023. Sanofi Belgium - MAT-BE-2400434-1.0-06/2024

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General Knowledge about Sudden Infant Death Syndrome Prevention Measures among Flemish Mothers

Prospective Study with an Anonymous Survey

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Keywords

Sudden Infant Death Syndrome ; Prevention ; Parental knowledge.

Abstract

Objective

Sudden Infant Death Syndrome (SIDS) is influenced by various environmental and parental factors, despite existing preventive measures. At present little is known about the knowledge of Flemish mothers to reduce SIDS.

Methods

This study aimed to evaluate Flemish mothers' awareness of SIDS prevention methods through an anonymous online survey.

Results

A total of 201 mothers participated, with an average score of 6.22 out of 9 (69.11%) on the evidence-based section. Most mothers (89%) recognised the supine sleeping position as safest, but fewer acknowledged the benefits of breastfeeding (46%) or pacifier use (19%). Only 42% acknowledged the limited effectiveness of monitoring devices. Higher education correlated with better knowledge ($P<0.001$, OR = 3.194), as did cohabitation ($P = 0.086$, OR = 2.519). Mothers with more children tended to have higher scores than those with two children, but lower scores than those with one child. Non-scientific information mainly came from friends, family, and social media. Confidence in doctors' information about SIDS was highest among young mothers (79.1%).

Discussion and conclusion

The study suggests updating prevention recommendations and campaign strategies in Belgium, targeting specific demographics such as lower socio-economic backgrounds, lower education levels, and single mothers. While Flemish mothers show encouraging awareness levels, there's still a need for focused interventions to improve knowledge and adherence to preventive measures.

Introduction

Cot death or sudden infant death syndrome (SIDS) describes the sudden death of a child younger than one year without obvious cause after a full investigation including autopsy, examination of the circumstances of death and review of the child's medical history (1). The peak incidence of this phenomenon is between the age of two and four months. Sudden unexpected infant death (SUID) is a broader term referring to “a sudden and unexpected death, whether explained or unexplained, occurring during infancy” and includes SIDS and other sleep-related infant death such as ill-defined death and accidental suffocation and strangulation in bed as described by the American Academy of Pediatrics (AAP) (2). Jullien S. (2021) states that “for any SUID, if the cause of death after case investigation is not attributed to an explained cause such as asphyxia, suffocation, infection or metabolic disease, the case is classified as SIDS, which is a definitive diagnosis reached by exclusion” (3). Sudden infant death always occurs during sleep, either at night or during daytime sleep. Following the introduction of safe sleep campaigns such as the Back to Sleep Campaign in the early 1990s, the incidence has fallen dramatically. However, it has not been reduced to zero and has stagnated in recent years (4). SIDS therefore remains the leading cause of infant mortality in high-income countries (an average of 19.8/100 000 livebirths across 14 European countries between 2005 and 2015) and the third leading cause of infant death worldwide (3). Since the 1990s, the figures in Belgium show a significant decrease in sleep related deaths in infants. The most recent figures are from 2018, with 6 cases of SIDS. This corresponds to a rate of 21.2/100 000 live births in Belgium.

To date, no biological explanation for this phenomenon has been found. However, over time, several theories have been put forward as to the possible causes and mechanisms of SIDS. The most influential theory was developed by Wedgwood in 1972 and later revised by Filiano and Kinney and is better known as the ‘Triple Risk Model’. According to this model, SIDS occurs or becomes more likely when several risk factors converge, particularly when a vulnerable baby is exposed to external risk factors during a critical developmental period (5). Although the pathophysiology of sleep-related death is not yet fully understood, the triple risk model can help us to conceptualize SIDS as a complex and multifactorial syndrome. The external factors mentioned in the model refer to several risk factors known to be associated with the child’s immediate environment on the one hand and with parental behaviour on the other (5). Current preventive measures address these risk factors. The American Academy of Pediatrics recommendations (updated in 2022) provide the most evidence-based summary of SIDS prevention (2). Previous research has shown that these guidelines are not yet sufficiently followed or even not known by young parents. In this study, we intend to investigate the knowledge of Flemish mothers about measures to reduce SIDS in newborns and infants.

Materials and methods

Study design

The survey consisted of three parts. In the first part the demographic information (age, education level, parity and living situation) was documented. In the second part of the survey, the parental knowledge of SIDS prevention measures was measured using fourteen true or false

statements. The third part explores the subjective value of different information sources. We included statements that were evidence-based but also statements that have no scientific basis but often circulate on social media. The evidence-based statements were adapted from a validated questionnaire (Rohana et al. 2018) based on the SIDS risk reduction guidelines of the AAP (6). These statements were adapted for a Flemish audience using the appropriate translation-backtranslation method. The non-scientific statements were selected from posts or websites in the context of popular social media. For each of these statements, we also questioned from what source people learned this information: doctor (paediatrician/gynaecologist/family doctor) – other healthcare provider (nurse/midwife) – Kind en Gezin – family and friends – social media. Kind en Gezin (K&G) is a preventive health service for children aged 0-3 years in Flanders. In the final part of the survey, we asked the participants which source of information on the subject they trust most: doctor (paediatrician/gynaecologist/family doctor) – other healthcare provider (nurse/midwife) – K&G – family and friends – social media. This was done on a ranking basis (most reliable to least reliable). After completion of the survey, all participants could access an additional part of the survey that provided feedback on the abovementioned statements with information if that statement was evidence-based or not. To ensure content validity, the survey items were reviewed for their relevance and coverage of the AAP guidelines by a panel of 5 experts. Items were refined according to panel feedback.

The questionnaire was created using the Qualtrics XM program. The IP address of the participants is not stored in this program, so the study was completely anonymous. We investigated the research question "What is the knowledge of Flemish mothers about SIDS risk reduction measures?".

Participants

The survey was distributed via Facebook and through the communication channels of the VVOC (Flemish association for parents of incubated children) in order to also reach the young parent population. To avoid multiple responses within the same household, only mothers were allowed to participate. We excluded women who could not read the questionnaire in Dutch and all incomplete responses. The study was conducted between 26 March 2023 and 22 September 2023 and the self-administered, three – part questionnaire was completed by 201 Flemish mothers. The study protocol was approved by the Research Ethics Committee of KU Leuven (No. MP023085).

Statistical analysis

We performed a descriptive analysis of the responses, and logistic regressions and odds ratios were used in order to investigate the relationship between variables. $P<0.05$ was considered significant. All statistical analyses were performed in IBM SPSS version 29.0.1.0.

Results

Demographics of participants

A total of 201 mothers completed the questionnaire and were included in the study. Of these 89 (44.3%) were aged between 30 and 40 years, 140 (69.7%) had a university degree, 83 (41.3%) had two children and 178 (88.6%) were either married or living with their partner. Table 1 illustrates the remaining maternal demographic details.

Knowledge regarding preventive measures for SIDS

The advisory against employing pillows or other bedding accessories was well-known, as evidenced by 99% of mothers exhibiting familiarity with this recommendation. Furthermore, a notable 95% demonstrated awareness that co-sleeping elevates the susceptibility to SIDS. In relation to sleep practices, it was observed that a majority of participants, constituting 89%, acknowledged the supine position as the most secure sleeping posture for infants.

A noteworthy percentage (88%), comprehended the deleterious impact of exposure to individuals who smoke, recognizing it as a hazard that amplifies the risk of SIDS. The practice of placing toys and stuffed animals in an infant's cot should be deemed hazardous, was not perceived as a risk by a distinct minority, accounting for 25% of participants. Similarly, the potential peril associated with sleeping on a sofa or soft mattress was not adequately recognized by 30% of the participants. Notably, a minority subset demonstrated awareness that breastfeeding serves as a mitigating factor, reducing the risk of SIDS (46%).

Table 1: Demographical characteristics of the study population.

DEMOGRAPHICAL CHARACTERISTICS	N	%
Relationship to the child		
Mother	**201**	**100**
Age of the participants		
20-30y	**46**	**22,9**
30-40y	**89**	**44,3**
>40y	**66**	**32,8**
Education level		
Non-university (High school)	**61**	**30,4**
University (Bachelor's degree/Master/PhD)	**140**	**69,7**
Number of infants		
1	**70**	**34,8**
2	**83**	**41,3**
≥3	**48**	**23,9**
Living/family situation (marital status)		
Cohabiting (married/cohabiting)	**178**	**88,6**
Non-cohabiting (unmarried/divorced)	23	11,4

Table 2: Proportion of correct answers for each question and question number as in the survey with the correct answer in quotation marks.

STATEMENTS (QUESTION NUMBER, CORRECT ANSWER)	ANSWERED CORRECTLY (N)	ANSWERED CORRECTLY (%)
Propping my baby up on a pillow while he/she is sleeping is safe (Q6, False)	**199**	**99,0**
The safest place for my baby to sleep is in the bed with me (Q2, False)	**190**	**94,5**
Placing my baby on his/her back to sleep helps decrease his/her risk of SIDS (Q1, True)	**178**	**88,6**
Being around someone who smokes increases my baby's risk of SIDS (Q3, True)	**177**	**88,1**
Putting toys and stuffed animals in the baby's bed does not increase the risk of SIDS (Q9, False)	**150**	**74,6**
Sleeping on a sofa or soft mattress increases the risk of SIDS (Q8, True)	**141**	**70,2**
Breastfeeding reduces the risk of SIDS (Q4, True)	**92**	**45,8**
Monitor that tracks my baby's heart rate or breathing decreases my baby's risk of SIDS (Q5, False)	**85**	**42,3**
Offering a pacifier for sleep after establishment of breastfeeding is recommended because it reduces the risk of SIDS (Q7, True)	**39**	**19,4**

Additionally, the limited efficacy of monitoring devices, such as those tracking the baby's heart rate or breathing, in preventing the incidence of SIDS was acknowledged by only 42% of the participants. The least known advisory was the fact that offering a pacifier after breastfeeding can be a protective measure (19%). All data are outlined in Table 2.

Figure 1: Histogram of total scores: frequencies of scores in accordance with each score from a total of 9 points, average score = 6.22/9, median = 6/9, std. dev. = 1.454, n = 201.

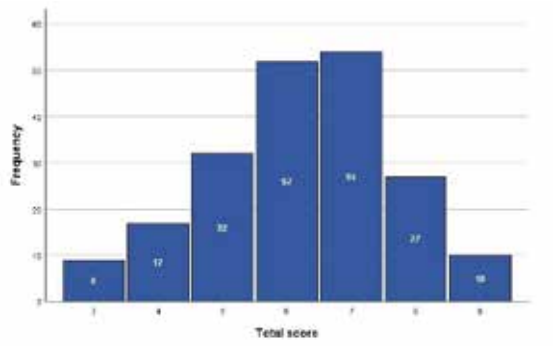

Figure 2: Heatmaps of the percentage of correct answers to each question per subgroup of the statistically significant variables; A. Education level, B. Number of infants.

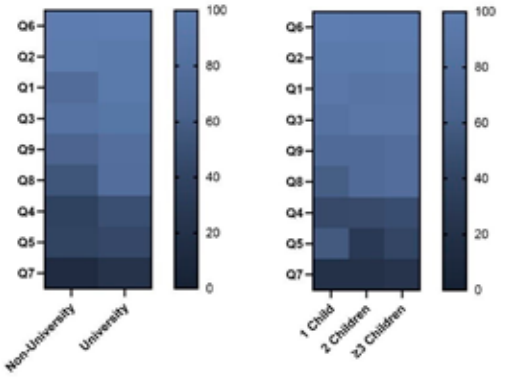

Figure 3: Bar chart ranking most to least reliable source of information according to participants.

Participant characteristics vs SIDS knowledge status

Participants were categorically stratified into two groups based on their responses to the nine evidence-based questions assessing knowledge: those with sufficient knowledge (≥7/9 correct answers) and those with insufficient knowledge (<7/9 correct answers). The mean score across participants was 6.22/9, as illustrated in Figure 1. Notably, 54.7% of individuals were found to have arbitrarily failed the questionnaire. To explore potential determinants of knowledge outcomes, we employed logistic regression, considering variables such as age, educational level, number of infants and marital status. Our analyses revealed a statistically significant association between educational attainment and performance on evidence-based questions ($P<0.001$, OR = 3.194). Specifically, a positive correlation was identified, indicating that a higher level of education was linked to a superior knowledge score. Mothers who went to university were 3.194 times more likely to pass the questionnaire. A significant difference was observed in the number of infants a participant has in passing or failing the questionnaire ($P=0.022$). However, a subgroup analysis shows no significant differences in the subgroups compared to women with one child. Mothers with three or more children exhibited higher survey scores than those with two children ($P = 0.241$, OR = 1.660). In contrast, mothers with two children demonstrated lower scores than mothers with one child ($P = 0.116$, OR = 0.565). Furthermore, we see tendency towards better results in cohabiting women compared with non-cohabiting women ($P = 0.086$, OR = 2.519). Mothers who are married or living with their partner are 2.519 times more likely to pass the survey. There is no influence of age on the pass/fail outcome of the survey. All data are outlined in Table 3. A subgroup analysis showed that participants had difficulties with questions 4,5 and 7. This is independent of the subgroups of statistically significant variables (non-university vs university/one child vs two or ≥ three children) as illustrated in Figure 2. The best-known evidence-based statements were mostly shared or acquired from Kind en Gezin (K&G).

Non-evidence-based statements and source of information

The non-scientific statements were mostly learned from non-professional sources such as social media and family or friends according to the participants themselves. 77 out of 201 mothers (38.3%) learned from social media that a fan above the cot has no effect on SIDS. The non-evidence-based statement that a sound source prevents the baby from falling into a deep sleep and therefore reduces the risk was mainly heard through social media and family/friends, 35.8% and 31.3% respectively. The controversial advice about baby swaddling and its effect on SIDS was also given by other healthcare providers (26.9%), although most respondents had heard about baby swaddling from social media (29.9%). Advice on vaccination and the use of cot bumpers or mattresses was most commonly reported to have been given by Kind en Gezin (K&G), 33.8% and 25.9% respectively, or by other professional caregivers such as doctors (21.9%) and nurses/midwives (17.9%). Table 4 shows the details of the responses.

Reliability of information on cot death

Young mothers have the highest level of confidence (79.1%) in doctors (paediatricians, gynaecologists, general practitioners) when it comes to the accuracy of information on SIDS. Other medical professionals like nurses and midwives follow second. For 47.8% of the participants, the third most trusted source is K&G. Family and friends were ranked 4th with 55.7% of participants. For 87.1% of the mothers surveyed, the media was the least reliable source of information concerning SIDS. Findings are displayed in Figure 3.

Discussion

The level of awareness regarding SIDS risk reduction recommendations among Flemish mothers is encouraging, particularly when juxtaposed with findings from analogous studies conducted in different countries. The average score on the evidence-based part of the questionnaire was 6.22 out of 9 (69.11%). A comparison with the study by Rohana et al. (2018) from which our survey was adapted, reveals a stark contrast, where not even half of the parents provided correct responses to at least 5 out of the 9 questions pertaining to cot death (6). It is conceivable that this knowledge disparity can be attributed, in part to the fact that a very high proportion of participants in our study had a high educational level and in part to differences in socio-economic levels between European and Asian countries. However, analogous European studies, despite sustained awareness campaigns, have produced comparable low results. For instance, a French study administered a questionnaire probing knowledge of SIDS risk factors, yielding an average score of 57.2% (4). In Portugal, merely 8.7% of participants responded accurately to at least 75% of the questions related to cot death risk factors (7). On the other

Table 3: Descriptive results of logistic regression (reference group = odds to pass).

								95% C.I. for EXP (B)	
		B	S.E	Wald	df	Sig.	Exp(B)	Lower	Upper
a		**20-30y (ref.)**			2.835	2	.242		
Age		**30-40y**	.466	.393	1.405	1	.236	1.594	.737	3.447
		< 40y	-.089	.455	.038	1	.845	.915	.375	2.230
Education level		**University vs non-university (ref.)**	1.161	.350	10.979	1	<.001	3.194	1.607	6.347
		1 child			7.591	2	.022		
Number of infants		**2 children**	-.572	.364	2.464	1	.116	.565	.276	1.153
		≥ 3 children	.507	.432	1.376	1	.241	1.660	.712	3.870
Marital status		**Cohabiting vs non-cohabiting (ref.)**	.924	.538	2.950	1	.086	2.519	.878	7.230
		Constant	-1.926	.651	8.747	1	.003	.146		

a. Variable(s) in the Equation

hand, a study by Strömberg et al. in Sweden reported commendable parental adherence to national safe sleeping guidelines (8). It is worth noting that prior research has revealed suboptimal compliance with recommendations from the American Academy of Pediatrics (AAP).

Our primary objective was to assess the knowledge of Flemish mothers on the risk factors associated with a child's environment and parental behaviour. Our findings indicate that, on the whole, mothers exhibit sound awareness of safe sleeping guidelines, with the majority providing correct responses to most of the statements. The use of pillows and other soft objects such as toys and stuffed animals in the infant's cot was deemed hazardous by 99% and 75% respectively. In contrast, in other countries, an alarming rate of positive response to the use of harmful bedding accessories was found. A recent study in Croatia showed that 86% of the infants slept on a pillow or with stuffed animals (9). Similarly, Gemble et al. in France reported that only a third of respondents answered correctly regarding the use of dangerous accessories (4). A study conducted in the Netherlands, which analysed Instagram images to gauge compliance with Dutch safe sleeping advice, found that only 16.8% of the 514 collected images depicted an empty bed devoid of toys, pillows, sleeping nests, or other soft bedding (10). The AAP guidelines advocate for infants to sleep in the same room as their parents but on separate surfaces, reducing the risk of SIDS by as much as 50% (2). On the other hand, a significant proportion of Flemish mothers, approximately 95%, recognized the potential risks associated with co-sleeping. In comparison, bed-sharing practices in other countries paint a less favourable picture: 41% in Croatia (9), 40% in Portugal (7), 19% in France (4), 11.2% in the United States (11) and 7.8% in the Netherlands (12).

Of paramount importance, the recommendation for infants to sleep in the supine position was well comprehended by 89% of Flemish mothers. This figure is heartening, especially when compared to other countries where the supine sleeping position is less commonly identified as a risk factor: 51.4% in Spain (13), 49% in Croatia in 2020 (9), 48.5% in the UK in 2017 (14), 47% in France (4), 43.3% in Portugal (7), 31.25% in Australia in 2001 (15) and 27.6% in the Netherlands (12). These disparities underscore the significance of this particular recommendation. Furthermore, a notable 88% of respondents demonstrated an understanding of the adverse effects of passive smoking on infants, correctly identifying it as a hazard that heightens the risk of SIDS.

Nevertheless, our findings revealed that several protective factors were not well understood. Inquiries regarding the protective effects of breastfeeding and the utilization of a pacifier after breastfeeding is well established were

Table 4: Non evidence-based statements with question number as in the survey and source of information as reported by participants.

SOURCE OF INFORMATION, N (%)					
	Social media	Family/ friends	K&G	Other healthcare provider	Doctor
A fan above the cot to promote airflow has no effect (Q3)	77 (38,3)	55 (27,4)	14 (6,9)	47(23,4)	8 (3,9)
A sound source (e.g. music) during sleep prevents my baby from falling into a too deep sleep and therefore reduces the risk of SIDS (Q5)	72 (35,8)	63 (31,3)	22 (10,9)	37 (18,4)	7 (3,5)
Baby swaddling reduces the risk of SIDS (Q2)	60 (29,9)	51 (25,4)	25 (12,4)	54 (26,9)	11 (5,5)
The use of cradle bumpers or mattress supports reduces the risk (Q4)	47 (23,4)	47 (23,4)	52 (25,9)	36 (17,9)	19 (9,5)
Vaccination increases the risk of cot death and should be delayed until after the age of one year (Q1)	26 (12,9)	33 (16,4)	68 (33,8)	30 (14,9)	44 (21,9)

areas where a higher incidence of incorrect responses was observed, indicating the need for special attention in future prevention campaigns. A French study revealed that only 16% of participants were aware that using a pacifier reduces the risk of SIDS and merely 36 % recognized breastfeeding as a protective factor (4). Similarly, in Portugal and Spain, awareness of breastfeeding's ability to reduce the risk of SIDS by up to 50% stood at only 30.2% and 41.3%, respectively (7,13). The AAP acknowledges that although the mechanism is yet unclear, studies have reported a protective effect of pacifiers on the incidence of SIDS (2). A contentious issue in the realm of SIDS risk reduction strategies pertains to the use of commercial devices and home cardiorespiratory monitors (CRM). Although home CRM are used in very specific situations for infants at higher SIDS risk, such as extreme prematurely born infants, their use in the general population is not recommended, as multiple studies have demonstrated. Nevertheless, only 42% of the surveyed individuals acknowledged this recommendation (2,16).

To investigate the factors associated with infant sleep environment knowledge, we examined whether there existed any relationships between knowledge and specific demographic characteristics of the participants. We observed that mothers with a higher level of education exhibited superior knowledge of safe sleep practices. This finding aligns with numerous prior studies that have consistently indicated that lower levels of education are associated with poorer awareness of SIDS prevention measures (14,15,17). Furthermore, our results indicated that mothers who were married or cohabiting with their partners achieved higher scores on the questionnaire, possibly attributed to the collaborative thinking and mutual support of two parents. Additionally, the number of children in the household did not appear to exert a discernible effect. In contrast to some other studies, age did not seem to influence knowledge about safe sleeping practices, although studies by Pease et al. in the UK and Walcott et al. in Georgia demonstrated a positive correlation between increasing age and knowledge scores (14,18). Moreover, our findings corroborate the significance of socio-economic status and ethnicity as influential factors, a notion supported by other research (15,19). The study by Walcott et al. indicates that respondents identifying as white tended to be more likely to practice “back to sleep” and less likely to practice bed sharing than black respondents (18). A 2017 integrative review aimed at elucidating the reasons for parental noncompliance with the “Back to sleep” recommendation. They found that the sources of advice, the child’s comfort and sleep quality, and concerns about the child’s safety (e.g. suffocation) were the most important factors. Non-compliance was notably higher among parents who were single, less educated, of lower income, or of African American descent (20). These findings are consistent with our own observations.

In recent years, a substantial volume of non-scientific information pertaining to the subject has proliferated through popular social media platforms. As anticipated, our observations reveal that social media, along with other non-professional sources such as friends and family, are frequently employed channels for acquiring non-evidence-based information on the topic. Notably, we found that information concerning vaccination and the use of cot bumpers in relation to cot death often emanated from professional sources. This phenomenon may be attributed to parents encountering such content on dubious websites and subsequently seeking clarification from medical professionals. Numerous studies have highlighted social media as the primary source of information for parents who are informed about SIDS. According to the survey conducted by Douglas et al., magazines and television advertisements were among the most frequently accessed sources of information regarding SIDS (15).

This underscores the prevailing uncertainty regarding the accuracy of information disseminated through social media. As Rohana et al. elucidate, in a study utilizing Google to search for information on SIDS and safe sleep habits, more than 50% of the websites yielded either inaccurate or irrelevant information (6). Consequently, there is a compelling case for intensifying efforts to utilize media as a channel for disseminating precise and reliable information. While we acknowledge the indispensability of social media as a communication medium in contemporary society, it is essential to underscore that healthcare providers emerge as the most significant and, as our survey findings indicate, the most trusted role models for young parents. As such, they bear the responsibility of educating and guiding them. To counteract the propagation of inaccurate information, health authorities and organizations dedicated to children's well-being should leverage social media platforms to disseminate authoritative and accurate health-related information.

This study is not without its limitations. Our participant group is definitely a result of selection bias, as our survey exclusively targeted women who possessed the ability to comprehend Dutch in order to complete the questionnaire. Additionally, we were unable to definitively establish the representativeness of our study population in relation to the broader demographic. The possibility of non-representativeness in our sample, characterized by a higher proportion of married, highly educated, and native respondents, could potentially influence the relatively high percentage of correct responses recorded. Moreover as we also recruited through communication channels of the VVOC, several participants can be mothers who had presumably preterm children (cared for in a NICU setting), stayed with their infants probably longer in the hospital, had infants with significant medical problems and could perceive the preventive measures in a different way than mothers of newborns without any medical problem. Furthermore, there can be a participation bias with mothers who did not return the survey, possibly due to a lack of awareness. While the sample size of the survey (n=201) was modest, it was deemed adequate for statistical analyses. It is worth noting that the questionnaire did not encompass all the known risk factors associated with SIDS. Due to practical constraints, certain other well-established measures were excluded from the questionnaire. It is conceivable that a more nuanced response option, such as 'I don't know', could have been included alongside the binary true/false choices. Notably, for questions regarding the sources of information, an option indicating 'never heard of' could have been beneficial, especially given that some statements were rooted in non-scientific content.

Conclusion

In conclusion, the level of awareness regarding safe sleeping recommendations among Flemish mothers is a cause for optimism, especially in comparison to other European countries. Notably, this study represents the first published research in Belgium aimed at assessing knowledge concerning Sudden Infant Death Syndrome (SIDS) prevention measures. Our findings underscore the necessity for the implementation of newly updated recommendations within a revised campaign strategy for Belgium. Emphasis should be placed on promoting the beneficial effects of breastfeeding and the utilization of pacifiers. Furthermore, addressing the limited effectiveness of home cardiorespiratory monitors in preventing SIDS is imperative.

To better educate the newest generation of parents, it would be advantageous to reinforce policies that have been in place for an extended period and enjoy broader recognition. In recent years, social media has emerged as a significant information source on this subject; however, concerns persist regarding the accuracy of the information disseminated through these channels. Nevertheless, medical professionals bear the fundamental responsibility of serving as authoritative sources of information and guiding young parents in their adherence to safe sleeping practices for their newborn children. Educating parents about trustworthy social media platforms for reference purposes can be a constructive measure to counter the spread of inaccurate and non-scientific information.

Targeting specific demographic groups, such as parents from lower socio-economic backgrounds, those with lower levels of education, and single mothers, is essential. Future endeavours aimed at formulating campaign strategies to inform parents about safe sleeping recommendations, with the goal of mitigating the risk factors associated with Sudden Infant Death Syndrome, may draw valuable insights from the findings of this study.

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Conflict of interest statement

The authors declare that there are no conflicts of interest with regards to the acquisition and reporting of the data of the study presented in this manuscript.

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Non-Invasive Ventilation and NIV-NAVA in Preterm Infants: a Prospective Observational Cohort Study

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Keywords

Preterm infant ; noninvasive ventilation ; interactive ventilatory support ; bronchopulmonary dysplasia ; prospective studies.

Abstract

Objective

To study the use of non-invasive ventilation (NIV), and in particular non-invasive neurally adjusted ventilatory assist (NIV-NAVA) in our neonatal intensive care unit (NICU), assessing its feasibility, safety and outcome.

Methods

We conducted a prospective, single-centre observational cohort study, enrolling preterm infants who received at least 24 hours of NIV. Primary endpoints were indication and duration of various NIV modes. Secondary endpoints included significant adverse events such as complications, treatment failure, and the incidence of bronchopulmonary dysplasia (BPD).

Results

Sixty-eight infants were included, with a median gestational age (GA) of 31.3 weeks (IQR 29-32.7) and a median birth weight of 1475 g (IQR 1110-1850). Among them, 36 infants received NIV-NAVA, predominantly as primary support (69.4%). Infants receiving NIV-NAVA had a mean LUS-score at inclusion of 8.6 (SD 2.4, range 3-12) and a median duration of NIV of 32 days (IQR 16.3-65.8). We observed 1 case of pneumothorax and 1 case of pulmonary haemorrhage. The treatment failure rate among infants receiving NIV-NAVA was 22.2%, increasing to 45.5% in extremely premature infants. BPD was diagnosed in 9 (15%) infants.

Conclusion

This study is one of the first prospective trials studying all NIV modes including NIV-NAVA from birth to NICU discharge. Our findings illustrate the feasibility and safety of NIV-NAVA across various ranges of GA, despite higher failure rates in extremely preterm infants. The incidence of BPD among our study population was 15%.

Introduction

Bronchopulmonary dysplasia (BPD) remains a common and severe complication in preterm infants, particularly those born at 28 weeks' gestational age (GA) or less (1,2). Despite substantial progress in perinatal care, the incidence of BPD has not declined (1-3). Initially attributed to aggressive mechanical ventilation and high oxygen exposure ('old BPD'), it has evolved into a condition characterised by impaired alveolar development and pulmonary vascular dysregulation ('new BPD') (1,4,5).

Treatment strategies for BPD primarily focus on minimizing lung injury by avoiding invasive ventilation (1). Non-invasive neurally adjusted ventilatory assist (NIV-NAVA) is a form of non-invasive positive pressure ventilation (NIPPV) that delivers synchronised, proportionally assisted ventilatory support using the diaphragm's electrical activity (Edi), offering comfortable and potentially lung-protective support (6). A recent meta-analysis found no difference in treatment failure or adverse events between NIV-NAVA and nasal continuous positive airway pressure (nCPAP) in preterm infants (7). According to a review by Shi et al., some studies on NIV-NAVA have shown promising results, with improved synchronisation compared to NIPPV and a reduced need for intubation in comparison to nCPAP (8). However, both studies concluded that limited data and low-certainty evidence currently prevent a clear determination of NIV-NAVA's effectiveness and safety (7,8).

Following a small exploratory study on NIV-NAVA in our unit, we initiated a more comprehensive study on its use in preterm infants (9). Our aim is to investigate the feasibility and safety of NIV-NAVA alongside other non-invasive ventilation (NIV) modes.

Methods

Study design

This prospective, single-centre observational cohort study was conducted at the neonatal intensive care unit (NICU) of the University Hospital of Brussels.

Inclusion

All neonates admitted to our NICU between February 2023 and January 2024 were screened for inclusion. Eligible infants were those born before 37 weeks' gestation and requiring at least 24 hours of NIV, including (heated humidified) high flow nasal cannula ((HH)HFNC), nCPAP or NIV-NAVA. Infants with major congenital pathology were excluded.

Respiratory support strategy

In our unit, preterm infants diagnosed with respiratory distress syndrome (RDS) are primarily supported with nCPAP or NIV-NAVA. Extremely preterm infants, born before 28 weeks' gestation, generally receive NIV-NAVA, while those born at or after 28 weeks' gestation typically begin with nCPAP. NIV-NAVA is also used as a weaning mode following extubation, in cases of nCPAP failure and during less invasive surfactant administration (LISA). nCPAP is often used after weaning from NIV-NAVA, while HHHFNC is mainly used in the later stages of weaning.

Generally, the following settings are employed: positive end expiratory pressure (PEEP) ranging from 4 to 8 cmH_2O, NAVA levels between 0

and 2.5 $cmH_2O/\mu V$ and titrated to achieve normal Edi-peak values of 5 to 15 µV, apnoea time between 2 and 5 seconds, back-up frequency of 40 to 55 per minute and back-up pressure above PEEP (PAP) between 5 and 10 cmH_2O. Saturation targets for oxygen therapy are set at 90 to 95% (10). Continuous transcutaneous carbon dioxide monitoring is used as often as possible, and lung ultrasounds, particularly using the lung ultrasound score (LUS), are routinely performed (11).

Table 1: BPD definition according to NICHD consensus (Values are percents).

Grades	Invasive IPPV*	NCPAP, NIPPV, nasal cannula ≥ 3 L/min	Nasal cannula flow of 1 - <3 L/min	Hood O_2	Nasal cannula flow of < 1L/min
I	/	21	22-29	22-29	22-70
II	21	22-29	≥ 30	≥ 30	≥ 70
III	> 21	≥ 30			
IIIa	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (e.g. necrotising enterocolitis, intraventricular haemorrhage, redirection of care, episodes of sepsis, …)				

* Excluding infants ventilated for primary airway disease or central respiratory control conditions

Invasive ventilation is initiated if non-invasive methods fail to adequately support the infant, with a preference for invasive NAVA. If this is not feasible, alternative modes such as volume-controlled conventional ventilation or high frequency oscillation ventilation are used.

All infants on NIV-NAVA or invasive ventilation were ventilated with a Servo-n ventilator (Getinge, Sweden, System version 2.01). nCPAP is delivered by a Servo-n ventilator or by a bubble CPAP system (Fisher and Paykel®). For all infants, the Flexitrunk™ nasal interface (Fisher and Paykel®) was employed, alternating binasal prongs and nasal mask. HFNC is delivered by the Optiflow™ system (Fisher and Paykel®).

Caffeine is initiated for all infants born at a gestational age of 32 weeks or less, and for older infants experiencing frequent or severe apnoeas. A loading dose of 10 mg/kg is given as soon as possible, followed by a maintenance dose of 2.5 to 5 mg/kg/day initiated 24 hours later. During the NIV study, our unit participated in the DOXA-trial, where infants with severe and persistent apnoeas on NIV and at risk of reintubation were randomly assigned, following parental consent, to receive either placebo or doxapram in a double-blinded fashion (12).

Infants requiring invasive ventilation beyond the first week of life are eligible for corticosteroid treatment with dexamethasone to facilitate extubation. Typically, a low-dose regimen, consistent with the DART study protocol, is used, with a total cumulative dose of 0,9 mg/kg (13). For those experiencing severe side-effects or requiring prolonged treatment, an individualised dosing scheme is applied with a maximum cumulative dose set at 4 mg/kg to avoid the risk of cerebral palsy (14).

All preterm infants requiring intubation at birth promptly receive surfactant, usually within the first hour of life. For others, early selective surfactant administration is used, utilising a fraction of inspired oxygen (FiO_2) > 0.3 or a LUS-score > 8 (10,15). Surfactant is administered via the LISA procedure whenever feasible, with an initial dose of 200 mg/kg and subsequent doses of 100 mg/kg. During the LISA procedure, infants are supported with NIV-NAVA while being sedated with propofol.

Outcomes

The primary objective of this study is to evaluate the use of NIV in our NICU, with a particular focus on NIV-NAVA, assessing its feasibility and safety. Primary endpoints include the duration and indications of various NIV support modes. Secondary endpoints encompass adverse events, including complications, treatment failure, the incidence of BPD and the need for prolonged oxygen therapy at home.

A mode is considered 'failed' if a transition to a higher level of respiratory support is required, such as from HFNC to nCPAP or NIV-NAVA, from CPAP to NIV-NAVA or if intubation is necessary. The escalation of respiratory support, as determined by the attending physician, typically occurs when there is a PCO_2 exceeding 60-65 mmHg with a pH below 7.2, an FiO_2 surpassing 40%, or frequent apnoea despite maximal settings for the chosen support mode.

BPD is defined according to the 2018 National Institute of Child Health and Human Development (NICHD) criteria. A premature infant (<32 weeks' GA) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks of post-menstrual age requires 1 of the following FiO_2 ranges/oxygen levels/ O_2 concentrations for ≥ 3 consecutive days to maintain arterial oxygen saturation in the 90-95% range, as shown in Table 1 (16).

Infants requiring prolonged oxygen therapy at home, despite not meeting the criteria for BPD as mentioned above, were retrospectively classified as having BPD.

Data collection

Prospective data collection involved chart review and daily extraction of blood gases and ventilatory data on a fixed time point. All gathered data were exported into an Excel file. Lung ultrasound was performed regularly using a high-frequency linear probe (Esaote MyLab twice®). Data collection stopped at discharge from the NICU.

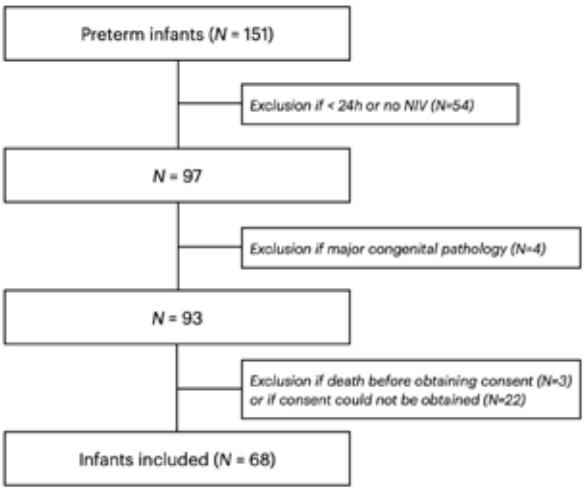
Statistical analysis

Descriptive statistics were conducted to summarize the characteristics of all participants. Continuous variables are reported as either medians with interquartile ranges (IQR) or means with standard deviations (SD) and ranges, depending on their distribution. Categorical variables are presented as counts (n) and percentages (%). The normality of continuous variables was assessed through visual inspection, skewness and kurtosis analysis, and the Shapiro-Wilk test. Continuous variables were analysed using the independent t-test and Mann–Whitney U test as appropriate. A p-value < 0.05 was considered to be statistically significant. Boxplots were used to visually represent the distribution of continuous variables. Statistical analysis was carried out using SPSS, version 29 (IBM, US).

Ethical approval

The study protocol was approved by the UZ Brussel Medical Ethics Committee and prospectively registered on ClinicalTrials.gov (https://clinicaltrials.gov ; NCT05987800). Signed written consent by the parents was obtained prior to inclusion.

Figure 1: Flowchart of inclusion.



Results

Inclusion

During the study period, 151 preterm infants were admitted to our unit, with 97 meeting the eligibility criteria. Of these, 68 infants were ultimately included. Figure 1 outlines the inclusion process in detail.

Baseline characteristics

The median gestational age at birth was 31.3 weeks (IQR 29-32.7), with 12 (17.6%) infants born before 28 weeks' gestation. The median birth weight was 1475 g (IQR 1110-1850). Detailed baseline characteristics are provided in Table 2.

Primary endpoints

General overview

Respiratory distress syndrome (RDS) was the primary reason for initiating NIV in 63 (92.6%) infants. At the time of inclusion, 40 (58.8%) infants were supported with nCPAP, while 28 (41.2%) infants received NIV-NAVA. The mean LUS-score at inclusion was 7.9, (SD 2.6, range 2 - 12). Surfactant was administered to 29 (42.6%) infants, with 23 infants receiving their first dose via LISA. Invasive ventilation was required in 10 (14.7%) infants, and the median duration of NIV was 13.5 days (IQR 6-38.5).

Important differences in the duration of respiratory support were observed across GA groups. Infants born at a GA between 24 and 27 6/7 weeks had a median NIV duration of 65.5 days (IQR 51.3-74), significantly longer than those born between 28 and 31 6/7 weeks, with a median duration of 20 days (IQR 8-33) ($p < 0.05$), and those born between 32 and 36 6/7 weeks ($p < 0.05$), with a median duration of 6 days (IQR 3.5-13). Furthermore, a significant difference was found between the latter two groups ($p < 0.05$). A detailed overview of these primary endpoints is presented in Table 3.

Table 2: Baseline characteristics.

Characteristics	*N* = 68
GA at birth, median weeks (IQR)	31.3 (29-32.7)
- 24 - 27 6/7 weeks, *n (%)* - 28 - 31 6/7 weeks, *n (%)* - 32 - 36 6/7 weeks, *n (%)*	12 (17.6) 27 (39.7) 29 (42.6)
Birth weight, median g (IQR)	1475 (1110-1850)
Male/female, *n/n*	38/30
Antenatal steroids, *n (%)*	52 (76.5)
Caesarean delivery, *n (%)*	51 (75)
Chorioamnionitis, *n (%)*	5 (7.6)
Caffeine, *n (%)*	53 (77.9)

Table 3: Detailed overview of primary endpoints.

Characteristics	All participants *N* = 68	GA 24 - 27 6/7 weeks (*N* = 12)	GA 28 - 31 6/7 weeks (*N* = 27)	GA 32 - 36 6/7 weeks (*N* = 29)
Reason for respiratory support - RDS, *n (%)* - TTN, *n (%)*	 63 (92.6) 5 (7.4)	 12 (100)	 27 (100)	 24 (82.8) 5 (17.2)
Respiratory support at inclusion				
Mode - nCPAP, *n (%)* - NIV-NAVA, *n (%)*	 40 (58.8) 28 (41.2)	 1 (8.3) 11 (91.7)	 17 (63) 10 (37)	 22 (75.9) 7 (24.1)
Indication - Primary support, *n (%)* - Post-extubation, *n (%)*	 65 (95.6) 3 (4.4)	 10 (83.3) 2 (16.7)	 26 (96.3) 1 (3.7)	 29 (100)
LUS-score at inclusion, mean (SD, range)	7.9 (2.6, 2-12) (*N*=40)	10 (6-12) [a] (*N*=9)	7.33 (2, 3-10) (*N*=15)	7.8 (2.5, 3-12) (*N*=16)
Surfactant, n (%)	29 (42.6)	10 (83.3)	11 (40.7)	8 (27.6)
Amount - One dose, *n* - Two doses, *n* - Three doses, *n*	 22 4 3	 5 3 2	 9 1 1	 8 0 0
Administration initial dose - LISA, *n* - INSURE, *n* - Endotracheal tube, *n*	 23 2 4	 8 2	 9 1 1	 6 1 1
Doxapram	1	1		
DOXA-trial study medication	1	1		
Total duration, median days (IQR)	14.5 (6-45.5)	74 (55, 87.5)	20 (8-34)	6 (3.5-13.5)
Duration of - Invasive support, median days (IQR) - NIV, median days (IQR) - NIV-NAVA, median days (IQR) - nCPAP, median days (IQR) - HFNC, median days (IQR)	 10 (14.7)[b] 13.5 (6-38.5) 1 (0-5) 4 (2.3-8) 7 (2.3-15)	 0.5 (0-16.8) 65.5 (51.3-74) 33 (6.8-41.8) 20 (10-31.5) 12 (7.5-25.8)	 2 (7.4) b 20 (8-33) 1 (0-3) 4 (3-8) 13 (3-20)	 2 (6.9) b 6 (3.5-13) 0 (0-3) 3 (1.5-5) 3 (0-8)

[a] represented as median (IQR)
[b] represented as number of infants receiving invasive support ((number of infants receiving IV)/(total number of infants in this category)%)

Table 4: Comparison of characteristics of infants with and without NIV-NAVA.

Characteristics	NIV-NAVA (*N*=36)	No NIV-NAVA (*N*=32)	*p*-value
GA at birth, mean weeks (SD, range)	29.6 (27.5-32) [a]	32.2 (1.8, 27-35 4/7)	< 0.05
- 24 - 27 6/7 weeks, *n (%)*	11	1	
- 28 - 31 6/7 weeks, *n (%)*	15	12	
- 32 - 36 6/7 weeks, *n (%)*	10	19	
Birth weight, mean g (SD, range)	1245 (914-1750) [a]	1711 (438, 903-2795)	< 0.05
Male/female, n/n	22/14	16/16	
Antenatal steroids, *n (%)*	28 (77.8)	24 (75)	
Caesarean delivery, *n (%)*	27 (75)	24 (75)	
Chorioamnionitis, *n (%)*	2 (5.9)	3 (9.4)	
LUS-score at inclusion, mean (SD, range)	8.6 (2.4, 3-12) (*N*=26)	6.5 (2.6, 5.5-7.5) (*N*=14)	< 0.05
Surfactant, *n (%)*	25 (69.4)	4 (12.5)	
Amount			
- One dose, *n*	18	4	
- Two doses, *n*	4	/	
- Three doses, *n*	3	/	
Administration initial dose			
- LISA, *n*	20	3	
- INSURE, *n*	1	1	
- Endotracheal tube, *n*	4		
Total duration of NIV, median days (IQR)	32 (16.3-65.8)	6.5 (3.3-11.8)	< 0.05

[a] data represented as median (IQR)

NIV-NAVA

Of the 68 infants included in the study, 36 (52.9%) received NIV-NAVA. These infants were born at a significantly lower median GA of 29.6 (IQR 27.5-32) weeks, compared to those who received only nCPAP and/or HFNC ($p < 0.05$). The median birth weight of infants receiving NIV-NAVA was 1245 grams (IQR 914-1750). For this group, the mean LUS-score at inclusion was 8.6 (SD 2.4, range 3-12). The median total duration of NIV in infants treated with NIV-NAVA was 32 days (IQR 16.3-65), contrasting to 6.5 days (IQR 3.3-11.8) for those only receiving nCPAP and/or HFNC. For a detailed comparison between the two groups, please refer to Table 4.

The majority of infants receiving NIV-NAVA, totalling 25 (69.4%) infants, were supported with NIV-NAVA as their primary mode of respiratory support, while 6 (16.7%) were transitioned to NIV-NAVA following nCPAP failure. The median duration of NIV-NAVA was 4.5 days (IQR 3-28.3). Stratification by GA revealed notable differences in NIV-NAVA duration. Infants born between 24 and 27 6/7 weeks of GA had a significantly longer median duration of 37 days (IQR 9-42), compared to both the 28 to 31 6/7 weeks GA group ($p<0.05$) and the 32 to 36 6/7 weeks

Table 5: Indication, duration and baseline settings of NIV-NAVA, nCPAP and HFNC.

Characteristics	NIV-NAVA (*N*=36)	nCPAP (*N*=65)	HFNC (*N*=58)
Indication first use			
- Primary support mode, n (%)	25 (69.4)	40 (61.5)	
- Weaning mode, n (%)	3 (8.3)	24 (36.9)	52 (89.7)
- Weaning failure, n (%)		1 (1.5)	6 (10.3)
- nCPAP failure, n (%)	6 (16.7)		
- HFNC failure during sepsis, n (%)	2 (5.6)		
Settings at inclusion			
NIV-NAVA			
- Level, median cmH2O/µV (IQR)	1.5 (1.2-1.8)		
- PEEP, median cmH2O (IQR)	7 (7-8)		
- FiO2, median % (IQR)	26 (21-35)		
- Apnoea time, median seconds (IQR)	3 (2-3)		
- Back-up PAP, median cmH2O (IQR)	7 (5-8)		
- Back-up frequency, median per minute (IQR)	50 (45-50)		
CPAP			
- PEEP, median cmH2O (IQR)		6.5 (6-7)	
- FiO2, median % (IQR)		21 (21-24)	
HFNC			
- Flow, median L/min (IQR)			4 (3.8-5)
- FiO2, median % (IQR)			21 (21-21)
(Duration of respective modes, median days (IQR)			
Total	4.5 (3-28.3)	4 (3-8.5)	9.5 (4.8-16.8)
- 24 - 27 6/7 weeks	37 (9-42) (*N*=11)	20 (10-31.5) (*N*=12)	12 (7.5-25.8) (*N*=12)
- 28 - 31 6/7 weeks	3 (2-18) (*N*=15)	4 (3-8) (*N*=24)	14 (5-20.5) (*N*=25)
- 32 - 36 6/7 weeks	3 (3-5) (*N*=10)	3 (1.5-5) (*N*=29)	6 (3-11) (*N*=21)

GA group (p<0.05). However, no significant difference was observed between infants born at 28 to 31 6/7 weeks and those born at 32 to 36 6/7 weeks (p=0.919). Table 5 provides a detailed overview of these findings, including the NIV-NAVA settings at inclusion, while figure 2 offers a visual representation.

NCPAP

In our cohort, 65 (95.5%) infants received nCPAP at some point during their NICU stay. For 40 (61.5%) infants, nCPAP was the primary mode of respiratory support, while 24 (36.9%) used it as part of their weaning process from NIV-NAVA. Only 1 (1.5%) infant required nCPAP after HFNC failure. The overall median duration of nCPAP for all infants was 4 days (IQR 3-8.5), while infants born between 24 and 27 6/7 weeks of GA had a median duration of 20 days (IQR 10-31.5). These results, along with the nCPAP settings at inclusion, are summarised in Table 5.

HFNC

Out of the 68 infants analysed, 58 (85.3%) received HFNC. Among them, 52 (89.7%) were initiated on HFNC following weaning from nCPAP and/or NIV-NAVA. Six (10.3%) infants got HFNC for the first time after weaning failure, when the discontinuation of NIV directly from nCPAP failed. The overall median duration of HFNC for all infants was 9.5 days (IQR 4.8-16.8). Infants born between 24 and 27 6/7 weeks of GA had a median HFNC duration of 12 days (IQR 7.5-25.8). A detailed summary, along with the HFNC settings at initiation, can be found in Table 5.

Secondary endpoints

Adverse events

Among the 36 infants treated with NIV-NAVA, 1 developed a pneumothorax, and another 1 had a pulmonary haemorrhage. No other adverse events, such as spontaneous intestinal perforation, were observed. Additionally, no adverse events were reported during the use of nCPAP or HFNC. There was no mortality in our study population.

Treatment failure

Out of the 36 infants treated with NIV-NAVA, 8 (22.2%) experienced treatment failure. The causes included oxygenation failure in 3 infants, hypercapnia in 1, combined hypercapnia and oxygenation failure in another 1, severe apnoea in 2, and acute collapse during pulmonary haemorrhage in 1. Among infants with a GA between 24 and 27 6/7 weeks, treatment failure occurred in 5 out of 11 cases (45.5%). For those born between 28 and 31 6/7 weeks, treatment failure was observed in 2 out of 15 (13.3%), while in infants between 32 and 36 6/7 weeks, the rate was 1 out of 10 cases (10%). The median NIV-NAVA settings prior to reintubation were: NIV-NAVA level of 2 $cmH_2O/\mu V$ (IQR 1.3-2), PEEP of 7 cmH_2O (IQR 7-8.8) and FiO_2 of 32.5% (IQR 21 - 55).

In the cohort of 65 infants who received nCPAP, 8 (12.3%) experienced treatment failure. The failures included hypercapnia in 3 infants, oxygenation failure in 1, combined hypercapnia and oxygenation failure in 1, severe apnoea in 2, and increased work of breathing in 1. Among the 55 infants who received HFNC, only 1 (1.8%) experienced treatment failure, which was attributed to hypercapnia.

Length of NICU stay

The median duration of NICU stay for all infants in the study was 27 days (IQR 15.3-53). Infants receiving NIV-NAVA had a median NICU stay of 46.5 days (IQR 23.3-77).

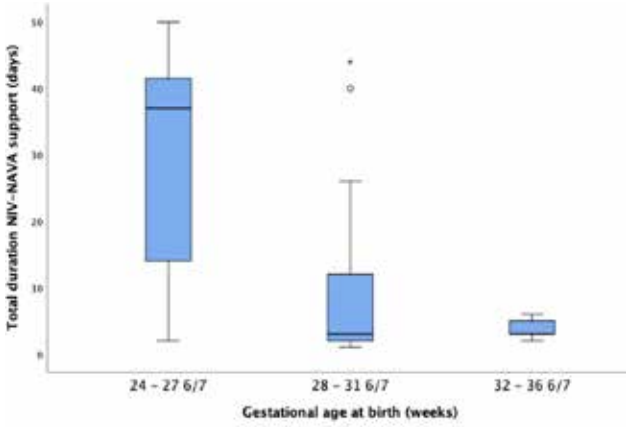
Use of corticosteroid treatment

Out of the 68 infants, 6 (8.8%) were treated with systemic corticosteroids.

Bronchopulmonary dysplasia

Of the 68 infants, data for assessing BPD were available for 60 infants, as some were transferred to secondary-level hospitals before data collection was completed. Among these infants, 8 (13.3%) were diagnosed with grade I BPD, and 1 (1.7%) with grade 2 BPD. The overall incidence of BPD among the 31 infants who received NIV-NAVA was 29%.

Figure 2: Differences in duration of NIV-NAVA across groups of different GA receiving NIV-NAVA.



Since BPD is defined as occurring in infants born before 32 weeks of GA, our comparison between infants with and without BPD focuses exclusively on neonates younger than 32 weeks GA. This resulted in 39 eligible neonates, with outcome data available for 32 of them.

Infants diagnosed with BPD had a lower, though not statistically significant, mean GA at birth, of 27.5 weeks (SD 1.2, range 26-29.1), and a significantly lower mean birth weight of 891 g (SD 257, range 510-1300), compared to those without BPD. The mean LUS-score at inclusion was 9.6 (SD 1.7, range 7-12) for infants with BPD, compared to 7.3 (SD 3, range 2-12) for those without, although this difference was not statistically significant. The median duration of NIV was 66.5 days (IQR 65-71.8) for infants with BPD, compared to 21 days (IQR 8-57.8) for those without BPD. A detailed comparison between infants with and without BPD is presented in table 6.

Home support

Since our centre provides follow-up for all infants requiring respiratory support after discharge, we were able to analyse data from 68 infants. Of these, 1 infant required nCPAP at discharge, and 2 needed home oxygen therapy.

Discussion

Our research is among the first prospective observational studies to investigate NIV-NAVA in preterm infants. Unlike the few existing prospective studies on NIV-NAVA, which are primarily interventional and focus on comparing NIV-NAVA with nCPAP in controlled clinical settings, our study is purely observational and descriptive (17-20). It documents local practices from birth to discharge, across all gestational ages. While our study did not directly compare NIV-NAVA with other modes of NIV, it provides valuable insights into its feasibility, safety and practical application in everyday clinical settings.

Previous studies by Kallio et al., Lee et al. and Yagui et al., focused on comparing NIV-NAVA with nCPAP as the primary respiratory support mode, while Shin et al. focused solely on infants receiving NIV-NAVA after extubation (17-20) These studies had varying inclusion criteria, some recruited only infants with a GA above 28 weeks, while others specifically included infants with a GA below 30 weeks or a birth weight below 1500 grams (17-20). In contrast, our study is the first to include preterm infants across all GA, using NIV-NAVA both as the primary support mode, post-extubation and after nCPAP failure.

In our study, 36 infants received NIV-NAVA. These infants had a significantly lower median gestational age of 29.6 weeks (IQR 27.5-32) and a significantly lower median birth weight of 1245 g (IQR 914-1750) compared to those not receiving NIV-NAVA. The median duration of NIV-NAVA was 4.5 days (IQR 3-28.3), with infants born below 28 weeks of GA had a notably longer median duration of 37 days (9-42). These infants had more severe RDS, reflected in higher surfactant requirements, longer durations of NIV and higher LUS scores.

Table 6: Comparison of characteristics of infants with and without BPD.

Characteristics	BPD (*N*=8)	No BPD (*N*=24)	*p*-value
Degree of BPD - Grade I - Grade II - Grade III	 7 1		
GA at birth, median weeks (IQR) - 24 - 27 6/7 weeks, *n (%)* - 28 - 31 6/7 weeks, *n (%)*	27.5 (1.2, 26-29.1)[a] 4 (50) 4 (50)	29.9 (27.1-31.3) 8 (33.3) 16 (66.7)	0.061
Birth weight, mean g (SD, range)	891 (257, 510-1300)	1274 (418, 427-1896)	< 0.05
Male/female, *n/n*	6/2	13/11	
Antenatal steroids, *n (%)*	7 (87.5)	20 (83.3)	
Caesarean delivery, *n (%)*	7 (87.5)	17 (70.8)	
Chorioamnionitis, *n (%)*	1 (12.5)	4 (16.7)	
LLUS-score at inclusion, mean (SD, range)	9.6 (1.7, 7-12) (*N=7*)	7.3 (3, 2-12) (*N=14*)	0.077
Surfactant, *n (%)* Amount - One dose, *n* - Two doses, *n* - Three doses, *n* Administration initial dose - LISA, *n* - INSURE, *n* - Endotracheal tube, *n*	7 (87.5)) 4 1 2 7 0 0	10 (41.7) 6 3 1 8 0 2	
Total duration respiratory support, median days (IQR) Duration of - Invasive support, median days (IQR) - NIV, median days (IQR) - NIV-NAVA, median days (IQR) - nCPAP, median days (IQR) - HFNC, median days (IQR)	81.6 (20.2,53-114)[a] 4.5 (0-20.5) 66 .5(65-71.8) 32.5 (7-41.5) 22.6 (8.7,10-35)[a] 11 (7.5-14.5)	21 (8-64.8) 4 (16.7)[b] 21 (8-57.8) 2 (0-15.8) 5 (3-10) 11.5 (5-22.5)	< 0.05 < 0.05 < 0.05 < 0.05 < 0.05 0.695
Corticosteroid treatment, *n (%)*	5 (62.5%)	1 (4.2%)	
Home therapy, *n (%)* nCPAP Oxygen	 1 (12.5) 2 (25)		
Failure of NIV-NAVA, *n (%)*	4 (50)	3 (23.1) (*N=13*)	
Length of NICU stay, median days (IQR)	83.8 (19.5, 54-115) a	39 (22-71.3)	< 0.05

[a] data represented as mean (SD, range)
[b] represented as number of infants receiving invasive support ((*number of infants receiving IV*)/(*total number of infants in this category*)%)

When examining the total duration of NIV in infants receiving NIV-NAVA, the median was 32 days (IQR 16.3-65.8), similar to the 35.5 days (IQR 9.8-44.8) reported by Lee et al., but substantially longer than the 127 hours reported by Yagui et al. (18-19). These differences may stem from differing approaches to NIV-NAVA weaning, as evidence-based guidelines are currently lacking, with only an eminence-based guideline available (21). Additionally, Yagui et al. did not specify the criteria for defining NIV in their study, and the high standard deviation in their reported NIV duration suggest considerable variability in their cohort (19).

We observed a 22.2% treatment failure rate among infants receiving NIV-NAVA, comparable to the 20.3% reported by Yagui et al., though lower than the 30-35% failure rates documented by Kallio et al. and Lee et al. (17-19). These differences are likely due to varying definitions of treatment failure. Additionally, Lee et al. maintained a constant PEEP and a NIV-NAVA level of 1 $cmH_2O/\mu V$, while effective unloading of the infants' respiratory effort typically requires individualized titration of NAVA levels based on the patient's Edi values (9,18). Therefore, higher NAVA levels may be necessary to optimally support infants with respiratory distress and to prevent treatment failure. Shin et al. supports this theory, as they used higher levels of NIV-NAVA before reintubation, with a median level of 2.5 $cmH_2O/\mu V$, and documented a lower failure rate of 8.6% (20). In our study, the median NIV-NAVA level before reintubation was 2 $cmH_2O/\mu V$ (IQR 1.3-2).

Subgroup analysis in our study revealed a higher failure rate (45.5%) in infants born below 28 weeks of gestation, compared to those born after 28 weeks (12%). This highlights the considerable challenges encountered with the application of NIV-NAVA in extremely premature infants, likely due to a combination of pulmonary immaturity and poor respiratory drive. Nevertheless, despite these challenges, our

experience suggests that most infants in this subgroup ultimately achieve successful weaning to NIV-NAVA.

Regarding BPD, 9 (15%) infants in the overall cohort developed the condition, with the incidence rising to 29% among those treated with NIV-NAVA. However, because of the relatively low overall incidence of BPD in our cohort and the complex, multifactorial nature of the disease, no definitive conclusions can be drawn. We found no statistically significant difference in the mean LUS-score at inclusion between infants with BPD and without BPD, consistent with the findings of Woods et al, suggesting that early LUS scores may offer little beyond the established early clinical markers (22).

In terms of safety, we observed 1 case of pneumothorax and 1 case of pulmonary haemorrhage among infants receiving NIV-NAVA. To our knowledge, this is the first reported case of pulmonary haemorrhage in an infant receiving NIV-NAVA. However, as both conditions are known complications of RDS, the primary indication for initiating NIV in these infants, it is difficult to establish a definitive causal link with NIV-NAVA. Gastrointestinal symptoms related to gastrointestinal air associated with NIV-NAVA were not reported due to the lack of clear definitions for these complications, which is a recognized limitation of our study.

Another important limitation of our study arises from its observational nature, which inherently restricts the ability to draw causal relationships. The study is subject to potential confounding factors and selection bias, particularly since not all eligible infants were included. Additionally, the single- centre design limits the generalizability of our findings, and the small sample size in certain subgroups make it difficult to draw definitive conclusions about specific outcomes, such as BPD or treatment failure rates.

Despite these limitations, our study demonstrates that NIV-NAVA is a feasible and safe mode of respiratory support for preterm infants, even in those with significant with significant respiratory challenges. Its use across a wide range of GA, alongside other modes of NIV, highlights its adaptability in clinical practice.

Future research should aim to deepen our understanding of the physiological effects of NIV-NAVA, as this could be useful to develop evidence-based guidelines for its use and weaning. Larger studies with extended follow-up are necessary to assess long-term outcomes, including BPD and other adverse events. Multi-centre trials are necessary to enhance the external validity of our findings, and randomised controlled trials comparing NIV-NAVA with other NIV modes, are crucial to definitively establish its efficacy and safety.

Conclusion

Our study is one of the first prospective observational studies investigating NIV-NAVA in relation to more commonly used forms of NIV in preterm infants from birth to discharge from the NICU. Our findings illustrate the feasibility and safety of NIV-NAVA across various ranges of GA and alongside other modes of NIV, despite higher failure rates observed in extremely preterm infants. The incidence of BPD among infants receiving NIV-NAVA was 29%. Further research is needed to achieve a more comprehensive understanding of NIV-NAVA's efficacy and safety profile. It is also crucial to gain a deeper understanding of its psychological effects for optimizing its application and to obtain a clearer view of long-term outcomes.

None of the investigators had any conflicts of interest.

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Infatrini: A Pioneering Solution to Support Optimal Growth in Infants and Combat Undernutrition

Early childhood is a critical phase marked by rapid growth and increased nutritional needs. Between 0 and 4 years of age, a child doubles in length and quintuples in weight, with brain development occurring at a rate of approximately 1 gram per day. This period of accelerated development demands significantly high energy requirements, making infants particularly vulnerable to undernutrition risks.[1-4]

The importance of early detection of undernutrition

Undernutrition in children is often underestimated, affecting 10% of infants[5]. Its causes can be diverse, ranging from severe medical conditions to more common factors such as reflux issues or selective eating behavior. The consequences of growth delay can be significant, both short- and long-term, including an increased risk of infections, reduced muscle mass, and cognitive development delays, which can impact IQ and learning capacity.[6-10]

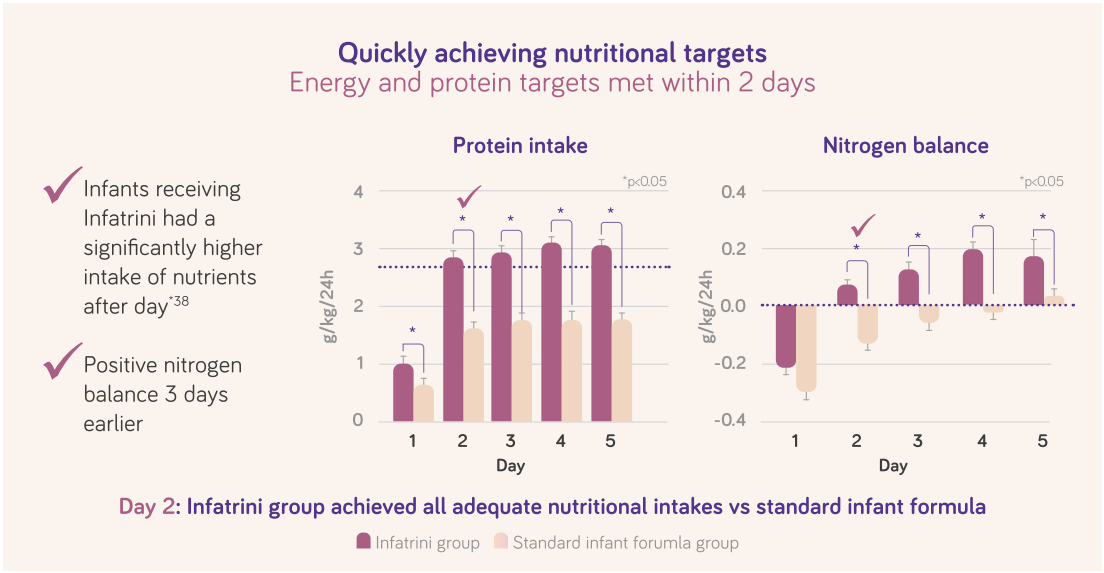
Furthermore, in cases of hospitalization, malnourished infants typically exhibit poorer clinical outcomes, including longer hospital stays, higher healthcare costs, and a greater need for nutritional support.[11]

It is therefore crucial to identify nutritional issues at the earliest signs, especially when a slowdown in growth is observed. Experts recommend intervention as soon as a drop of one standard deviation (-1 SD) on the growth chart is noted after one month.[12]

A renewed composition for a unique formula: now enriched with HMO 2'-FL

When an infant shows signs of growth delay or increased energy needs, it is essential to provide nutrition that supports optimal catch-up growth without promoting excessive fat accumulation. When infants with growth delays or increased energy needs are provided with standard formulas or modular additions, such as a 20% solution with Fantomalt, there is a notable risk of disproportionate fat mass accumulation relative to lean body mass. Unlike these approaches, Infatrini ensures a balanced protein-to-energy ratio that supports targeted catch-up growth while avoiding excessive fat deposition. Unlike standard formulas, enriched formulas like Infatrini provide energy and protein intake in line with the World Health Organization (WHO) recommendations. These guidelines advocate for a minimum composition of 8.9% to 11.5% of energy derived from protein to support effective catch-up growth.[13]

Infatrini stands out as a comprehensive and innovative nutritional solution for infants with increased energy needs or growth delay. It is the only formula enriched with HMOs (human milk oligosaccharides) while maintaining an optimal protein-to-energy ratio of 10.4%EN, as specified by the WHO. This careful balance helps maintain appropriate body composition during critical growth phases, avoiding the unintended consequences of fat gain associated with less balanced alternatives.



The incorporation of 2'-fucosyllactose (2'-FL), one of the most prevalent HMOs in human milk, marks a significant advancement for Infatrini. Combined with the unique blend of scGOS/lcFOS (9:1) prebiotic fibers, Infatrini's oligosaccharides closely resemble those found in human milk in terms of quantity, diversity, and complexity.[14,15]

The HMOs 2'-FL inhibit the growth of pathogenic bacteria by preventing their adhesion and entry, thus reinforcing intestinal barrier integrity. The scGOS/lcFOS (9:1) prebiotic blend promotes the growth and activity of beneficial bacteria, fostering a healthy gut microbiota. Additionally, the combination of scGOS/lcFOS (9:1) with 2'-FL has a direct prebiotic and immunomodulatory effect, including the modulation of dendritic cell maturation. These oligosaccharides mimic the diversity and functionality of natural HMOs in breast milk, suppressing pathogenic growth and strengthening the infant's immune system[16-29]. Over 40 studies and 90 publications have confirmed the clinical efficacy of scGOS/lcFOS in reducing infections, with significant decreases in gastrointestinal infections (-55%), infections requiring antibiotics (-33%), respiratory infections (-37%), and overall infections (-30%).[30-40]

Clinical and practical benefits of using Infatrini

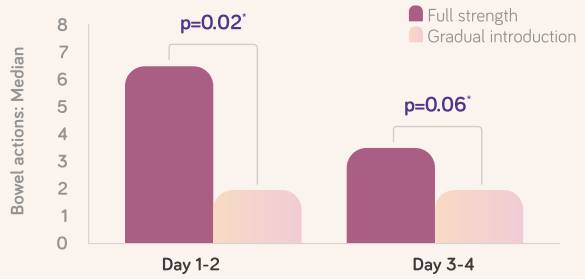
Infatrini is designed to be well-tolerated by infants, even those with complex conditions. Studies have shown that it is well accepted when administered from

day one, and a gradual introduction may be considered for infants under 12 weeks old. However, most infants benefit from full introduction from the beginning.[30]

Infatrini also helps achieve nutritional targets quickly, with adequate energy and protein intake reached within two days. Infants receiving Infatrini have significantly higher nutrient intake and achieve a positive nitrogen balance three days earlier than with standard formulas ($p<0.05$ for both parameters).[41]

Clinically, Infatrini contributes to a reduction in hospital stays by 29% ($p = 0.057$ vs. standard formula) and a decrease in antibiotic use by 31% ($p = 0.047$ vs. standard formula), thereby supporting clinical goals and improving the care pathway for young patients. Additionally, 93% of severely ill infants who received Infatrini demonstrated significant weight gain.[42,43]

Infatrini appears to be well tolerated in infants when administered from day 1[37]



Younger infants (<12 weeks) may benefit from a gradual introduction to Infatrini. However, for the majority of infants with faltering growth, Infatrini can be introduced at full strength from day 1.

The role of healthcare professionals in managing infant undernutrition

Early detection and nutritional management of undernutrition in children are essential to prevent its harmful short- and long-term effects, such as growth and cognitive development issues. To support healthcare professionals, Professors Koen Huysentruyt, Atul Singhal, Koen Joosten, and Rosan Meyer have developed a comprehensive online training program. This course, comprising four modules, provides in-depth knowledge and essential skills for recognizing, diagnosing, and treating growth delays in infants and children under two years of age. The program includes practical tools to effectively address this critical issue in pediatrics. It is certified and endorsed by ASPEN and accredited for 1 EACCME point.

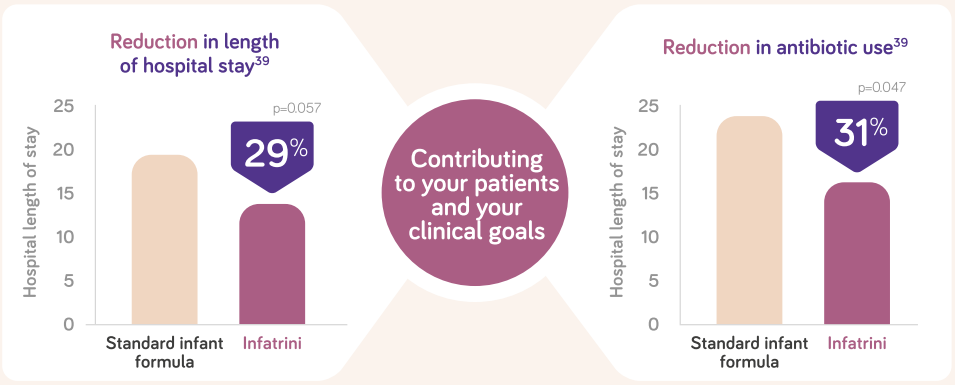
To access the training, scan this QR Code.

Infatrini, against undernutrition

Infatrini represents a significant advancement in addressing infant undernutrition, combining a nutrition profile that meets international standards with innovation through the addition of 2'-FL to support holistic child development. By promoting growth[38], digestive tolerance[37], and immune strengthening[16-29], Infatrini plays a key role in tackling undernutrition in infants, which can have a short- and long-term impact on the health of the child.

Infatrini is a food for special medical purposes and must be used under medical supervision after full consideration of all feeding options by the Healthcare professional including breastfeeding. For the dietary management of disease related malnutrition, faltering growth, increased energy requirements and/or water restriction. Information for health care professionals only.

Supporting additional clinical benefits



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Clinical Decision Support for Parents through Mobile Applications: A Systematic Assessment of Pediatric Fever Management Apps

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Keywords

Medical decision tools ; mobile applications ; triage ; fever.

Abstract

Objective

This study aimed to identify existing apps for paediatric fever management and compare their decision algorithms with current evidence-based guidelines.

Methods

From May to July 2022, mobile applications were systematically searched in the Apple App Store and Google Play Store using specific terms. The apps underwent four rounds of screening to match predefined criteria. Each app was evaluated by five independent reviewers using the Mobile Application Rating Scale (MARS). The decision support algorithms of each app were analysed for adherence to existing fever management recommendations, including the NICE guidelines for children under five years of age and the Schmitt-Thompson triage protocol for children under and over three months of age.

Results

Out of 878 apps retrieved, 6 met the selection criteria and were 3 finally assessed. The apps scored high on overall quality, averaging a MARS rating of 4.3 out of 5. Kinsa and FeverApp scored the highest (4.4 out of 5), followed by FeverFriend (4.0 out of 5). FeverFriend showed the highest adherence to the NICE guidelines, followed by Kinsa and FeverApp. For the Schmitt-Thompson protocol, Kinsa showed the highest adherence, followed by FeverFriend and FeverApp.

Conclusion

The availability of evidence-based fever management apps with parental decision support systems is limited. Kinsa emerged as the top-performing app based on quality assessment.

Introduction

Fever, defined as a body temperature exceeding the normal range (36.6°C to 37.9°C), is a natural physiological response that boosts the immune system and combats infection, potentially shortening the duration of illness (1). It is a common childhood condition as children between the ages of 3 and 36 months typically experience about six febrile episodes annually (2). This underscores the fact that fever is usually a symptom of other illnesses rather than a disease itself (3). Although fever in children under five is often linked to benign viral infections, it can also be associated with serious health issues.

This makes fever management very challenging for parents, mostly due to misconceptions about its significance and effects (4). Caregivers fear harm either from the fever itself or the underlying illness (5). They are thus confronted with the decision to treat symptoms at home or seek medical attention, which leads to overuse primary care and specialized secondary care systems (6,7).

The surge in mobile technology usage has led to the emergence of health-related applications, including those aimed at assisting parental decision-making. These apps, which include symptom checkers and self-triage tools, promise to be transformative, yet their integration of evidence-based medicine remains inadequately examined (8, 9, 10). This study focuses on evaluating mobile applications equipped with parental decision support systems (PDSS) for the management of paediatric fever. We aim to compare these apps' decision-making algorithms with current evidence-based guidelines and examine their potential in aiding caregivers to make informed choices about managing fever, which could help reduce unnecessary use of antipyretics and reduce the burden on healthcare facilities.

Material and Methods

Search Strategy

The initial identification of existing triage applications, was obtained by entering the keywords "pediatrics" OR "fever" OR "pediatrics, fever" OR "pediatrics, symptom" OR "fever, children" OR "fever, child" OR "fever, symptom" OR "febrile, symptom" in the search engines of both the Apple App store for iOS and the Google Play store for Android. Searches were performed within these digital distribution platforms from May to July 2022.

After the identification process, preliminary selection and assessment of mobile applications was based upon a prespecified set of inclusion and exclusion criteria as defined in Table 1. Selected applications were subject to four rounds of screening.

Since the apps were obtained by systematic searches in two sources (the Apple App Store and the Google Play Marketplace) using multiple search terms, results were screened for duplicates. Duplicate apps, i.e. identical features in the same app listed independently in both app stores or listed in the same app store using different search terms, were excluded in the first round. Applications by the same developer, similarly named, but not having identical feature sets were treated as two individual apps.

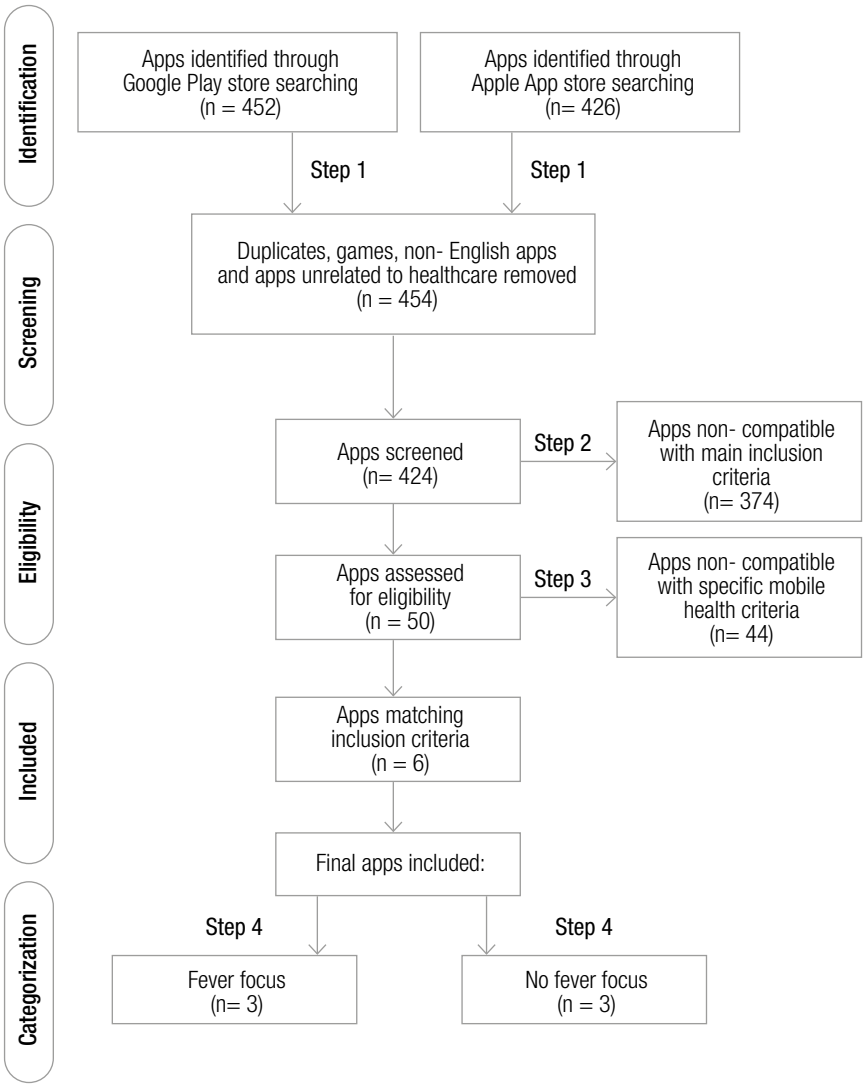
Table 1: Inclusion and exclusion criteria.

Main inclusion criteria	Specific mobile health criteria	Exclusion criteria
• Children health assessment • Pediatrics • Fever management support	• Parental decision support system • No exclusive focus on fever monitoring and fever registration • No exclusive focus on telemedicine/ video consultation • Ability to function independently of a medical device • Ability to function without possession of a US phone number	• Games • No relation to healthcare and medical services • No English user interface • Health care workers as primary audience

Additionally, games or applications without presence of English user interface were excluded in the first round as well. The second round of screening was performed based on title/name and available summary description within the app stores. Applications that were non- compatible with main inclusion criteria were excluded. The general target population in this study includes non- clinical app users, i.e. parents and caregivers. Apps aimed at the provision of fever management guidance within clinical settings, that is with target users being physicians and healthcare professionals, were also excluded as a part of round two.

In the third round, the remaining applications were downloaded and manually assessed for evaluation of specific mobile health criteria. The apps inconsistent with our criteria were eliminated. In the fourth round apps with main focus on fever management in children were differentiated from those that provide fever management decision support, without fever management in children being the app's main target, by dividing them into two groups. Thus, the first group of apps focuses entirely on assisting parents who are dealing with a febrile child while the second group of apps provide a decision support system for numerous symptoms in a variety of ages, including fever. The flowchart in Figure 1 illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology described.

Figure 1: Flowchart of the selection process.



Quality assessment: the Mobile Application Rating Scale

First, the applications were independently evaluated by a team of five reviewers (parents without medical background) using the Mobile Application Rating Scale (MARS). MARS is a widely used standardized tool developed by the Queensland University of Technology. It provides a multidimensional measure of mobile health app quality by assessment in three sections. The first section is divided into four objective dimensions, i.e. engagement, functionality, aesthetics, and information quality. In short, the scale measures whether an app is interesting, interactive (e.g. sends alerts, messages, reminders or feedback) and easy to learn. It analyses the gestural design and examines the quality and quantity of information provided. In the first section nineteen items are rated on a 5-point scale (1= inadequate, 2= poor, 3= acceptable, 4= good, and 5= excellent). The mean score of each dimension is then calculated and used to compute the app overall quality score (11, 12). The second and third section, being the app subjective quality score and the app specific quality score, are equally determined by rating of respectively 4 and 6 additional items. Supplementary, ambiguous items were discussed and clarified to ensure full comprehension of the scale (13).

Table 2: Adherence of existing fever management apps to the NICE guideline concerning fever under the age of five.

NICE guideline	FeverFriend	Kinsa	FeverApp*	Points of comparison
FEVER				
Fever (T < 38°C) Under 3 months	No Fever (T ≤ 38°C) Under 3 months	No Fever (T < 38°C) Under 3 months	No Fever (T ≤ 38°C) Under 4 months	**Fever under 3 months**: Both the Feverfriend and Kinsa app identified the symptom as high risk, thereby matching the guideline. The FeverApp app underestimated the symptom compared to the guideline, by classifying it as an intermediate risk of serious illness. The FeverApp app additionally mentioned both 3 months and 4 months as a cut off in age. **High Fever between 3 to 6 months**: None of the apps matched the guideline perfectly. Both the Feverfriend and Kinsa app identified 'fever (T ≥ 38°C) between 3 and 6 months' as an intermediate risk of serious illness, thereby overestimating the symptom compared to the guideline. The FeverFriend app additionally identified a 'high fever (T ≥ 39°C)' within this age group as a high risk symptom.The FeverApp app did not mention this symptom. **Fever duration**: None of the apps matched the guideline perfectly. The FeverFriend app identified a 'fever duration > 5 days' as a high risk symptom, thereby overestimating the symptom compared to the guideline. The FeverApp app used a different cut off of in time of 3 days. The Kinsa app did not mention this symptom. **Type of measurement**: Every app recommended fever measurement by usage of a infra-red tympanic thermometer, thereby matching the guideline. Yet, placement preference and usage of the electronic and chemical dot thermometer varied among the apps and did not match the guideline. **Rigors**: The Kinsa app underestimated the symptom compared to the guideline by classifying it as a low risk of serious illness.The FeverFriend and FeverApp app did not mention the symptom.
Fever (T < 39°C) Between 3-6 months	No Fever (T ≤ 38°C) Between 3-6 months	No Fever (T < 38°C) Between 3-6 months		
Fever (T ≥ 38°C) Above 6 months	No Fever (T ≤ 40°C) Above 6 months	No Fever (T < 40°C) Above 6 months	Fever (T > 38°C) Above 4 months	
Electronic thermometer axillary Chemical dot thermometer axillary Infra- red tympanic thermometer	Digital thermometer rectal/oral * Chemical thermometer rectal/oral * Infra- red tympanic thermometer	Rectal- type of thermometer unspecified * Infra- red tympanic thermometer *	Rectal - type of thermometer unspecified * Infra- red tympanic thermometer	
Fever < 5 days	Fever < 3 days		Fever < 3 days	
No rigors		Chills		
High Fever (T ≥ 39°C) Between 3-6 months	Fever (T > 38°C) Between 3-6 months	Fever (T ≥ 38°C) Between 3-6 months	Fever (T > 38°C) Under 4 months	
	High Fever (T > 40°C) Above 6 months			
Fever ≥ 5 days	Fever 3-5 days		Fever > 3 days	
Rigors				
Fever (T ≥ 38°C) Under 3 months	Fever (T > 38°C) Under 3 months	Fever (T ≥ 38°C) Under 3 months		
	High Fever (T > 39°C) Between 3-6 months			
	Very high Fever (T > 41°C) Above 6 months	High Fever (T ≥ 40°C)		
	Fever > 5 days			
SKIN CONDITION AND COLOR				
Normal color of skin, lips and tongue	Normal color of skin	Normal color of skin and lips		**Color of skin**: Both the FeverFriend and Kinsa app identified a bluish skin as a high risk symptom, thereby matching the guideline. However, the FeverFriend app matches the guideline in its entirety by also classifying pallor as an intermediate risk symptom. The FeverApp app did not include skin color in its triage system. **Rash**: Both the Feverfriend and the FeverApp app identified a non-blaching rash as a high risk symptom, thereby matching the guideline. However, the FeverFriend app matches the guideline in its entirety by also classifying a blaching rash as an intermediate risk symptom. The FeverApp app identified a blaching rash as an intermediate risk symptom, only when present for more than 3 days, thereby not perfectly matching the guideline. The kinsa App specified the type of rash in its triage system, where the differentiation between a blanching rash as an intermediate risk symptom and a non- blaching rash as a high risk symptom remained unclear.
No rash	No rash	No rash	No rash	
		Rash Above 2 years	Blanching rash Present for < 3 days	
Pallor	Pallor			
Blanching rash	Blanching rash	Rash Under 2 years	Blanching rash Present for > 3 days	
		Hives		
Pale, mottled, ashen, blue skin	Grey, bluish, purplish skin	Bluish skin or lips		
Non- blanching rash	Non- blanching rash	New purple or blood- colored spots/dots	Non- blanching rash	
		Blisters, sores or pus		
		Rash developing after taking new medication		
		Sudden and severe skin peeling		
RESPIRATORY				
No tachypnea *	No tachypnea *	No tachypnea *	No tachypnea *	**Tachypnea**: The FeverFriend app did not match the guideline perfectly by having somewhat different cut offs to differentiate tachypnea and severe tachypnea and classifying them as a intermediate and high risk symptom, respectively. The Kinsa app identified a respiratory rate above 60 breaths per minute as a high risk symptom, thereby matching the guideline. No further specifications were made. The FeverApp app defined a respiratory rate above 60 breaths per minute as an intermediate risk symptom, thereby underestimating the symptom compared to the guideline. Breathing frequency cut offs are specified below. **Signs of dyspnea**: The Kinsa and FeverApp app both defined shortness of breath by using a series of clinical observations. The Kinsa app matched few clinical observations compared to the guideline by classifying 'grunting' and the presence of 'retractions' or 'chest indrawing' as a high risk symptom. 'Nasal flaring' was classified as a high risk symptom, thereby overestimating the symptom compared to the guideline.The FeverApp app matched no clinical observations to the guideline. The FeverFriend app defined shortness of breath trough a scale, making comparison to the guideline difficult. The scale is specified below.
No signs of dyspnea	No signs of dyspnea	No signs of dyspnea	No signs of dyspnea	
Tachypnea *	Tachypnea *		Severe tachypnea *	
Nasal aring				
	Difficult or laboured breat hing ≤ 3/5 *		Enforced or constrained breathing	
	Slight wheezing			
		Barking cough		
Severe tachypnea *	Severe tachypnea *	Severe tachypnea *		
		Difficult breathing		
		Unable to finish a sentence		
		Nasal flaring		
Grunting		Grunting		
Moderate or severe chest indrawing		Retractions		
	Strong wheezing, stridor	Wheezing, stridor		
CIRCULATION AND HYDRATION				
No tachycardia *	No tachycardia *		No tachycardia *	**Tachycardia**: None of the apps matched the guideline perfectly.The FeverFriend and FeverApp app both defined anomalous cut offs compared to the guideline when defining tachycardia. The FeverFriend app differentiated tachycardia and severe tachycardia whereas the guideline did not. The Kinsa app did not mention this symptom. Heart rythm cut offs are specified below. **Poor feeding in infants**: The FeverApp app classified the symptom 'last time drinking > 8 hours in infants' as an intermediate risk symptom, thereby matching the guideline. The guideline does not specify the symptom in time, therefore 'last time drinking > 8 hours in infants' was considered a match to the guideline. The FeverFriend app differentiated poor and severly poor feeding by cut off in time. However, since no specification for infants was made by the app, as stated within the guideline, the symptom did not match the guideline perfectly. The Kinsa app equally did not specify an age group and identified 'last time drinking > 8 hours' as a high risk symptom, thereby not matching the guideline. **Dry mucous membrane**: The FeverApp app identified the symptom as an intermediate risk symptom, thereby matching the guideline. The Kinsa app overestimated the symptom compared to the guideline by classifying it as a high risk symptom. The FeverFriend app differentiated a 'dry tongue with decreased tears' from 'absence of tears' by classifying it as an intermediate and high risk symptom, respectively. Since the guideline mentions 'absence of tears' as part of 'dry mucous membrane', classifying 'no tears when c rying' as a high risk symptom overestimates the guideline.Therefore, the FeverFriend app only matched the guideline partially. **Reduced skin turgor**: The FeverFriend app differentiated a somewhat reduced skin turgor from a severely reduced skin turgor by classifying it as an intermediate risk symptom and a high risk symptom, respectively. However since the guideline defines any form of reduced skin turgor as a high risk of serious illness, the symptom did not match the guideline perfectly. The FeverApp app underestimated the symptom compared to the guideline, by classifying it as a intermediate risk symptom. The Kinsa app dit not mention this symptom. **Reduced urine output**: The FeverFriend app differentiated a reduced urine output from a severely reduced urine output by classifying it as an intermediate risk symptom and a high risk symptom, respectively. The guideline does not specify the symptom in time, therefore 'last urination > 6-12 hours' was considered a match to the guideline. The FeverApp app matched the guideline by classifying the symptom as an intermediate risk symptom. The Kinsa app overestimated the symptom compared to the guideline by classifying it as a high risk symptom
No signs of dehydration	No signs of dehydration	No signs of dehydration	No signs of dehydration	
Tachycardia *	Tachycardia *		Tachycardia *	
Poor feeding in infants	Drinking less than normal Last time eating > 12 hours		Last time drinking > 8 hours in infants *	
Dry mucous membrane *	Dry tongue, decreased tears when crying		Dry mucous membrane *	
CRT ≥ 3 seconds				
	Somewhat reduced skin turgor		Reduced skin turgor	
	Reduced urine output (Last urination > 6-12 hours)		Reduced urine output (Not specified)	
	Severe tachycardia *			
	Last time drinking > 12 hours Last time eating > 24 hours		Last time drinking > 8 hours	
	No tears when crying		Dry mucous membrane *	
Reduced skin turgor	Severely reduced skin turgor			
	Severely reduced urine output (Last urination > 12 hours)		Reduced urine output (Last urination > 8 hours)	
GENERAL CONDITION AND ACTIVITY				
Normal response to social cues	Normal response to social cues	Normal reactions to social cues, making eye contact	Normal response to social cues	**Response to social cues**: A normal respons to social cues is not specified in content or time by the guideline. The FeverFriend app defined 'odd reaction > 5 hours' as an intermediate risk symptom, however since the lack of specificity, it was considered no match to the guideline. Both the FeverFriend and the Kinsa app mentioned clinical observations indicating an absence of response to social cues. These symptoms were classified as high risk symptoms, thereby matching the guideline. The FeverApp app defined 'acting differently' and 'apathy' as high risk symptoms. However since the lack of specificity, comparison to the guideline remained difficult and no match could be concluded. **Awareness**: All apps identified an increased tendency to fall asleep as an intermediate risk symptom, thereby matching the guideline by indicating a slightly decreased state of awareness and a decreased level of acitivity. A severely altered conciousness was classified as a high risk symptom by all apps, thereby matching the guideline. **Irritability**: No app identified the absence of smile as an intermediate risk symptom. The Kinsa app identified a crooked smile as a high risk symptom, thereby not matching the guideline. All the apps identified a continous, weak or high pitched cry or screaming (as a sign ofirritability) as a high risk symptom, thereby matching the guideline. **Swelling or pain of joint or limb**: The FeverApp app identified 'swelling of a joint' as an intermediate risk symptom, thereby matching the guideline. The FeverFriend app identified 'swelling of body part' as a high risk symptom, thereby overestimating it compared to the guideline. Avoidance of using an extremity was not mentioned by any of the apps. Howerever, the FeverFriend app did identify 'protection of body part' as a high risk symptom. **Seizure**: The guideline defines 'status epilepticus' or 'a focal seizure' as high risk symptoms. The Kinsa and the FeverApp app both identify status epilepticus as a high risk symptom, thereby matching the guideline. A feverish seizure itself was equally classified by all apps as a high risk symptom. The FeverApp app specified only the first seizure as a high risk symptom. Ambiguity remains within the guideline concerning the management of a feverish seizure. **Bulging fontanelle**: The FeverFriend app underestimated the symptom compared to the guideline, by classifying it as an intermediate risk symptom. The Kinsa app identified the symptom as a high risk symptom, thereby matching the guideline. The FeverApp app did not mention this symptom. **Stiff neck**: The FeverFriend and the Kinsa app both identified the symptom as a high risk symptom, thereby matching the guideline. The FeverApp app underestimated the symptom compared to the guideline, by classifying it as an intermediate risk symptom.
Able to stay awake or awakens quickly, no decreased activity	Normal awareness	Normal awareness	No lethargy	
No signs of irritability or pain; content or smiles, not crying or strong crying	No signs of irritability or pain; not crying or strong crying	No signs of irritability or pain	No signs of irritability or pain	
No swelling of a limb or joint and normal usage of all extremities	No swelling of a body part and normal usage of all extr emities		No swelling of the joints	
No seizure or focal neurological signs	No seizure	No seizure	No seizure	
No bulging fontanelle	No bulging fontanelle	No bulging fontanelle		
No stiff neck	No stiff neck	No stiff neck	No stiff neck	
Not responding normally to social cues	Odd reactions > 5 hours			
Wakes only with prolonged stimulation, decreased activity	Sleepy	Fatigue	Lethargy	
No smile				
Swelling of a limb or joint			Swelling of a joint	
Non- weight bearing/ not using an extremity			Pain in the limb ≥ 3 days	
	Bulging fontanelle			
			Stiff neck	
No response to social cues	No reaction to social cues	Not making eye contact, acts 'out of it' or confused	Acting differently, apathy	
Unable to rouse or if roused does not stay awake	No awareness	Inability to wake up, unresponsive	Clouded consciousness	
Weak, high- pitched or continuous cry	Weak, high- pitched or continuous cry	Inconsolable crying, shrill screaming	Shrill screaming	
		Touch sensitivity	Touch sensitivity	
		Crooked smile		
	Seizure	Seizure	First seizure	
Status epilepticus		Status epilepticus	Status epilepticus	
Focal seizures				
Focal neurological signs				
Bulging fontanelle		Bulging fontanelle		
Stiff neck	Stiff neck	Stiff neck		
		Swelling of body part(s)		
		Protection of body part(s)		

Table 3: Adherence of existing fever management apps to the Smitt- Thompson protocol concerning fever in children < and > 3 months of age.

Smitt- Thompson protocol	Kinsa	FeverFriend	FeverApp*	Points of comparison
FEVER				
No fever (T ≤ 38°C) Under 3 months	**No Fever (T < 38°C) Under 3 months**	**No Fever (T ≤ 38°C) Under 3 months**	**No Fever (T ≤ 38°C) Under 4 months**	**Fever under 3 months**: Both the Feverfriend and Kinsa app identified the symptom as high risk, thereby matching the guideline. The FeverApp app underestimated the symptom compared to the guideline, by classifying it as an intermediate risk of serious illness. The FeverApp app additionally mentioned both 3 months and 4 months as a cut off in age. **High Fever between 3 to 6 months**: None of the apps matched the guideline perfectly. Both the Feverfriend and Kinsa app identified fever (T ≥ 38°C) between 3 and 6 months as an intermediate risk of serious illness, thereby overestimating the symptom compared to the guideline. The FeverFriend app additionally identified a high fever (T ≥ 39°C) within this age group as a high risk symptom.The FeverApp app did not mention this symptom. **Very high fever**: The guideline identified a cut off of 40.6 °C body termperature. Both the FeverFriend and Kinsa app specified a different cut off, thereby not matching the guideline. The FeverApp app did not mention this symptom. **Fever duration**: The FeverFriend and the FeverApp app both identified a 'fever duration > 3 days' as an intermediate risk symptom, thereby matching the guideline. However, the FeverFriend app mentioned another cut off in time of 5 days, classifying a 'fever duration > 5 days' as a high risk symptom and thereby not matching the guideline in its enterity. The Kinsa app did not mention this symptom. **Type of measurement**: Every app recommended fever measurement rectally, thereby matching the guideline. However, the guideline specifies the age from wich oral en tympanic fever measurements are recommended. Due to absent age specification by the apps, no additional match to the guideline could be concluded. **Rigors**: The Kinsa app did not specify a time lapse within the presence of chills and identified the 'presence of chills' as a low risk symptom, thereby underestimating the symptom compared to the guideline.The FeverFriend and FeverApp app did not mention the symptom.
Fever (T ≤ 39°C) Between 3-6 months	No Fever (T < 38°C) Between 3-6 months	No Fever (T ≤ 38°C) Between 3-6 months		
Fever (T ≤ 40.6°C) Above 6 months	No Fever (T < 40°C) Above 6 months	No Fever (T ≤ 40°C) Above 6 months	Fever (T > 38°C) Above 4 months	
Rectal - type of thermometer unspecified Oral - type of thermometer unspecified (not under 3 months) Infra- red temporal artery thermometer Inra- red tympanic thermometer (not under 6 months)	**Rectal- type of thermometer unspecified *** Infra- red tympanic thermometer * - age unspecified	**Rectal - digital or chemical thermometer *** Oral - digital or chemical thermometer - age unspecified * Infra- red tympanic thermometer - age unspecified	**Rectal - type of thermometer unspecified *** Infra- red tympanic thermometer - age unspecified	
Fever < 3 days		**Fever < 3 days**	**Fever < 3 days**	
No shaking chills	Chills			
High Fever (T ≥ 39°C) 3-6 months	Fever (T ≥ 38°C) Between 3-6 months	Fever (T > 38°C) Between 3-6 months	Fever (T > 38°C) Under 4 months	
	High Fever (T > 40°C) Above 6 months			
Fever > 3 days		**Fever 3-5 days**	**Fever > 3 days**	
Fever (T ≤ 38°C) Under 3 months	**Fever (T ≥ 38°C) Under 3 months**	**Fever (T > 38°C) Under 3 months**		
Very high Fever (T ≥ 40.6°C)	High Fever (T ≥ 40°C)	High Fever (T > 39°C) Between 3-6 months		
		Very high Fever (T > 41°C)		
		Fever > 5 days		
Shaking chills > 30 minutes				
SKIN CONDITION AND COLOR				
Normal color of skin, lips and tongue	**Normal color of skin and lips**	**Normal color of skin**		**Color of skin**: Both the FeverFriend and Kinsa app identified a bluish skin as a high risk symptom, thereby matching the guideline. The FeverApp app did not include skin color in its triage system. **Rash**: The Kinsa app identified the presence of 'purple or blood- colored spots' as a high risk symptom, thereby matching the guideline. The FeverFriend app and the FeverApp app did not specify a 'non-blanching rash'. Due to absent content specification by the apps, no match to the guideline could be concluded.
No rash	**No rash**	**No rash**	**No rash**	
	Rash Above 2 years		Blanching rash Present for < 3 days	
		Pallor		
	Rash Under 2 years	Blanching rash	Blanching rash Present for > 3 days	
	Hives			
Bluish lips or face	**Bluish skin or lips**	**Grey, bluish, purplish skin**		
Widespread rash with purple or blood- colored spots or dots	**New purple or blood- colored spots/dots**	Non- blanching rash	Non- blanching rash	
	Blisters, sores or pus			
	Rash developing after taking new medication			
	Sudden and severe skin peeling			
RESPIRATORY				
No signs of dyspnea	**No signs of dyspnea**	**No signs of dyspnea**	**No signs of dyspnea**	**Signs of dyspnea**: The Kinsa and FeverApp app both defined shortness of breath by using a series of clinical observations. The Kinsa app matched some clinical observations compared to the guideline by classifying 'grunting' and being 'unable to finish a sentence' as a high risk symptom. Both the FeverFriend and the Kinsa app identified difficult breathing as a high risk symptom, thereby matching the guideline. However, the FeverFriend app defined shortness of breath trough a scale, thereby making comparison to the guideline difficult. The '> 4/5' was concluded as similar to 'struggling for each breath', therefore a partial match to the guideline was concluded.The scale is specified below. The FeverApp app matched no clinical observations to the guideline. **Excessive spitting, drooling**: The Kinsa app identified the symptom as a high risk symptom, thereby matching the guideline. The FeverFriend and FeverApp app did not mention this symptom.
No spitting of saliva	**No spitting of saliva or fluids**			
		Difficult or laboured breathing ≤ 3/5 *	Enforced or constrained breathing	
		Slight wheezing		
	Barking cough			
	Nasal flaring			
Difficult breathing, struggling for each breath	**Difficult breathing**	**Difficult or laboured breathing > 4/5 ***		
Unable to speak or cry	**Unable to finish a sentence**			
Grunting	**Grunting**			
	Retractions			
	Wheezing, stridor	Strong wheezing, stridor		
Unable to swallow fluid or excessive spitting	**Unable to swallow fluid or excessive spitting**			
CIRCULATION AND HYDRATION				
No signs of dehydration	**No signs of dehydration**	**No signs of dehydration**	**No signs of dehydration**	**Poor feeding in infants**: The FeverFriend app differentiated poor and severly poor feeding by cut off in time. However, since no specification for infants was made by the app, as stated within the guideline, the symptom did not match the guideline perfectly. The FeverApp app classified the symptom 'last time drinking > 8 hours in infants' as an intermediate risk symptom, thereby underestimating the symptom compared to the guideline. The Kinsa app equally did not specify an age group and identified 'last time drinking > 8 hours', thereby not matching the guideline perfectly. D**ry mucous membrane**: The Kinsa app identified the symptom as a high risk symptom, thereby matching the guideline.The FeverFriend app differentiated a 'dry tongue with decreased tears' from 'absence of tears' by classifying it as an intermediate and high risk symptom, respectively. Since the guideline mentions 'absence of tears' as part of 'dry mucous membrane', classifying 'no tears when crying' as a high risk symptom matched the guideline. However since a dry tongue was identified as an intermediate risk symptom and the guideline mentions 'dry mouth' as part of 'dry mucous membrane', the FeverFriend app only matched the guideline partially. The FeverApp app identified the symptom as an intermediate risk symptom, thereby not matching the guideline. **Reduced urine output**: The FeverFriend app differentiated a reduced urine output from a severely reduced urine output by classifying it as an intermediate risk symptom and a high risk symptom, respectively. The guideline does not specify the symptom in time, therefore 'last urination > 12 hours' was considered a match to the guideline. The Kinsa app identified the symptom as a high risk symptom, thereby matching the guideline. The FeverApp app identified the symptom as an intermediate risk symptom, thereby underestimating it compared to the guideline.
		Drinking less than normal Last time eating > 12 hours	Last time drinking > 8 hours in infants *	
		Dry tongue, decreased tears when crying	Dry mucous membrane *	
		Reduced urine output (Last urination > 6-12 hours)	Reduced urine output (Not specified)	
Poor feeding in infants	Last time drinking > 8 hours	Last time drinking > 12 hours Last time eating > 24 hours		
Dry mucous membrane *	**Dry mucous membrane ***	**No tears when crying ***		
Reduced urine output	**Reduced urine output (Last urination > 8 hours)**	Severely reduced urine output (Last urination > 12 hours)		
GENERAL CONDITION AND ACTIVITY				
No altered mental status or decreased activity	**Normal awareness**	**Normal awareness**	**No lethargy**	**Altered mental status**: An altered mental status was described by the guideline as a confused state with impaired alertness. Both the FeverFriend and the Kinsa app mentioned clinical observations indicating an altered mental status. These symptoms were classified as high risk symptoms, thereby matching the guideline. The FeverApp app defined 'acting differently' and 'apathy' as high risk symptoms. However, since the lack of specificity, comparison to the guideline remained difficult and no match could be concluded. The FeverFriend app defined 'odd reaction > 5 hours' as an intermediate risk symptom. No intermediate risk symptoms were specified by the guideline. **Awareness**: A limited conciousness or absent awareness was classified as a high risk symptom by all apps, thereby matching the guideline. All apps additionally identified an increased tendency to fall asleep as an intermediate risk symptom. No intermediate risk symptoms were specified by the guideline. **Irritability**: All the apps identified an inconsolable, weak or high pitched cry or screaming (as a sign of irritability) as a high risk symptom, thereby matching the guideline. The Kinsa and the Feverapp app both additionally identified 'touch sensitivity' as a high risk symptom, thereby matching the guideline in its entirety. **Usage of extremities**: Avoidance of using an extremity was not mentioned by any of the apps. Howerever, the FeverFriend app did identify 'protection of body part' as a high risk symptom. Since the guideline specified an extremity, 'protection of body part' was considered too broad to match the guideline perfectly. **Seizure**: The FeverFriend and Kinsa app both identified a feverish seizure as a high risk symptom, thereby matching the guideline. The FeverApp app specified only the first seizure as a high risk symptom, thereby not matching the guideline perfectly. **Bulging fontanelle**: The Kinsa app identified the symptom as a high risk symptom, thereby matching the guideline. The FeverFriend app underestimated the symptom compared to the guideline, by classifying it as an intermediate risk symptom. The FeverApp app did not mention this symptom. **Stiff neck**: The FeverFriend and the Kinsa app both identified the symptom as a high risk symptom, thereby matching the guideline. The FeverApp app underestimated the symptom compared to the guideline, by classifying it as an intermediate risk symptom. **Painfull urination**: The FeverFriend app identified the symptom as an intermediate risk symptom, thereby underestimating it compared to the guideline. The Kinsa and FeverApp app did not mention this symptom.
No signs or irritability or pain	**No signs of irritability or pain**	**No signs of irritability or pain; not crying or strong crying**	**No signs of irritability or pain**	
Normal usage of all extremities		No swelling or pain of a body part	No swelling or pain of the joints	
No seizure	**No seizure**	**No seizure**	No seizure	
No bulging fontanelle	**No bulging fontanelle**	**No bulging fontanelle**		
No stiff neck	**No stiff neck**	**No stiff neck**	**No stiff neck**	
No painful urination		**No painful urination**		
		Odd reactions > 5 hours		
	Fatigue	Sleepy	Lethargy	
			Swelling of a joint	
			Pain in the limb ≥ 3 days	
		Bulging fontanelle		
			Stiff neck	
		Painful urination		
Altered mental status; awake but not alert, not focused, confused or slow to respond	**Not making eye contact, acts 'out of it' or confused**	**No reaction to social cues**	Acting differently, apathy	
Unresponsive or difficult to waken	**Inability to wake up, unresponsive**	**No awareness**	**Clouded consciousness**	
Limp, weak or not moving	**Limp, not moving**			
Inconsolable crying, irritable	**Inconsolable crying, shrill screaming**	**Weak, high- pitched or continuous cry**	**Shrill screaming**	
Cries every time if touched, moved or held	**Touch sensitivity, crying when touched**		**Touch sensitivity**	
Seizure	**Seizure**	**Seizure**	First seizure	
Bulging fontanelle	**Bulging fontanelle**			
Stiff neck	**Stiff neck**	**Stiff neck**		
		Swelling of body part(s)		
Won't move arm or leg normally		Protection of body part(s)		
Burning feeling or pain with urination				

Statistical Analysis

The MARS scores were subjected to descriptive analysis. Interrater reliability (IRR) of the MARS subscales and total score was additionally determined by calculating the intraclass correlation coefficient (ICC). This statistic allows assessment of rater agreement and is a number found to have a value between 0 and 1. Zero indicating no reliability among raters and one indicating perfect reliability among raters. ICC estimates and their 95% confident intervals were calculated using SPSS statistical package version 28, based on a mean- rating (k=5), absolute- agreement, 2- way mixed- effects model (14).

Quality assessment: adherence to EBM guidelines

Secondly, adherence to existing fever management recommendations was appraised through comparison against the National Institute of Care and Excellence (NICE) guideline on fever in children under five years of age (15). The Schmitt-Thompson triage protocol for fever in children (under 3 months to 3 months to 6 years of age) was also used for evaluation (16). Our goal was to gain a better understanding of the decision algorithm being used in these mobile applications promoting fever management, as well as to review whether the propositions made are in line with existing prespecified evidence and recommendations. Therefore the mobile applications with a main focus on paediatric fever management were each manually run using 5 profiles with 5 different ages, i.e. 1 month, 3 months, 6 months, 1 year and 5 years. Within each age group, the decision support algorithm was mapped by exploration (given that each app contains a decision support system as stated in the specific mobile health inclusion criteria).

By mapping out these answer options, a set of symptoms was identified validating an alteration in advice. These disease symptoms were stratified into a traffic light system. For example, when the app adjusted its guidance to an advice expressing an urgent need for consultation, the present symptom upon which this adjustment was based was qualified within the colour red indicating a high risk of serious illness. When the app adjusted its guidance to an advice expressing a non-urgent need for consultation the present symptom upon which this adjustment was based, was qualified within the colour yellow indicating an intermediate risk of serious illness. When the app's advice was 'home care', expressing an absent need for consultation, the present symptom was qualified within the colour green indicating a low risk of serious illness. The NICE guideline itself includes a traffic light system chart for febrile illness in children under the age of five for identifying the likelihood of serious illness. The Schmitt-Thompson protocol does not use such a system. Therefore this protocol was also converted into a traffic light system chart by stratification of disease symptoms, allowing comparison of features.

Results

Search Results

Out of the 878 apps retrieved from initial searches in the Apple App Store and the Google Play Store, 6 applications matched our prespecified selection criteria. From these 6 apps, 3 apps were additionally excluded given the lack of paediatric fever focus. The results of these applications will therefore not be discussed within this section. The include apps are the Kinsa app, the FeverFriend app and the Feverapp (17, 18, 19).

Evaluation against the NICE guideline

All three applications were evaluated against the NICE guideline using stratification of disease symptoms into five categories, i.e. fever, skin condition and colour, respiration, circulation and hydration, general condition and activity. Within the NICE traffic light chart, 51 disease symptoms were identified. Each symptom was screened for within the apps' algorithm. Presence of the symptom and stratification within the accurate level of risk according to the guideline, was identified as a match between app and guideline. Absence of the symptom or stratification within an inaccurate level of risk was identified as a no match between app and guideline.

The FeverFriend app showed the highest adherence to the guideline with a total of 26 matches (51%), closely followed by the Kinsa app with a total of 24 matches (47%) and the FeverApp app with a total of 20 matches (39%), respectively. A detailed summary of the results can be found in Table 2.

Evaluation against the Schmitt-Thompson protocol

All three applications were equally evaluated against the Schmitt-Thompson protocol, using stratification of disease symptoms into the five categories. Within the Schmitt-Thompson traffic light chart, 42 disease symptoms were identified. The Kinsa app showed highest adherence to the protocol with a total of 28 matches (67%), followed by the FeverFriend app with a total of 21 matches (50%) and the FeverApp app with a total of 12 matches (29%), respectively. A detailed summary of the results can be found in Table 3.

MARS App Quality Scores

Looking at the first section and including all three applications, the average MARS overall quality score was 4.3 out of 5 with a standard deviation (SD) of 0.2 and a range of 4.0-4.4. Functionality was found to be the highest scoring domain (mean 4.5 [SD 0.4]; range 4.2-4.9), followed by aesthetics (mean 4.4 [SD 0.5]; range 3.9-4.8), engagement (mean 4.1 [SD 0.4]; range 3.7-4.4) and information (mean 4.0 [SD 0.4]; range 3.5-4.2) respectively. Subjective app quality, as a measure of rater satisfaction, was the lowest scoring MARS section (mean 3.5 [SD 0.8]; range 2.6-4.0). Likelihood for behavioural impact, being the third and final section, had an acceptable average score (mean 3.8 [SD 0.5]; range 3.3-4.1). With regard to the total quality rating within the

individual apps, the Kinsa app and the FeverApp app were equally the highest scoring mobile applications

(4.4 out of 5). Within the app specific subjective quality rating, we find similar scores when looking at the Kinsa app and the FeverFriend app (4.0 and 3.9 out of 5 respectively). The FeverApp however scores markedly lower in this section (2.6 out of 5). Independent ratings on the overall MARS total score and the overall subjective quality score of

Table 4: Summary of the Mobile App Rating Scale scores across the 3 reviewed apps.

MARS Scores and Intraclass correlation coefficient					
MARS domain	**Kinsa**	**FeverApp**	**FeverFriend**	**Mean [SD] 95% CI)**	**ICC (95% CI)**
Engagement	4.4	4.2	3.7	4.1 [0.4] (3.2 - 5.0)	0.90 (0.47 - 1.00)
Functionality	4.5	4.9	4.2	4.5 [0.4] (3.7 - 5.4)	0.84 (0.25 - 1.00)
Aesthetics	4.4	4.8	3.9	4.4 [0.5] (3.2 - 5.5)	0.89 (0.46 - 1.00)
Information	4.2	3.5	4.2	4.0 [0.4] (3.0 - 5.0)	0.95 (0.68 - 1.00)
Total MARS Quality	4.4	4.4	4.0	4.3 [0.2] (3.7 - 4.8)	0.82 (0.17 - 1.00)
Subjective Quality	4.0	2.6	3.9	3.5 [0.8] (1.6 - 5.4)	0.95 (0.71 - 1.00)
Likelihood of Behavioral Impact	4.1	3.3	4.1	3.8 [0.5] (2.7 - 5.0)	0.95 (0.74 - 1.00)

Abbreviations:
MARS = Mobile Application Rating Scale; SD = standard deviation; ICC = Intraclass correlation coefficient.

the three applications demonstrated an appropriate level of interrater reliability (ICC = 0.82, 95% CI 0.17-1.00 and ICC = 0.95, 95% CI 0.71-1.00 respectively) (17). A detailed summary of the quality assessment scores and ICC of the included apps is presented in Table 4.

Discussion

To our knowledge, our study is the first to evaluate the performance and accuracy of mobile self-assessment applications assisting parents in the assessment of fever in their children. Our research therefore provides insight into whether a mobile application with parental decision support system has the potential to reduce pressure on primary and secondary care clinics in a safe and patient-friendly way.

To date, several studies have investigated the usefulness of mobile applications in different fields of healthcare. Self-assessment tools, based on computerized clinical algorithms have been described in the literature for primary care for children and adults through the use of symptom checker applications (8). Semigran et al. evaluated the triage accuracy of 15 symptom checker tools. In 57% of cases an 'appropriate level of care' was found (20). However, the performance of the mobile application varied depending on clinical severity. Patient evaluations in emergency care showed a markedly higher percentage of correct triage advice (80%) than those for which self-care was used (33%) (20). Verzantvoort et al. assessed a self-triage app for several symptoms in the context of acute primary care. An accurate level of care was advised in 81% of cases (8). Our study identified remarkably lower percentages. On average the applications advised an appropriate level of care in 46% and 48% of cases, respectively, compared with the NICE guideline and the Schmitt-Thompson protocol. Self-assessment tools as described in the studies mentioned above, have been promoted as a means of reducing unnecessary office visits. However, analysis of these tools in the past has identified a risk-adverse tendency. On one hand over-triaging may improve patient safety since it lowers the chances of missing a red flag symptom. On the other hand overly cautious triaging by the mobile applications might encourage consultation and cause unnecessary care seeking. In our study, no tendency towards risk adverseness could be identified within the FeverFriend App or the FeverApp app. The Kinsa app however, did show an over-triaging propensity.

Fever management advice was compared to two sets of guidelines. The NICE guideline concerning fever management under the age of 5 on one hand and the Schmitt-Thompson protocol concerning fever under and above the age of 3 months on the other. The National Institute for Health and Care Excellence is an executive non- departmental public body in England known to publish updated, EBM recommendations guiding health promotion in a (cost-) effective and safe manner (15). Schmitt-Thompson Clinical Content is the leading source of telephone triage guidelines in North America, providing high quality protocols offering practical evidence-based decision support (16). In our study 3 mobile applications were assessed. The FeverFriend App was developed under direction of the University of Pecs in Hungary. The FeverApp was similarly developed under direction of the University of Witten in Germany, in cooperation with the Professional Association of Paediatricians (BVKJ) and the German Society for Paediatric and Adolescent Medicine (DGKJ). The Kinsa App was created by Kinsa Inc., a health technology company headquartered in the United States of America. Both European and American applications were thus included within this study. Identical selection of a European and American guideline limited the bias in results that arises from comparing an American app with a European guideline or vice versa.

Following the Cicchetti guidelines for interpretation of ICC interrater agreement measures, we identified an excellent level of IRR on all MARS domains (21). However, since all calculated limits of the 95% confidence intervals reach below 0.75, the ICC should not be regarded as truly excellent. Based on the ICC results for information, subjective app quality and likelihood of behavioural impact, we can conclude the IRR to be good to excellent. This is because the true ICC value supposes to land on any point within the ranges identified by the 95% CI. For the engagement and aesthetics domain we conclude the IRR to be fair to excellent. For the functionality domain and the total MARS quality score, we conclude the IRR to be appropriate (14).

There are several limitation of the current study. First, despite thorough search of earlier specified digital distribution platforms, we cannot be certain that all currently available mobile applications with a parental decision support system handling fever in children were identified and assessed within this study. Second, only one out of the 3 applications (the FeverFriend app) identified 3 levels of risk as shown in table 2 and 3. The Kinsa app identified 5 levels of risk and the FeverApp app generally acknowledged only 2 levels of risk ('do not call a doctor' or 'call a doctor'), with exception of few alarming symptoms ('call a doctor now'). In the process of implementation only the advices with clearly urgent implication, for example 'call a doctor now', were triaged red. This process of stratification might have played a role in the over- and under- triaging tendency identified within the Kinsa and FeverApp app respectively. Third, we did not measure the user's intention to follow the advice given by the app. Therefore, no insight in the efficiency of gatekeeping tools and the effect it has on healthcare seeking behaviour in real life was obtained.

Future app design in the field of medical decision making should ensure that established, evidence-based guidelines are incorporated upfront, that reliable and transparent algorithm design is used (e.g. providing the decision tree that is used as metadata), ensure regular updates and reviews in case guidelines change, while focusing on quality assurance and user friendly design in the interface of the app.

Conclusion

E-health is expected to get a more prominent place within healthcare. Given the low operational cost, self-triage- and management mobile applications could lower the pressure on the healthcare system by empowering parents to self-manage in a safe and cost- effective manner (8). However, there are some potential negative aspects such as changing the waiting room prevalence and pretest probability due to self-triage, data privacy concerns, inequity in access to these apps as well as legal and ethical concerns.

Moreover the limited availability of evidence based parental decision support applications for fever in young children remains a weakness. In this study we identified the Kinsa app as the most evidence based mobile application at present.

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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Mast Cell Activation Syndrome in Children: a Nuanced Approach to Diagnosis and Patient Care

A Narrative Review Illustrated by Two Case Reports

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Keywords

Mast cell activation syndrome ; mast cell activation disorder ; tryptase.

Abstract

Mast cell activation syndrome (MCAS) covers a range of conditions resulting from recurrent mast cell degranulation, sometimes manifesting as anaphylaxis. It is defined by three criteria: a clinical presentation of mast cell activation (clinical criterion), an increase in tryptase levels (biological criterion), and a favourable response to treatment (treatment criterion). A new classification has been developed that includes mast cell activation disorders (MCAD) that do not strictly meet the above criteria (in particular the biological criterion). This leads to an increasing number of patients being detected, some of whom may however benefit from MCAS treatment. MCAS can be divided into primary (clonal), secondary and idiopathic forms. There are also forms that combine MCAS with mastocytosis, hereditary alpha-tryptasemia and/or allergy. This diagnosis of exclusion needs to be assessed by a specialised multidisciplinary team, to avoid over- and under-diagnosis. Moreover, patients often experience a prolonged medical journey, requiring management of the significant psychosocial and financial repercussions for the child and his family.

Introduction

Mast cells are effectors of the innate immune system, whose granules contain numerous vasoactive and inflammatory mediators such as tryptase, prostaglandins and histamine. They are widely and abundantly spread in the human body, particularly in connective and mucosal tissues. Mast cell degranulation results in multisystemic symptoms of variable intensity and may result from both immunological and non-immunological triggers (1). Mast cells are involved in many pathologies, including allergy (ranging from acute urticaria to anaphylaxis), chronic urticaria, mastocytosis, hereditary alpha-tryptasemia (HαT), and mast cell activation syndrome (MCAS) (which is included in the mast cell activation disorders that are discussed within this article).

MCAS encompasses a heterogeneous group of clinical presentations, resulting from the release of mast cell mediators during mast cell activation. MCAS can be evoked in cases of systemic, recurrent, and severe symptoms of mast cell degranulation (sometimes manifesting as anaphylaxis), after exclusion of the various differential diagnoses (2).

To date, the literature defines mast cell activation based on the combination of clinical, biological and response criteria. However, these criteria are rarely fulfilled in paediatric clinical practice. A broader classification of mast cell activation disorders (MCAD) is emerging, yet their management remains a matter of controversy. In this article, we present two cases of suspected paediatric MCAS and their multidisciplinary management (1,2).

Case description

Case 1: A 3-year-old boy was referred to the paediatric allergology department from the emergency department for acute angioedema.

His medical history recorded a resolved non-IgE-mediated cow's milk protein allergy, controlled atopic dermatitis, broccoli and spinach intolerance without allergic sensitisation, and gastroesophageal reflux. Family history revealed occasional episodes of skin oedema, urticaria and joint pain in his father.

The boy is presented to the emergency department with localised pruritus on one thigh and general discomfort, after eating a large amount of various industrial sweets on Halloween. In the morning, he developed multiple oedemas (labial, palpebral, perineal, left hand), followed by coughing and sneezing. The symptoms were relieved by the administration of antihistamines.

At the allergology visit, he was advised to perform a measurement of baseline tryptase and of the tryptase elevation in the event of a new episode consistent with mast cell degranulation. The absence of C1-inhibitor deficiency ruled out hereditary angioedema. During the following month, the patient presented with several episodes of urticaria, and angioedema (face-perineum-hand) associated with abdominal symptoms (pain, and sometimes vomiting or diarrhoea). These events did not seem to be related to specific foods. However, two reactions occurred after taking ibuprofen, which had previously been tolerated.

A thorough anamnesis revealed punctual episodes of joint pain, irritability, sleep disturbances and rare episodes of constipation. The administration of antihistamines provided temporary relief of these symptoms. The association of these signs suggested a mast cell activation disorder. During one of the exacerbations, tryptase was measured at 6.4 ng/ml; however, this value is probably underestimated, as the sample was obtained 6 hours after the onset of symptoms. Baseline tryptase was measured at 2.7 ng/ml. The increase in the symptomatic phase is thus higher than 120% of baseline tryptase +2 ng/ml, which fulfils the MCAS biological criterion. Management was completed by the assessment of several specialists, in order to exclude other diseases. The dermatologist excluded cutaneous mastocytosis, and systemic mastocytosis criteria were not met (including genetic testing for *KIT* mutation). The gastropaediatrician did not report any digestive pathology, and an ENT specialist was consulted for persistent rhinitis. Following this exhaustive multidisciplinary assessment, probable MCAS was suspected and treatment with H1-antihistamines was initiated. The patient showed a favourable evolution within one month.

Our patient thus met the three diagnostic criteria for MCAS, and the diagnosis of idiopathic MCAS was established (in the absence of mast cell clonal disease or underlying pathology explaining the presentation). In addition to medical follow-up, the family received support from the team's dieticians and psychologists.

Case 2: A 3-year-old girl was referred to a combined paediatric gastroenterologist and allergology consultation for chronic abdominal pain.

Her past medical history was unremarkable. Family history revealed an allergy to raw egg white in her mother.

She had suffered from severe digestive discomfort since birth. Her symptoms of abdominal pain and alternating diarrhoea and constipation were followed by a paediatric gastroenterologist, but no digestive pathology was found. The implication of many foods has been suspected, but no allergy hs been demonstrated.

On presentation, the association of these symptoms with skin pruritus, transient perioral eruptions and leg pain raised the suspicion of MCAS. Biological assessment showed a normal baseline tryptase of 4.2 ng/ml. No tryptase was measured in the symptomatic phase, given the absence of clear acute reactions. Despite this absence of biological criteria, MCAS was suspected and treatment with antihistamines and sodium cromoglicate was initiated. The patient and her family also met with the paediatric pain team, as well as a psychologist and a dietician.

The treatment resulted in a rapid and spectacular regression of symptoms, thus fulfilling the response criterion at the follow-up visit 3 months later. The diagnosis is therefore unspecified MCAD, as the biological criterion was missing, that nevertheless showed a favourable response to MCAS treatment.

Discussion

Diagnostic criteria

As illustrated in the above clinical cases, no symptom is specific for mast cell degranulation. MCAS remains a diagnosis of exclusion and consists of the association of a clinical criterion (multisystem clinical signs of mast cell degranulation), a biological criterion (increased tryptase during a reaction) and finally a response criterion (response of symptoms to treatment) (1). Table 1 summarises these criteria.

Importantly, some patients show persistently elevated tryptase levels. Elevation of baseline serum tryptase above >8 ng/ml may suggest other pathologies such as hereditary α-tryptasemia, mastocytosis or other myeloid pathologies (1,7). HαT is autosomal dominant genetic polymorphism and is due to an increased number of *TPSAB1* copies, coding for alpha and beta tryptase. This polymorphism is present in 5-6% of the general population and leads to an elevated basal tryptase level. Most patients remain asymptomatic while a few present with symptoms of mast cell activation (7,8). Mastocytosis corresponds to a clonal expansion of mast cells and results in different symptoms depending on its location and systemic character (7).

Classification

Once diagnosis of MCAS is made, further classification is needed. MCAS are currently classified in primary (including mastocytosis and monoclonal mast cell activation syndrome), secondary (due to autoimmune, allergic or tumoral pathologies) or idiopathic forms (Table 2) (1). Recent articles propose to expand this classification by adding combined forms (associating primary and secondary MCAS) and MCAS + HαT forms (1,2). These combined forms are at higher risk of potentially severe reactions; particularly in patients combining systemic mastocytosis with HαT and IgE-mediated allergy to Hymenoptera venoms, who may experience very severe anaphylaxis (1,6).

Table 1 : MCAS diagnostic criteria.

1. Clinical criterion	= signs of recurrent mast cell degranulation Involvement of at least two organs, not assignable to another pathology (3). - Cutaneous system (involved in 100% of cases): urticaria (62.8%), angioedema (48.8%), pruritus (44.2%), flushing (58.1%). - Digestive system (93%): abdominal pain (83.7%), nausea/vomiting (39.5%), diarrhoea (65.1%), gastroesophageal reflux disease (25.6%), multiple food reactions. - ENT/respiratory system: rhinorrhoea, nasal pruritus, laryngeal oedema, wheezing, conjunctival injection. - Cardiovascular system: tachycardia, hypotension, syncope, incontinence. - Neurological system: sleep disorders (48.8%), asthenia (30.2%), headache, difficulty concentrating, agitation, anxiety/sad mood. Massive degranulation can lead to systemic symptoms of anaphylaxis. Note that the presence of the neurological system in the MCAS criteria is debated. It is more likely to be an accompanying symptom, similar to many other aspecific and chronic symptoms (e.g. osteoarticular pain, pollakiuria, recurrent fever, dysmenorrhea, etc.) which many patients report, but are not included in the diagnostic criteria stricto sensu (4).
2. Biological criterion	= increase of mast cell-derived mediators in blood (tryptase) or urine (N-methyl histamine, methylimidazole acetic acid (MIMA), prostaglandin D2, leukotrienes C4) during the symptomatic reaction (1,4,5). The validated standard test is the temporary elevation during symptoms of serum tryptase ≥ 2ng/ml + 20% above the individual's baseline serum tryptase (BST) (1,6). Tryptase should be measured between 30 min and 2 hours after the onset of symptoms. The patient's baseline tryptase can be measured from 24 hours post-reaction (6).
3. Response criterion	= response of symptoms to treatment targeting mast cell activation, mast cell mediator activation, production, or effects (antihistamines, anti-leukotrienes, sodium cromoglicate).

Table 2 : MCAS classification.

Primary MCAS **(=clonal MCAS)** *ICD-10-CM* code: D89.42	Mast cells are clonal, increased in number and overly reactive to triggers. Clonal MCAS includes mastocytosis, for which the KIT D816V mutation is part of the diagnostic criteria. This genetic mutation results in mast cell expansion which is independent of its growth factor. Other patients present only one or two of the minor criteria of mastocytosis and are classified as Monoclonal Mast Cell Activation Syndrome (MMAS) (2,7,9).
Secondary MCAS *ICD-10-CM* code: D89.43	Due to allergic, inflammatory, tumoral, autoimmune or infectious pathologies.
Idiopathic MCAS *ICD-10-CM c*ode: D89.42	No aetiology is identified. This is the most common MCAS variant, typically manifesting as idiopathic anaphylaxis.
Combined MCAS *MCAS ICD-10-CM* code: D89.40 *HαT ICD-10-CM* code: D89.44 Various possible codes depending on allergy or mastocytosis subtype	MCAS criteria + at least two associations among the following conditions: mastocytosis, allergy/atopy, genetic predisposition (e.g. HαT).
MCAS + HαT	MCAS criteria are met and HαT is identified, but there is no associated mastocytosis or underlying pathology.

Table 3 : Mast cell activation disorders.

Probable MCAS	Mast cells are clonal, increased in number and overly reactive to triggers. Clonal MCAS includes mastocytosis, for which the KIT D816V mutation is part of the diagnostic criteria. This genetic mutation results in mast cell expansion which is independent of its growth factor. Other patients present only one or two of the minor criteria of mastocytosis and are classified as Monoclonal Mast Cell Activation Syndrome (MMAS) (2,7,9).
Other MCAD *ICD-10-CM* code: D89.49	Due to allergic, inflammatory, tumoral, autoimmune or infectious pathologies.
Unspecified MCAD **(= MCA not further specified » = MCA(D)-NOS)** *ICD-10-CM* code: D89.40	No aetiology is identified. This is the most common MCAS variant, typically manifesting as idiopathic anaphylaxis.

Mast cell activation disorders: when MCAS criteria are not met

As shown in our second case, several patients do not meet the MCAS criteria but may respond favourably to MCAS treatment. MCAD can be considered in patients with a clinical presentation of mast cell activation. This term includes MCAS but also less typical presentations (probable MCAS, other MCAD and unspecified MCAD), which are described in table 3 (1,2).

The "International Classification of Diseases -10- Clinical Modification" (ICD-10-CM) has recently created specific codes for these particular conditions. However, their definition and management are not uniform, and will certainly evolve in the future (2).

Expanding the inclusion criteria for MCAS is therefore complex and controversial, as it would significantly increase the number of patients labelled with MCAS (2,4,7).

These types of mast cell disorders that do not meet the strict criteria of MCAS, appear to be predominant in paediatrics. A revision of the paediatric inclusion criteria therefore seems necessary to identify patients who could benefit from a MCAS treatment protocol.

Diagnostic approach

Patients suffering from MCAS generally experience a long medical journey before reaching this diagnosis, which can have a significant psychosocial and financial impact on the child and its family.

Multidisciplinary teams specialised in mast cell disorders are not widespread (e.g. CEREMAST ("centre de référence des mastocytoses") in France), but are essential for the optimal and global management of these patients. These teams should ideally include specialised paediatricians (in allergology, gastroenterology, dermatology, rheumatology, haematology, etc.), psychologists, a pain management team, geneticists, dieticians, etc. MCAS is indeed a diagnosis of exclusion, requiring the expertise of several specialties to rule out other differential diagnoses and thus avoid over- and under-diagnosis (4,7).

The medical assessment obviously includes a detailed medical history and a meticulous clinical examination. Additional investigations are then carried out.

First, a basal and reactive serum tryptase assay is performed.

Second, a blood test will be performed, including a complete blood count, liver enzymes, renal function and ionogram, total IgE assay, *KIT* D816V mutation test or HαT (if mastocytosis is suspected or HαT, where an elevated basal tryptase will be seen) and urine metabolite test (if available in the institution's laboratory).

Finally, depending on the clinical findings, specialist referrals and specific additional investigations will be requested (thyroid and celiac disease investigations in the case of a change in the growth curve, allergological evaluation in the case of suspected allergy, gastroenterological evaluation in the case of signs suggestive of chronic inflammatory bowel disease or eosinophilic oesophagitis, dermatological evaluation to detect signs of cutaneous mastocytosis, etc.).

Treatment and evolution

Treatment is based on a combination of several molecules (1,7);

- H1-antihistamines (desloratadine or cetirizine)
- H2-antihistamines (cimetidine or famotidine)
- Anti-leukotrienes (montelukast)
- Sodium cromoglycate (as a second-line treatment, in the event of mainly dietary reactions or difficulty in stabilising symptoms)

However, there is no consensus on the specific practical details. These depend on the experience of specialised centres. H2-antihistamines and sodium cromoglycate are no longer available in Belgium.

Avoidance of triggers is also recommended, and an epinephrine autoinjector pen could be prescribed depending on the profile of each patient (10).

The response to these therapies serves as a diagnostic test (response criterion). After 3 months of treatment, the evolution of symptoms is assessed. Clinical scores exist but are not currently validated. However, they may be helpful to objectify the therapeutic response and thus to adjust the treatment (3).

Conclusion

Mast cell activation syndrome is characterised by multisystemic clinical symptoms, secondary to the effects of mediators released by mast cell degranulation.

The general classification includes three main categories (primary, secondary, and idiopathic MCAS). However, the association with hereditary alpha-tryptasemia, mastocytosis or allergic/atopic pathology needs to be assessed and complicates this classification.

Three criteria are required to confirm the diagnosis of MCAS: a clinical criterion, a biological criterion and a response criterion. However, many patients do not strictly meet these criteria, typically in the paediatric population. Nonetheless, some of these patients respond favourably to MCAS treatment (based on a combination of H1-, H2-antihistamines, anti-leukotrienes and/or sodium cromoglicate). These "incomplete" variants have recently been added to the classification. However, their definition and management are still not standardised.

The complexity and misunderstanding of these pathologies often leads to delayed diagnosis and a significant psychosocial impact on these children and their families,requiring multidisciplinary management in specialised centres.

Conflicts of Interest

The authors have no conflicts of interest to declare in relation to this manuscript.

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Enteroviral Meningitis and the Bacterial Meningitis Score

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Keywords

Enterovirus ; Bacterial meningitis score.

Abstract

Objectives

Enteroviral meningitis is currently the most prevalent type of meningitis in the pediatric population. The correct differentiation of bacterial from viral meningitis remains critical in determining appropriate therapy for the child with cerebrospinal fluid (CSF) pleocytosis. This can be challenging, especially in younger children. The Bacterial Meningitis Score (BMS) is a prediction rule developed by Nigrovic et al. to identify children who are at very low risk of bacterial meningitis, based on one clinical and four biochemical parameters.

Case report and literature review

We report a case of enteroviral meningitis in a two-year-old child and review the literature on the age-related differences in clinical presentation and CSF parameters, the use of the BMS in practice, and its impact.

Conclusions

Normative CSF parameters show wide variability, especially in neonates, indicating the need for age-specific reference values. In children older than two months without signs of invasive bacterial infections and without pre-treatment with antibiotics, BMS has been shown to be reliable and may be useful to assist in clinical decision making.

Introduction

As a result of successful vaccination programs against *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and more recently, after introduction of quadrivalent meningococcal conjugate vaccines against serogroups A, C, W and Y (Nimenrix®, Menveo®) and the monovalent recombinant protein vaccines against serogroup B (Bexsero®, Trumenba®), there has been globally a steady decline in the incidence of bacterial meningitis (1).

Aseptic meningitis (i.e. meningitis with negative cerebrospinal fluid (CSF) bacterial cultures, with both infectious and non-infectious causes) is now the most prevalent type of meningitis, with non-polio enterovirus (NPE) as the leading cause, accounting for more than 75% of viral meningitis cases with an identified pathogen (2,3). Nevertheless, there are still cases of meningitis caused by bacterial pathogens, highlighting the importance of prompt and accurate differentiation from its viral counterpart (2,4).

Assessing a pediatric patient for meningitis can be challenging, because of the wide variability in presenting symptoms and cerebrospinal fluid (CSF) parameters across various age groups (5,6). The current safe approach for patients with CSF pleocytosis is to administer empirical antibiotic therapy until either the reverse transcriptase polymerase chain reaction (RT-PCR) identifies the causal viral pathogen and/or the CSF culture remains negative for > 48 hours (3,7).

Immediate initiation of antibiotic therapy is life-saving in the case of bacterial meningitis, but prolonged use in suspected viral meningitis may be questionable given the potential adverse effects of antibiotics (2,8). Same et al. conducted a retrospective cohort study on the prevalence and characteristics of antibiotic-associated adverse effects in the pediatric hospitalized population (9). Of the 400 antibiotic courses studied, 21% had at least one adverse effect, with the most common adverse effects being hematologic (e.g. leukopenia, neutropenia), gastrointestinal (e.g. diarrhea, nausea) and renal (e.g. acute kidney injury), accounting for 31%, 15%, and 11% of adverse effects, respectively. Furthermore, 15% of adverse effects were caused by an unnecessary course of antibiotics (9).

The issue of starting and continuing empiric antibiotics in the setting of a probable viral meningitis in this setting remains controversial, and has led to the creation of several clinical prediction rules to assess whether one is at high risk for bacterial meningitis while also determining the probability of viral meningitis.

The Bacterial Meningitis Score (BMS) is a validated clinical prediction rule, created by Nigrovic et al., to calculate the risk of bacterial meningitis in patients with CSF pleocytosis, based on five variables: positive CSF Gram stain, CSF absolute neutrophil count ≥ 1000 cells/µL, CSF protein ≥ 80 mg/dL, peripheral blood absolute neutrophil count ≥ 10 000 cells/µL and history of seizure before or at the time of presentation (10). With a zero score, the risk of bacterial meningitis is estimated as very low.

We present a case of enteroviral meningitis in a 2-year-old toddler and will provide a brief review of the literature on clinical presentation and CSF parameters. In addition, we will discuss the use of the Bacterial Meningitis Score in the pediatric population and its applicability in clinical practice.

Methods

A thorough literature search on enteroviral meningitis was performed using the PubMed database. The search terms consisted of various combinations of keywords such as “Meningitis”[Mesh], “Enterovirus”[Mesh], “enteroviral”, “children”, “infants”, “neonates”, “Bacterial Meningitis Score”, “cerebrospinal fluid”, “guidelines” and “consensus”. English language restriction was applied. The results were evaluated on the basis of the title and abstract before the remaining parts of the article were analyzed. Relevant studies referenced in these articles were also included. This search yielded a total of 26 articles.

Case report

A 2-year-old male toddler with no relevant medical history presented to the emergency department with symptoms of vomiting, fever of 39 degrees Celsius and somnolence for 1 day. Because of terminal neck stiffness, lumbar puncture was performed. CSF analysis showed a WBC

count of 43 µL (normal range ≤ 5 WBC/µL), a normal erythrocyte count of < 1000/µL, a total protein concentration of 16 mg/dL (normal range 15-40 mg/dL) and a glucose concentration of 68 mg/dL (serum glucose level was 90 mg/dL (normal)). Gram stain was negative. In the peripheral blood sample, there were 14670 WBC/µL (normal range 6000-17000 WBC/µL), with an absolute neutrophil count of 8024 neutrophils/µL (normal range 1500-8500 WBC/µL), and a CRP of 17 mg/L (normal ≤ 5 mg/L). Ceftriaxone (100 mg/kg/day) was given until RT-PCR of the CSF confirmed the diagnosis of enteroviral meningitis. CSF culture remained sterile. The patient showed a complete recovery under symptomatic therapy and was discharged after 3 days.

Discussion

Age-related differences in clinical presentation and CSF parameters in viral meningitis

Non-polio enterovirus is the most prevalent cause of viral meningitis. Although young age is a known predisposing host factor, it can affect a wide range of age groups, from neonates to adults (6). Especially in the (very) young age group, enteroviral infections can be very serious and sometimes fatal due to overwhelming infection.

Regarding the clinical presentation of meningitis, healthcare professionals must always keep in mind that classic symptoms such as photophobia and nuchal rigidity are more typical in adults and older children. Neonates and infants are more likely to present with one or more non-specific findings on clinical examination, such as fever, irritability, lethargy and a bulging fontanelle. In older children, gastrointestinal or respiratory symptoms such as nausea, vomiting, cough, as well as headache and rash, are more common in association with neck stiffness and a positive Kernig sign (6,11,12). Recognizing these features and promptly performing lumbar puncture with subsequent CSF analysis is crucial for the diagnosis of meningitis and initiation of symptomatic and possible causal therapy.

Biochemically, CSF parameters are undoubtedly of paramount importance in the assessment of a child with clinical suspicion of meningitis. The significant age-related difference in the normative range of CSF analysis parameters needs to be addressed. Wong et al. showed that CSF protein levels tend to decrease rapidly in the course of the first few months of life (a phenomenon attributed to the reduced permeability of the blood-brain barrier), reach a minimum at approximately 6 months of age, and remain steady before gradually increasing toward normal adult levels during adolescence (13). A multicenter, cross-sectional study by Thomson et al. in infants ≤ 60 days of age, showed that especially infants ≤ 28 days of age differed in CSF parameters from infants 29 – 60 days of age: WBC counts (upper limit: 15 WBC/µL versus 9 WBC/µL, p<.001) and protein levels (upper limit: 127 mg/dL versus 99 mg/dL, p<.001) were higher, glucose levels (lower limit: 25 mg/dL versus 27 mg/dL, p<.001) were lower in infants ≤ 28 days of age (14).

These findings implicate that the current one-size-fits-all approach where only one normative range is provided for different age groups is not the most appropriate in the pediatric population. It is important to note that the present evidence is based on studies with rather small study populations. Therefore, further research in larger cohorts is warranted to determine the most appropriate age-specific reference values.

Regarding CSF pleocytosis in younger infants with enteroviral meningitis, Tan et al. observed a wide variability (0-4608 WBC/µL in the age group < 90 days, compared to 0-1290 WBC/µL in the age group 90 days-1 year), with some of the outliers having levels even suggestive for bacterial meningitis (5). On the other hand, some studies report a lower CSF pleocytosis in infants compared to older children (15). Furthermore, up to 60% of infants with enteroviral meningitis may have no CSF pleocytosis, which more common in infants younger than 90 days of age, and it is hypothesized that this is due to their immature immune system, which is unable to mount a robust inflammatory response (5,11).

Bacterial Meningitis Score: its use and application to our case

The Bacterial Meningitis Score (BMS) is a validated clinical decision rule developed by Nigrovic et al., to help identify patients at very low risk for bacterial meningitis among patients with CSF pleocytosis, based on one clinical and four biochemical parameters (Table 1) (10,16,17).

Table 1 : Components of Bacterial Meningitis Score. Applicable in infants above the age of 2 months, clinically not ill-appearing, not pretreated with antibiotics. If none of these variables are present (BMS = 0), patient is classified as low risk for bacterial meningitis..

Components of Bacterial Meningitis Score
Positive cerebrospinal Gram stain (2 points)
Cerebrospinal fluid absolute neutrophil count ≥ 1000 cells/µL (1 point)
Cerebrospinal fluid protein ≥ 80 mg/dL (1 point)
Peripheral blood absolute neutrophil count ≥ 10 000 cells/µL (1 point)
History of seizure before or at time of the presentation (1 point)

The initial article was published in 2002, in the 'post-*Haemophilus influenzae* vaccination era', based on meningitis patients from one institution (10). According to their subsequent study in 2007 (in the 'post-Pneumococcus vaccination era'), based on patients from several institutions, the BMS showed a high accuracy and a sensitivity of 100% (95% CI [96.9%;100%]), a specificity of 63.5% (95% CI [61.4%;65.6%]) and a negative predictive value of 100% (95% [99.8%;100%]), under the exclusion criteria that it should not be applied in children younger than 2 months or who were pretreated with antibiotics (16). The BMS had indeed misclassified 2 patients with bacterial meningitis, aged between 1 and 2 months, as low-risk patients (16).

In the later published meta-analysis of all published validation studies, the BMS still showed a very high sensitivity of 99.3% (95% CI [98.7%;99.7%]) (17,18). Compared to the 2007 publication, the authors formulated and emphasized their recommendations for the use of BMS, stating that it should be used only in non-ill-appearing patients over the age of 2 months without physical examination findings suggestive of invasive bacterial infection (e.g. petechiae, purpura) and without prior antibiotic administration, although further specification of signs suggestive of invasive bacterial infection was not formulated (17).

In our case of the 2-year old-child, the application of the BMS yielded zero points and thus can be classified as very low risk for bacterial meningitis according to the BMS.

Besides the BMS, other clinical prediction rules (CPRs) are available, such as the modified BMS, Bonsu score, modified Bonsu score, Oostenbrink score, Meningitest rule and others (19). Each CPR uses its own combination of clinical predictors to assess the possibility of bacterial meningitis. Furthermore, novel biomarkers such as CSF lactate and serum procalcitonin are being investigated (20).

The number of comparative studies for these CPRs is limited, but an European retrospective multicenter cohort study comparing the performance of BMS and Meningitest demonstrated that although the sensitivity of both CPRs are similar, the specificity was higher in the BMS (52%, 95% CI [42%;62%] vs 36%, 95% CI [27%;46%]) (21).

Wu et al. developed a new CPR for bacterial meningitis in infants aged 29-90 days using three predictors resulting a total score of five points: procalcitonin ≥ 3.80 ng/mL (2 points), CSF glucose ≤ 1.86 mmol/L (2points) and CSF protein ≥ 1269 mg/dL (1point) (22). This new model identified bacterial meningitis with 100% sensitivity (95% CI [46.6%;72.9%]) in the study population, while BMS had a sensitivity of 90.9% (95% CI [78.3%-97.4%]). However, the limitations of this study are the limited study population and the lack of timely measurements of CSF glucose concentration (22).

Table 2: Patients with bacterial meningitis with a BMS of 0 from the meta-analysis of the external validation studies.

		Age (years)	CSF ANC (/µL)	CSF protein (mg/dL)	Peripheral blood ANC (/µL)	History of seizures before or at the time of presentation	Petechiae/ purpura	Identified pathogen
Nigrovic et al. (15)	1	0.2	0	31	8100	No	No	*E.Coli*
	2	0.1	497	65	6600	No	No	*E.Coli*
Dubos et al. (24)	3	0.3	≤13	61	7744	No	No	*N.meningitidis* (type B)
	4	0.7	32	25	3600	No	Yes	*N.meningitidis* (type B)
	5	5.4	≤30	30	9400	No	Yes	*N.meningitidis* (type C)
	6	3.4	60	20	1517	No	No	*N.meningitidis* (type C)
	7	0.1	≤8	46	3270	No	No	*S.pneumoniae*
Tuerlinckx et al. (23)	8	2.5	26	21	7683	No	Yes	*N.meningitidis* (unknown subtype)
	9	15	22	46	7689	No	No	*N.meningitidis* (unknown subtype)

Critical appraisal on the Bacterial Meningitis Score: External validation studies

Although the BMS is a highly sensitive scoring system with a high negative predictive value, it is of course not foolproof. It is intended to assist, not to replace, clinical decision making.

In the patient with CSF pleocytosis, we favor an approach in which clinical evaluation and observation, along with correct interpretation of the available laboratory tests, remain crucial.

First, a thorough clinical evaluation should be performed when examining the child. One should be alert for warning signs such as sick or toxic appearance, severe nuchal rigidity, vomiting, photophobia, etc.. However, neonates with bacterial meningitis can often present with atypical signs, and even beyond the neonatal period, there is no clinical sign of bacterial meningitis that is present in all patients (23).

If there is a suspicion of bacterial meningitis, it is imperative that blood cultures and cerebrospinal fluid (CSF) are obtained as soon as possible (7,24). In some cases, a CT scan of the brain prior to lumbar puncture is warranted to exclude intracranial, space-occupying lesions that may lead to increased intracranial pressure (7)

Based on the results of CSF analysis, the BMS can be calculated for the patient, taking into account the exclusion criteria as listed by Nigrovic et al. and as mentioned above. Their meta-analysis with a total of 5312 patients showed that the combined sensitivity and the negative predictive value were high, 99.3% (95% CI [98.7%;99.7%]) and 99.7% (95% CI [99.3%;99.9%]), respectively, although not 100% anymore as it was initially predicted (17).

In this study, we focus on the 9 cases from the external validation studies where the patient had bacterial meningitis and a BMS of 0 (Table 1). The majority of these patients were younger than one year whereof three were younger than 2 months (Table 2). Of the children older than one year (n=4), two had a petechial rash (in which case the use of BMS is contraindicated), and two others were infected with *N. meningitidis* (one with type C, the other unknown).

The epidemiologic landscape of causative pathogens of bacterial meningitis has undergone a considerable transformation since the introduction of vaccines against common pathogens (1). A study in the Netherlands showed a significant decline in the incidence of *H. influenzae* type b and *N. meningitidis* meningitis after the introduction of their respective vaccines in recent decades. On the other hand, the incidence of both non-typeable *H. influenzae* meningitis and pneumococcal meningitis caused by serotypes not covered by PCV7, PCV10 and PCV13 has increased (1,25).

In the light of the ever-evolving epidemiologic background of meningitis, it seems well-advised to re-evaluate BMS in this 'post-vaccination era', in terms of sensitivity and specificity, inclusion/exclusion criteria and the causative pathogens of false negative cases.

Use of Bacterial Meningitis Score in the clinic

The BMS can assist our clinical evaluation and consequently guide our therapeutic management.

In children with BMS of zero, empirical antibiotic therapy could be safely discontinued if the RT-PCR turns out to be positive for enterovirus, without awaiting the results of the bacterial cultures (26). In case of BMS ≥1 and negative culture, bacterial etiology must be excluded by multiplex PCR. Looking carefully at the characteristics of the misclassified patients in Table 2, one could consider an approach where the decision to treat with empiric antibiotics is individualized.

Conclusion

We presented a case of a two-year-old child with enteroviral meningitis, and discussed the age-related differences in clinical presentation and the need for age-specific normative values for CSF analysis. Furthermore, we reviewed the Bacterial Meningitis Score and its potential use in clinical practice. The BMS is able to estimate the risk of bacterial meningitis with high sensitivity and high negative predictive value in non-ill-appearing children without petechial rash or purpura, who are older than 2 months and not pretreated with antibiotics. Although a BMS of zero can be translated into a very low risk of bacterial meningitis, clinical judgment remains imperative.

Conflict of interest

The authors have no conflict of interest to declare.

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Publieksprijs **€ 86,52**

If you don't recommend MenB vaccination to your patients,

who will?

81% van de ouders beschouwt hun arts als een primaire bron van informatie over vaccinatie voor hun kinderen. (n=800)[2]

BEXSERO
Meningokokken groep B-vaccin
(rDNA, component, geadsorbeerd)

BEXSERO is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B.[1]

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN: Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL:** Bexsero suspensie voor injectie in voorgevulde spuit. Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd), EU/1/12/812/001-EU/1/12/812/002-EU/1/12/812/003-EU/1/12/812/004. 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. colicellen door recombinantDNAtechnologie - [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) - [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de volledige SPK. **FARMACEUTISCHE VORM:** Suspensie voor injectie. Melkwitte vloeibare suspensie. **KLINISCHE GEGEVENS: 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: Zuigelingen van 2 tot en met 5 maanden[a]: Primaire immunisatie:** Drie doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** 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]. - **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** 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]. **• Leeftijd bij eerste dosis: Zuigelingen van 6 tot en met 11 maanden: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis[c]. **• Leeftijd bij eerste dosis: Kinderen van 12 tot en met 23 maanden: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis[c]. **• Leeftijd bij eerste dosis: Kinderen van 2 tot en met 10 jaar: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. **• Leeftijd bij eerste dosis: Adolescenten (11 jaar of ouder) en volwassenen*: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • [a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. - [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. - [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor 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). **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):** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. 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:** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. 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. Huid en onderhuidaandoeningen: Niet bekend: huiduitslag. Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: myalgie, artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise. - Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België:** Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Afdeling Vigilantie - Postbus 97 - 1000 Brussel - Madou - Website: www.eenbijwerkingmelden.be - e-mail: adr@fagg.be. **Luxemburg:** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **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:** 26/04/2023 (v15). **AFLEVERINGSWIJZE:** Op medisch voorschrift.

References: 1. SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

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Exploring the Interferon Signature
Laboratory Elaboration and Clinical Perspectives

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Abstract

Type 1 interferonopathies encompass a group of autoinflammatory diseases in which overactivation of the type I interferon pathway is the keystone. In this article, we describe the elaboration and clinical aspects of the interferon signature (or score) at the level of these rare monogenic diseases, but also in more common rheumatologic conditions, discuss its potential implications for therapeutic options for patients, and open future perspectives of transcriptomic analysis in immunoinflammatory diseases.

Introduction

Type I interferon activity

Interferons (IFNs) are a group of cytokines involved in defence against viral infections of host cells by inhibiting viral replication, but also involved in protection against intracellular bacteria (e.g. mycobacteria for type II IFNs). IFNs are classified into three families: type I (IFNα/β/ε/τ/κ/ω/δ/ζ), type II (IFNγ) and type III (IFNλ) (1-3).

Type I IFNs, IFN-α and IFN-β, are the major cytokines of the host immune response. They are produced by most cell types. On one hand, they can be synthesised by stimulating pattern recognition receptors (PRRs) of the innate immune system, such as Toll-like receptors (TLRs), which recognise danger signals (Pathogen-Associated Molecular Patterns (PAMPs) constitutive of pathogens (e.g. nucleic acids or viral envelope glycoproteins) or Damage-Associated Molecular Patterns (DAMPs) released by damaged cells (e.g. stress signals such as cell death-related self-DNA or damaged proteins)). On the other hand, type I IFNs can be produced by other intracellular signalling pathways, such as the STING pathway or the helicase pathway, which are activated in infected cells (3-5). Once synthesised, these type I IFNs can act by binding specifically to their receptor: the Interferon-alpha/beta receptor (IFNAR1/IFNAR2). This binding activates the JAK/STAT (Janus kinases/signal transducers and activators of transcription) signalling pathway. This leads to the formation of a complex (ISGF3: Interferon-stimulated gene factor 3), which acts as a nuclear transcription factor that can induce the expression of ISGs (Interferons Stimulated Genes). These genes enable the production of antiviral proteins and pro-inflammatory cytokines (Figure 1) (4).

Molecular Mechanisms of Type 1 Interferonopathies

These IFNs therefore exert antiviral and antitumoral activity, via the JAK/STAT pathway, which is essential for the host, but overexpression of type I IFNs can be associated with autoinflammatory and possibly autoimmune processes giving rise to pathologies grouped under the term type 1 (6). Major groups encompass Aicardi-Goutières spectrum syndromes (AGS), familial chilblain lupus and different monogenic lupus, spondyolenchondrodysplasia, STING-associated vasculopathy with onset in infancy (SAVI) and COPA-associated inflammatory syndrome (COPA), proteasome-related autoinflammatory syndromes (PRAAS) (4, 5). These type 1 interferonopathies are rare monogenic genetic diseases characterised by autoinflammatory and autoimmune disorders due to the constitutive activation of the type 1 interferon antiviral axis signalling or a defect in its negative feedback control (5, 7). In the case of AGS and familial chilblain lupus, constitutive activation of signalling is caused by cytosolic accumulation of nucleic acids recognised as PAMPs or DAMPs. This cytosolic accumulation is due to the lack of enzymatic activity of the TREX1 and SAMHD1 proteins. In the case of PRAAS, it is the ubiquitinated proteins, accumulated in the cell due to defective immunoproteasome activity, which are recognised as DAMPs. In SAVI, chronic activation of the type 1 IFN response occurs via constitutive activation of the STING protein due to a gain-of-function mutation in *STING1*. Finally, Singleton-Merten syndrome, for example, is thought to result from constitutive activation of cytosolic MDA5 and RIG-I receptors due to of a mutation in the *IFIH1* and *DDX58* genes (Figure 1) (4). Other diseases with elevated interferon activity have been described, such as tricho-hepato-enteric syndrome, genomic instability syndromes (e.g.ataxia-telangiectasia, Bloom syndrome), X-linked reticulopigmentary disease, some mitochondriopathies (8). As in the case of polygenic “general” lupus, interferon production in these settings is possibly due to secondary lesional mechanisms with exposure of endogenous nucleic acids (excessive but adapted production of type I IFN) rather than to constitutive overexpression of the interferon pathway.

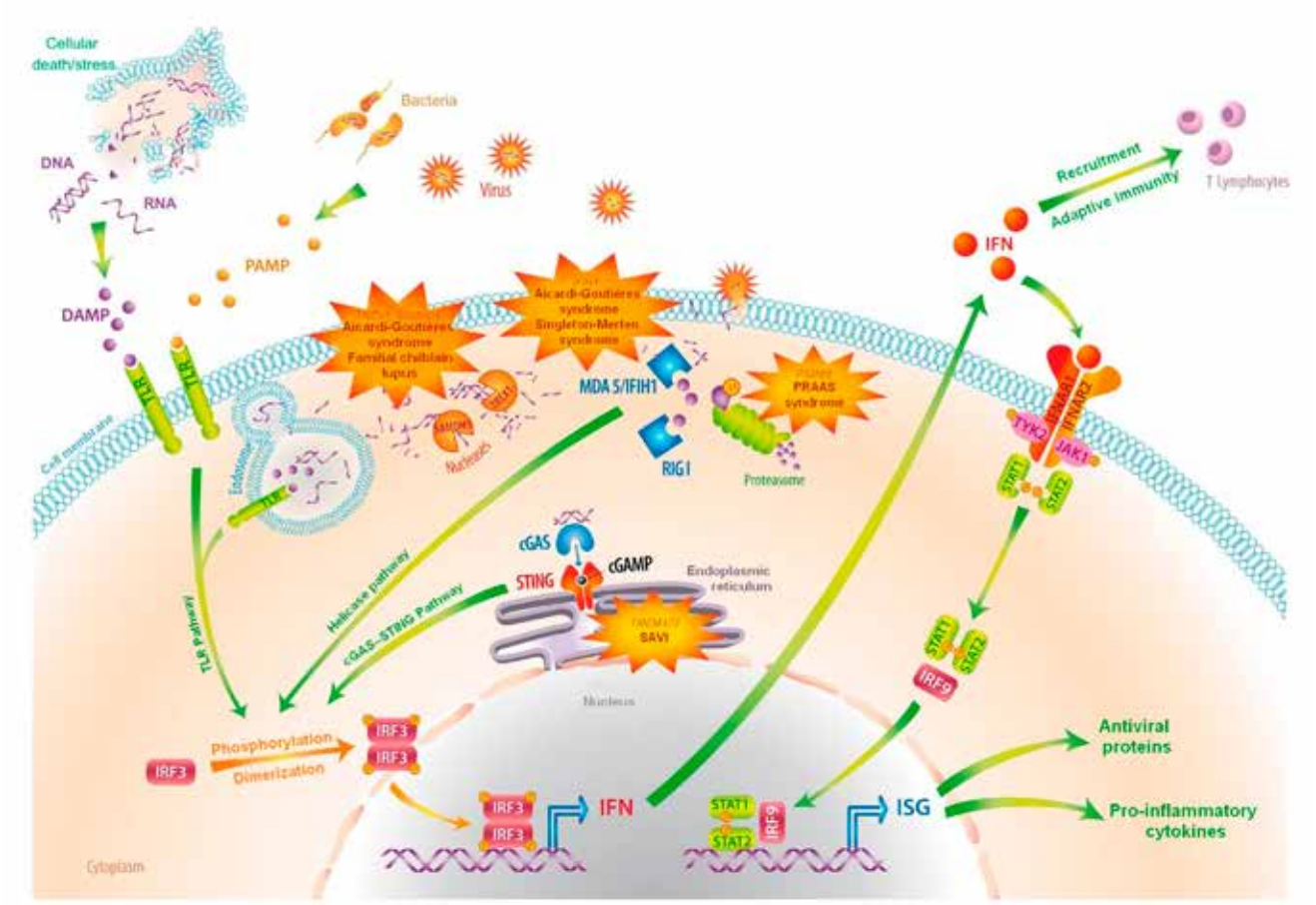
2. Diagnosis of Type 1 interferonopathies

Diagnosis of interferonopathies by conventional enzyme-linked immunosorbent assay (ELISA) is complicated. Indeed, interferons circulate in the blood at extremely low concentrations even following infection or interferonopathy (6, 9). Therefore, it is of interest to develop a routine diagnostic clinical test based on the interferon signature to indirectly assess type I IFN activity by measuring IFN-induced ISG gene expression. Techniques for routine measurement of IFN exposure to determine an IFN signature have recently been developed for the diagnosis and monitoring of type 1 interferonopathies (6).

Based on Pescarmona et al.'s 2019 landmark article, a series of quantitative PCR assays have been developed to assess the expression of a series of ISG genes for the diagnosis of interferonopathies. For this purpose, the RNA expression of 5 ISGs (*IFI27, IFI44L, IFIT1, ISG15, RSAD2*), previously described as the ISGs most overexpressed

Figure 1: Type 1 interferon signalling pathways and their mechanisms of overexpression in interferonopathies.

A signalling cascade leads to IFN synthesis (via phosphorylation and dimerization of nuclear transcription factors IRF). The TLR pathway is driven by the recognition of molecular patterns by TLRs, cellular membrane or endosomal receptors. The cGAS-STING pathway begins with the detection of cytosolic DNA by the cGAS enzyme, leading to the synthesis of cGAMP, which binds to the endoplasmic reticulum transmembrane protein STING. The RIG-I and MDA5/IFIH1 helicase pathway is activated by recognition of intracellular DAMPs and PAMPs. The IFNs thus produced bind to their membrane receptors IFNAR1/IFNAR2 and generate an activation signal propagated throughout the cell via the JAK/STAT signalling pathway. JAK protein kinases lead to the formation of a nuclear transcription factor composed of STAT1, STAT2 and IRF9. It binds upstream of ISGs to induce their expression and thus the production of proteins responsible for the antiviral properties of type 1 IFNs. Chronic activation of the type 1 IFN response can be generated by various dysfunctions as in the case of AGS and familial chilblain lupus, SAVI (Munoz et al., 2015).



in interferonopathies, could be quantified (6, 10). This quantification analysis allows us to obtain an IFN score that can be used as a biomarker of theses specific diseases.

3. Development of diagnostic tests based on the interferon signature at the Gosselies Institute of Pathology and Genetics.

Methodology

Participants and Sample Collection

Control samples were collected from 23 anonymous, healthy individuals (adults of various ages and of both sexes, with no known medical conditions or infections). Positive samples were obtained from 13 patients with infections such as influenza or COVID-19. Additionally, two patients exhibited symptoms of type 1 interferonopathies, such as chronic vasculitis or calcification of the basal ganglia.

RNA Extraction from EDTA Blood

Total RNA was extracted from whole blood collected in EDTA tubes using the MAXWELL RSC48 robot and the 'Maxwell RSC miRNA Plasma and Serum kit' (Ref. AS1680, Promega) following the manufacturer's instructions. The extracted RNA was then quantified using a Nanodrop spectrophotometer (Thermo ScientificTM NanoDrop One).

Reverse transcription

For both RT-qPCR and ddPCR, reverse transcription was conducted in two steps. Total RNA (0.4 to 1.0 µg) was therefore first subjected to reverse transcription in 20 µl of 'SuperScript™ IV VILO™ Master Mix' (Ref. 11756050 Invitrogen) to synthesise first strand cDNA.

RT-qPCR Procedure

After reverse transcription, the cDNA was diluted to a concentration of 5 ng/µl RNA equivalent. RT-qPCR amplification was performed in duplicate for each sample using the FastStart Universal SYBR Green Master (Rox) kit (Ref. 4913850001, Roche). The qPCR amplification was conducted using the QuantStudio5 system with the following program: a 10-minute cycle at 95°C (activation of the FastStart Taq DNA polymerase) followed by 40 amplification cycles of 15 seconds at 95°C followed by 1 minute at 60°C.

Five interferon-stimulated genes (ISGs) were studied: *IFI27* (interferon alpha inducible protein 27), *IFI44L* (interferon induced protein 44 like), IFIT1 (interferon induced protein with tetratricopeptide repeats 1), *ISG15* (interferon-stimulated gene 15) and *RSAD2* (radical S-adenosyl methionine domain containing 2). Three housekeeping genes (OAZ (ornithine decarboxylase antizyme), GAPDH (glyceraldehyde-3-phosphate dehydrogenase) and β-Actin) were used as internal controls. Primers were used at a final concentration of 0.3 µM in the PCR reactions.

ddPCR Procedure

For ddPCR, cDNA samples were diluted to a concentration of 0.2 ng/µl RNA equivalent. The ddPCR was performed in duplicate for each sample using the 'QX200 ddPCR EvaGreen Supermix' (Bio-Rad) for the same 5 ISGs. The final concentration of primers was 0.2 µM. The PCR mixes

(15 µl) were then added to 5µl of diluted cRNA in a 96-well plate. The plate was placed in the BioRad automated droplet generator to create the emulsion, followed by PCR amplification on the BioRad C1000 Thermocycler with the following program: starting with a 5-minute cycle at 95°C (enzyme activation) followed by 40 denaturation and annealing/extension cycles lasting 30 seconds at 95°C and 1 minute at 60°C respectively, followed by a signal stabilisation step lasting 5 minutes at 4°C and 5 minutes at 90°C with a ramp of 2°C/sec. The results were then read using the QX200 ddPCR reader.

Calculation the IFN score

Once the qPCR results were obtained, the IFN scores could be calculated. The relative abundance of each gene transcript is calculated using the formula: $E^{-Delta\ Ct}$ ($E = 10^{(-1/slope)}$ and represents the efficiency of the standard curve generated for each gene by 10-fold serial dilutions). ISG expression was normalised to the mean expression of 3 housekeeping genes: OAZ, GAPDH and β-Actin. The relative expression for each ISG is then calculated by dividing the normalised expression of patient ISGs by the median normalised expression of ISGs in the healthy controls. Finally, the IFN score is calculated using the median of the relative expression of the 5 ISGs.

An abnormal IFN score was defined as an IFN score more than 2 standard deviations above the mean IFN score of the control group.

Technique validation steps

Primer Validation and RT-qPCR Efficiency

RT-qPCR was initially performed on a few control samples to validate the primers selected for studying ISG expression. Two negative controls were included: first, a matrix-free control (water sample) to check for contamination by foreign nucleic acids and primer dimer formation and secondly, a reverse transcriptase-free control and secondly, a reverse transcriptase-free control was prepared at the time of the reverse transcription step, without adding reverse transcriptase to the total RNA. This control was used to assess the amount of DNA contamination in the samples.

PCR efficiency was calculated for each gene using a standard curve generated by 10-fold serial dilutions. The PCR efficiency was then calculated using the formula: $E = 10^{(-1/\ slope)}$-1. qPCR reactions were considered good if the efficiency was between 90% and 110%. This efficiency of the standard curve will also allow, in a second step, to calculate the relative abundance for each gene transcript. Melting curves were also observed to confirm the specificity of our qPCR for the different genes in each sample.

Clinical relevance of the calculated IFN score

In order to assess the clinical relevance of the IFN score, calculated with the RT-qPCR data and their classification as positive or negative control, a ROC (Receiver Operating Characteristic) curve (Figure 2), a graphical representation of the performance of a binary classification model, was generated (11). The area under the curve (AUC) of the ROC curve is an important measure that is used to quantify the overall performance of the classification model. An AUC of 1 indicates that the classification model is perfect, while an AUC of 0.5 indicates that the classification model is random. Here, the area under the curve measured was 0.844, which is associated with reliable performance for this model.

Threshold confirmation and calculation of sensitivity and specificity

Subsequently, the ROC curve (Figure 2) was then used to confirm the threshold for defining whether the scores obtained are considered normal or abnormal. In this case, it is especially important that both the probability of the disease not being present when the test is negative, and the probability of the disease being present when the test is positive, are high. These probabilities are known respectively as negative predictive value (NPV) and positive predictive value (PPV). A threshold score of 3.2 was set, giving a sensitivity of 84.6%, a specificity of 91.3%, a NPV of 92%, and a PPV of 84.6%. This threshold was comparable to the threshold calculated from the mean scores of healthy controls + 2SD.

Test reproducibility

The reproducibility of the test was demonstrated on 3 samples (2 positive and one negative) and assessed on 3 different days, by 3 different laboratory technicians, on 3 different qPCR machines. The results obtained validated the intermediate accuracy of the test.

Test accuracy

Additional RNA samples, 5 negative controls and 6 positive controls, were obtained from the CHU de Lyon and were used as controls with

Figure 2: ROC curve for IFN signature assay based on RT-qPCR data and classification of positive controls and healthy controls.

The ROC curve represents the rate of true positives (Sensitivity) on the y-axis versus the rate of false positives (1 - Specificity) on the x-axis. Each point on the curve represents a different threshold value used to classify positive and negative instances. By varying the threshold, we can adjust the trade-off between the true positive rate and the false positive rate. The blue diagonal reference line represents a random classifier with no discriminatory power. The curve is based on the scores of 23 healthy controls and 13 RTqPCR positive controls. The AUC is 0.844. With a threshold set at 3.2: sensitivity (Se) = 84.6% and specificity (Sp) = 91.3%.

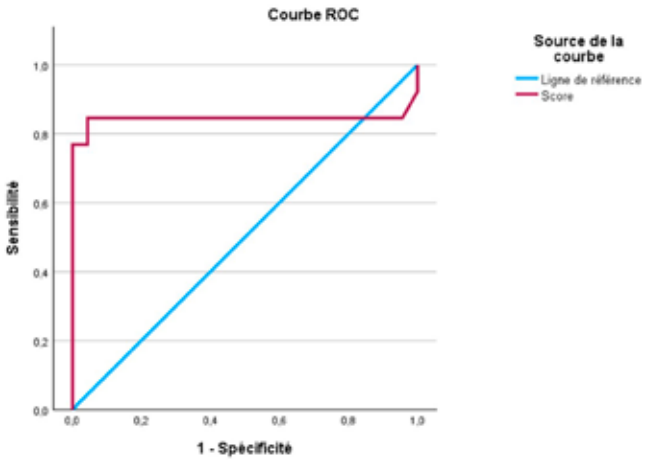


Figure 3: ROC curve for IFN signature assay based on ddPCR data and classification of positive control and healthy controls.

The ROC curve represents the rate of true positives (Sensitivity) on the y-axis versus the rate of false positives (1 - Specificity) on the x-axis. Each point on the curve represents a different threshold value used to classify positive and negative instances. The blue diagonal reference line represents a random classifier with no discriminatory power. The curve was constructed based on the scores of 9 healthy controls and 6 positive controls obtained by ddPCR. The AUC is 0.833. With a threshold set at 3.3: sensitivity (Se) = 83.3% and specificity (Sp) = 100%.

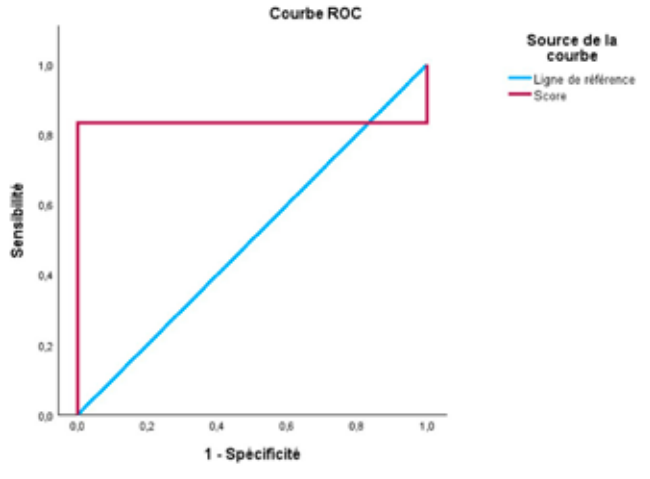


Table 1: PIFN scores in negative control groups, patients symptomatic for type 1 interferonopathy and positive controls obtained by RTqPCR and for of 9 samples from the negative control group and 6 positive controls obtained by ddPCR. Threshold set at 3.2 for RTqPCR and at 3.3 for ddPCR.

Samples	IFN scores (RTqPCR)	IFN scores
Healthy control 1	1,3	NA
Healthy control 2	1,8	NA
Healthy control 3	0,3	0,5
Healthy control 4	2,3	3,3
Healthy control 5	2,4	NA
Healthy control 6	3,8	NA
Healthy control 7	0,4	NA
Healthy control 8	0,6	NA
Healthy control 9	0,7	NA
Healthy control 10	0,5	NA
Healthy control 11	0,2	NA
Healthy control 12	1	0,8
Healthy control 13	0,3	NA
Healthy control 14	0,9	1,0
Healthy control 15	1,1	0,9
Healthy control 16	1,4	NA
Healthy control 17	0,8	0,7
Healthy control 18	0,9	1,0
Healthy control 19	1	0,9
Healthy control 20	2,3	NA
Healthy control 21	2,1	2,8
Healthy control 22	6,1	NA
Healthy control 23	0,6	NA
Patient with interferonopathy 1	3,6	NA
Patient with interferonopathy 2	0,8	NA
Positive controls 1	148,2	152,7
Positive controls 2	11,3	NA
Positive controls 3	0,1	NA
Positive controls 4	23,8	NA
Positive controls 5	46,8	39,9
Positive controls 6	23,1	NA
Positive controls 7	4,2	3,8
Positive controls 8	0,2	0,1
Positive controls 9	86,7	89,5
Positive controls 10	8,8	NA
Positive controls 11	7,8	NA
Positive controls 12	11	9,7
Positive controls 13	26,9	NA

a known IFN score to compare the results obtained by RTqPCR with the results obtained at the CHU de Lyon using the Nanostring method. The correlation between Nanostring results and RTqPCR results was calculated using the determination coefficient (R2). The scores obtained by RTqPCR were close to the scores given by CHU de Lyon, giving an R2 of 0.976.

ddPCR test and Comparison with RT-qPCR

The ddPCR was performed on the same transcripts as those used for RTqPCR, as described above. It was performed on 9 control samples and 6 positive samples previously tested by RTqPCR.

The performance of RTqPCR and ddPCR for measuring IFN scores was compared. The ROC curve (Figure 3) obtained from the ddPCR data gave an AUC of 0.833, and the threshold was established at 3.3 (comparable to the threshold calculated from the mean of the scores of healthy controls + 2SD), giving a sensitivity of 83.3%, a specificity of 100%, an NPV of 90% and a PPV of 100%. The ddPCR model performed almost identically to RTqPCR, both of which showed high sensitivity and specificity for the diagnosis of type 1 interferonopathies.

Results of the validation

Analysis of results

In the healthy control group, only 2 samples showed a positive and weakly positive IFN signature of 6.1 and 3.8 (8.7%).

In the positive control group, out of 13 samples analysed, 2 were negatives (13.3%). These 2 negatives results actually involved two patients for whom a negative result might have been expected. One had a residual viral load, but had been clinically infected 15 days previously, and the other was an incidental finding of an elevated viral load in the setting of sepsis following digestive perforation. It would therefore appear that these patients are simply asymptomatic or have a hyperstimulated inflammatory system in other inflammatory pathways, which could interfere with the IFN response. So, these are two cases where we would a priori have expected a negative or disturbed signature.

Finally, in patients with symptoms of interferonopathy, 1 sample was negative and the other positive (50%) (Table 1).

Comparison of RTqPCR and ddPCR results

The correlation between the results obtained by RT-qPCR and ddPCR was also analysed using the R2 for IFN scores and the relative expressions of each ISG. The R2 was 0.88 for *IFI27*, 0.9761 for *IFI44L*, 0.9816 for IFIT1, 0.9892 for *ISG15*, 0.9973 for *RSAD2* and 0.9975 for IFN scores.

All samples assessed in ddPCR showed identical results to those obtained in RTqPCR with close scores (Table 1). Once again, this shows that RT-qPCR and ddPCR have similar performance.

Advantages and disadvantages of the two interferon signature techniques

Both RTqPCR and ddPCR offer some advantages and disadvantages for interferon signature analysis. Indeed, ddPCR requires only a small amount of starting material, which can be advantageous when sample quantities are limited. However, ddPCR may require more time to perform the analysis due to the additional sample emulsification step compared to RTqPCR.

Limitations of diagnostic tests based on the interferon signature

Corticosteroids can partially suppress the interferon signature, as high-dose steroids can inhibit IFN responses (6, 12). This can lead to a reduction in ISG expression, which in turn can lower the IFN score and lead to a false-negative result. Therefore, it is usually recommended that the IFN signature be performed prior to the administration of this type of treatment and throughout an acute phase of the disease (6). JAK inhibitors, due to their specific action on JAK/STAT pathway, also modulate the signature.

It should also be noted that by the primary role of interferon system, interferon signature can be influenced by infections, mainly viral ones (6). Indeed, the interferon signature refers to a set of genes that are regulated by type 1 interferon, which is produced by the immune system in response to viral infections or other inflammatory stimuli (4). We observe as predicted that in our group of patients infected with the influenza virus, the IFN score can be remarkably high. Therefore, it is important that the patient could be assessed in the absence clinical signs of infection, or after eradication of the virus. In doubtful cases, diagnosis of type 1 interferonopathies can also be made at an early stage using a combination of clinical and genetic criteria (13).

Conclusion and clinical perspectives

In conclusion, RTqPCR and ddPCR are two comparable methods and, like the Nanostring method used by Pescarmona et al., both can be used routinely to study the IFN signature. The diagnosis of type 1 interferonopathies using the interferon signature has opened new perspectives in the management of these rare diseases. By continuing research and integrating technological, clinical and genetic advances, we can look forward to a more accurate, earlier and individualized diagnosis of type 1 interferonopathies, leading to better patient management. Furthermore, the interferon signature could also be used to assess the efficacy of treatments in patients with type 1 interferonopathies. Indeed, treatment of patients with type I interferonopathy, particularly with drugs targeting the type I IFN pathway, is associated with a decrease in the IFN signature. Another way of development could be treatment monitoring. By following ISG expression levels before and after treatment, it would be possible to determine whether treatment has been successful in reducing excessive interferon expression. The decrease in IFN score could then be used as an objective criterion of therapeutic efficacy, although the clinical correlation remains to be clarified (4, 14). On the other hand, many of the more common autoimmune pathologies ("non-monogenic" systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis and other inflammatory myositis, ...) demonstrate a positive interferon signature in some subgroups of patients, which would make it possible to discuss a more targeted therapeutic orientation. Some autosomopathies (mainly trisomy 21, with a probable gene dosage effect on interferon pathway receptors) or mitochondrial diseases are also concerned, and the role of the type 1 interferon pathway in the long-term manifestations of these pathologies, as well as possible therapeutic perspectives, opens up a field of research to be explored (15). Finally, the development of the interferon signature is one of the possible transcriptomic analyses, but the development of knowledge of other pathways specific to autoinflammation, which may have diagnostic and therapeutic implications in other mono or polygenic diseases, may suggest other applications, possibly in combination with precision cytokine assays such as the Single MOlecular Assay (SiMOA).

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The Diagnostic Approach of Hypercalcaemia in Childhood

An Illustrative Case Report and Narrative Literature Review

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Hypercalcaemia ; vitamin D ; CYP24A1 ; Idiopathic Infantile Hypercalcaemia (IIH) ; Infantile hypercalcaemia (IH).

Abstract

In this narrative review, we discuss the case of a 5-month-old girl who presented with feeding difficulties, failure to thrive, and clinical signs of dehydration. Blood examination revealed hypercalcaemia, elevated 1,25-dihydroxyvitamin D levels and suppressed parathyroid hormone. Renal ultrasound revealed nephrocalcinosis. Genetic testing identified two pathogenic variants in the *CYP24A1* gene and confirmed the clinical diagnosis of infantile hypercalcaemia (IH), formerly known as idiopathic infantile hypercalcaemia (IIH). This patient's hypercalcaemia normalised with fluid administration, dietary adjustments, discontinuation of vitamin D supplementation, and adjuvant treatment with fluconazole and intravenous bisphosphonates (pamidronate). Awareness of the symptoms of hypercalcaemia is crucial for an accurate diagnosis, effective treatment, and the prevention of complications. This manuscript highlights the clinical, biochemical, and management aspects of hypercalcaemia in childhood, including a flowchart of the diagnostic approach.

Introduction

Hypercalcaemia is defined as a serum adjusted calcium concentration greater than two standard deviations above the normal mean (1-3). Hypercalcaemia is a rare condition in the paediatric population, affecting approximately 1 in 500 children in a general hospital setting (2, 3).

Although a thorough clinical history and physical examination can provide valuable clues, the diagnosis of hypercalcaemia remains challenging – especially in young children - due to the often variable and non-specific symptomatology (2). Nevertheless, untreated hypercalcaemia can have serious clinical consequences, ranging from vague symptoms like fatigue and nausea to hypercalcaemic crisis, renal complications such as kidney stones and nephrocalcinosis, and severe neurological symptoms such as myoclonus, encephalopathy, hyperreflexia, and proximal muscle weakness (3, 4). The aetiology of hypercalcaemia in children is diverse and the frequency varies between age groups (2, 3). In neonates and infants, genetic or iatrogenic causes are often identified; while in older children, vitamin D intoxication, primary hyperparathyroidism, and immobilisation are more common causes (2, 5, 6).

To illustrate the symptomatology, diagnostic landscape, and initial management of hypercalcaemia in childhood, we describe a clinical case of a 5-month-old infant diagnosed with infantile hypercalcaemia and subsequently provide a narrative overview of the current diagnostic landscape and initial management of hypercalcaemia in children.

Case Report

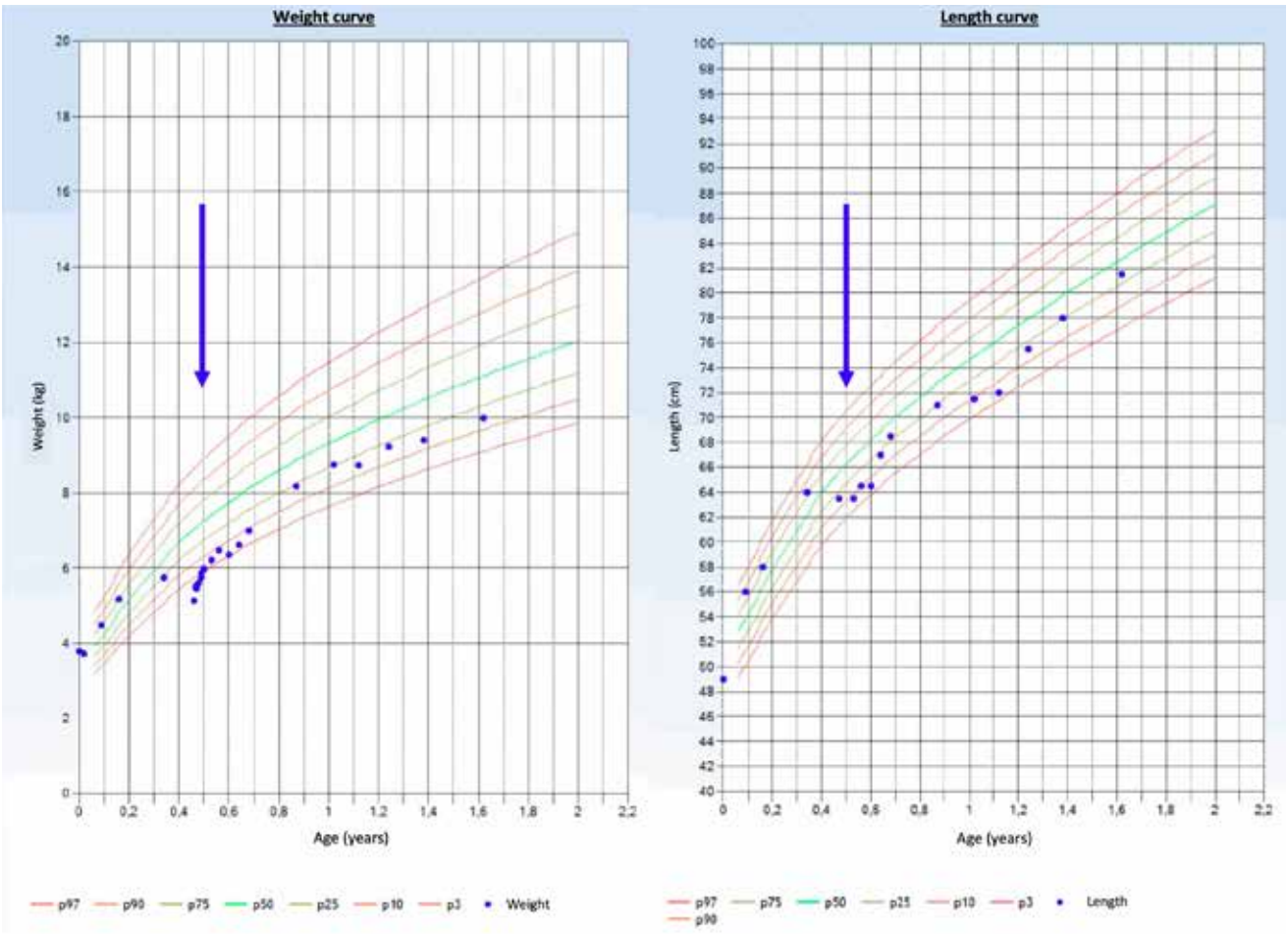
A 5-month-old female infant with an unremarkable medical history was presented to the emergency department because of feeding difficulties (with reported weight loss), being less active than usual and low-grade fever. On physical examination, signs of dehydration were noted, such as dry mucosa and lethargy. As shown in Figure 1, the patient's growth chart showed failure to thrive since the age of 2.5 months, with normal height for age but a weight loss of approximately -2.5 to -3.0 standard deviations over the previous months.

Initial blood tests showed hyponatraemia (sodium 124 mmol/L; reference range (RR) 139 - 146 mmol/L), hypercalcaemia (total serum calcium 3.98 mmol/L, RR 2.20 – 2.84 mmol/L); ionised calcium 2.04 mmol/L (RR 1.20 - 1.38 mmol/L); albumin 40 g/L (RR 30 – 54 g/L) and low bicarbonate of 14.9 mmol/L (RR 16 - 24 mmol/L). Elevated serum creatinine of 44.2 micromol/L (RR 13.3 – 26.5 micromol/L) and urea nitrogen (6.99 mmol/L, RR 1.40 – 6.40 mmol/L) were noted. Serum phosphate, liver and thyroid tests were all within normal limits. A urine sample revealed increased calcium excretion (calcium/creatinine ratio 9.18 mol/mol, 95th percentile for spot urine calcium/creatinine is < 2.2 mol/mol). Renal ultrasound showed bilateral nephrocalcinosis (added in Figure 2). An electrocardiogram was normal.

Her parents were not known to be consanguineous, and both they and the older siblings all had unremarkable medical histories. The patient had not been taking any medication other than the recommended daily dose of 400 IU of vitamin D; intoxication was considered unlikely. Further investigations revealed hypervitaminosis D (elevated serum 25-hydroxyvitamin D: >250 nmol/L, RR 75.5 – 200 nmol/L) and low serum parathyroid hormone (PTH) (< 0.64 pmol/L, RR 1.70 – 9.33 pmol/L). The clinical diagnosis of infantile hypercalcaemia was confirmed with genetic testing: i.e. compound heterozygous variants in *CYP24A1* (the gene encoding 25-hydroxyvitamin D 24-hydroxylase); i.e. c.443T>C (p.Leu148Pro) and c.1186C>T (p.Arg396Trp) (both class 5 pathogenic variants).

Initial management consisted of fluid administration with normal saline (0.9% NaCl), which normalised all electrolytes except for ionised calcium (Figure 2). Vitamin D supplementation was stopped and a

Figure 1: Growth chart. The arrow shows the time of diagnosis.



modified diet was introduced (Nutricia Milupa Basic-CaD formula (<5mg Ca / 100ml) and low calcium solid foods) along with breastfeeding. However, as serum ionised calcium levels remained high despite dietary modification, additional treatment with fluconazole and pamidronate (a bisphosphonate) was initiated. The patient was discharged home after 10 days. At follow-up, the patient showed favourable weight gain (Figure 1) with adequate dietary and medication intake. As shown in Figure 2, maintenance fluconazole was discontinued at 9 months and dietary modifications were slowly tapered and eventually stopped 14 months of age.

Discussion and narrative literature review

Hypercalcaemia is an uncommon entity in childhood with potentially significant morbidity (4). As diagnosis is often challenging and early adequate treatment can change the outcome of these patients, we present an update on the diagnostic and (early) management landscape of hypercalcaemia in childhood, illustrated by a case report of infantile hypercalcaemia due to a compound heterozygous pathogenic variant in *CYP24A1*.

Definition and reference values

The skeleton contains 98% of total body calcium; the remaining 2% circulates throughout the body. Only 1% of circulating calcium is free (ionised) calcium, the only form that has physiological effects (7). Normal serum calcium levels are maintained through the interplay of parathyroid, renal, and skeletal factors (4, 8). Hypercalcaemia is defined as a serum (adjusted for albumin or ionised) calcium concentration greater than two standard deviations above the normal mean. Serum calcium levels must be interpreted according to age, as reference values vary across different age groups (Table 1) (1, 4, 9, 10). There is no formal classification or grading system to define the severity of hypercalcaemia. However, the severity of clinical symptoms is more likely to be associated with greater elevations in serum calcium concentrations, and hypercalcaemia is generally considered to be mild, moderate, and severe for serum adjusted calcium concentrations < 3.0 mmol/L (< 12 mg/dl), between 3.0 to 3.5 mmol/L (12 and 14 mg/dl), and > 3.5 mmol/L (>14 mg/dl), respectively(2). A summary of the reference values of other biochemical markers commonly used in the diagnostic approach to hypercalcaemia in children is provided in Table 1 (10).

Symptomatology

Hypercalcaemia can be an incidental finding without clinical signs or symptoms (5, 11). Clinical manifestations affect the neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular system (7). The most frequent findings are lethargy, hypotonia, anorexia, weight loss or failure to thrive, polydipsia, polyuria, vomiting, bone pain, constipation and abdominal pain (1, 5, 12). The onset is usually insidious over a few weeks (11).

In severe cases, renal failure, marked hypovolaemia, cardiac arrhythmia and reduced consciousness may occur (5, 6, 11). A hypercalcaemic crisis manifests with dehydration, hypertension, and convulsions or coma. It may develop when adjusted serum calcium exceeds 3.5 mmol/l, and such high serum levels must be considered a pending crisis (7).

Epidemiology, aetiology and diagnostic landscape

The prevalence of hypercalcaemia in childhood is inversely related to age, with the highest occurrence in neonates (3, 4). The aetiology of paediatric hypercalcaemia is also age-dependent and includes a broad differential diagnosis (4, 11). Neonates and infants often experience genetic or iatrogenic aetiologies, while in childhood, vitamin D intoxication, primary hyperparathyroidism, and immobilisation are the main causes of hypercalcaemia (2, 5, 6). Hypercalcaemia is observed in less than 1% of children with cancer at the time of diagnosis (5).

Table 1: Reference values of laboratory tests commonly used in the diagnostic approach to hypercalcaemia in children.

CU = Conventional Units. SI = International System of Units. NR = Not Reported. Establishing reference intervals in the paediatric population is particularly challenging due to the necessity of recruiting a large cohort of healthy children and adolescents for accurate stratification by important covariates, including age and sex. The values for serum adjusted calcium, phosphate, albumin, and sodium were adapted from Bohn MK et al(10), where intervals were determined for 32 analytes using Siemens Healthineers Atellica® CH assays in the CALIPER cohort of healthy children and adolescents.

Biochemical markers	Infants (0-1y)	Children and adolescents (1-14y)
Total serum adjusted calcium	Premature: NR Full-term: 2.20 – 2.84 mmol/L (SI) or 8.80 – 11.36 mg/dL (CU)	2.25 – 2.69 mmol/L (SI) or 9.00 – 10.76 mg/dL (CU)
Ionised calcium	< 2 months: 1.05 - 1.37 mmol/L (SI) or 4.20 - 5.48 mg/dL (CU) > 2 months: 1.20 - 1.38 mmol/L (SI) or 4.80 - 5.52 mg/dL (CU)	1.20 - 1.38 mmol/L (SI) or 4.80 - 5.52 mg/dL (CU)
24h urine calcium	< 0,1 mmol/kg/day (SI) or < 4 mg/kg/day (CU)	1.20 - 1.38 mmol/L (SI) or 4.80 - 5.52 mg/dL (CU)
95th percentile for spot urine calcium/creatinine	< 2.20 mol/mol (SI) or < 0.81 mg/mg (CU)	1 – 3 years: < 1.40 mol/mol (SI) or < 0.53 mg/mg (CU) 3 – 5 years: < 1.10 mol/mol (SI) or < 0.41 mg/mg (CU) 5 – 7 years: < 0.80 mol/mol (SI) or < 0.30 mg/mg (CU) > 7 years: < 0.70 mol/mol (SI) or < 0.24 mg/mg (CU)
Phosphate	1.00 – 2.38 mmol/L (SI) or 3.10 – 7.37 mg/dL (CU)	1 - 2 years: 1.03 - 2.09 mmol/L (SI) or 3.19 – 6.47 mg/dL (CU) 2 - 4 years: 1.00 - 1.90 mmol/L (SI) or 3.10 – 5.88 mg/dL (CU) 4 - 10 years: 1.00 - 2.00 mmol/L (SI) or 3.10 – 6.19 mg/dL (CU) > 10 years: 0.80 - 1.80 mmol/L (SI) or 2.48 – 5.57 mg/dL (CU)
Magnesium	0.77 – 1.05 mmol/L (SI) or 1.87 – 2.55 mg/dL (CU)	0.69 – 0.92 mmol/L (SI) or 1.67 – 2.24 mg/dL (CU)
Albumin	Premature infants (until term age): 18 – 30 g/L (SI) or 1.8 – 3.0 g/dL (CU) Full term infants: 30 – 54 g/L (SI) or 3.0 – 5.4 g/dL (CU)	35 – 52 g/L (SI) or 3.5 – 5.2 g/dL (CU)
Sodium	139 – 146 mmol/L (SI) or 139 – 146 mEq/L (CU)	
Parathyroid hormone (PTH)	1.70 – 9.33 pmol/L (SI) or 16 – 88 ng/L (CU)	
25(OH)vitamin D	Reference range: 75.5 – 200 nmol/L (SI) or 30 – 80 ng/mL (CU) Severe deficiency: < 12.5 nmol/L (SI) or < 5 ng/mL (CU) Moderate deficiency: 12.5 – 29 nmol/L (SI) or 5 – 11.6 ng/mL (CU) Mild deficiency: 30 – 49 nmol/L (SI) or 12 – 19.6 ng/mL (CU) Sufficient: > 50 nmol/L (SI) or > 20 ng/mL (CU) Elevated: > 250 nmol/L (SI) or > 100 ng/mL (CU)	

Figure 2: Laboratory data. Data showed on the left Y-axis: 25-hydroxyvitamin D (25(OH)vit D) (orange graph line; reported unit in ng/ml) (deficiency if <20 ng/ml, values >100 ng/ml are not determined in our laboratory); 1,25-dihydroxyvitamin D (1,25(OH)2 vit D) (grey graph line; reported unit in mg/ml) (reference range (RR) 19 - 95 mg/ml in our laboratory); Parathyroid hormone (PTH) (yellow graph line; reported unit in ng/l) (RR 15-65 ng/l in our laboratory) and on the right Y-axis ionised calcium (blue graph line; reported unit in mmol/l) (RR 1.20-1.38 mmol/l). On X-axis the numbers 0 to 10 represent the days hospitalised at initial presentation, and day 38, 52, 80, 241 represent the follow-up consultations with biochemical evaluation. The arrows reflect the administration of Pamidronate (a bisphosphonate). Hyperhydration with intravenous normal saline (0.9% NaCl) from admission to day 8. The modified diet was started on day 3 and slowly tapered to stop at the age of 14 months (day 241). Fluconazole maintenance treatment was started as well on day 3 and discontinued on day 80. The renal ultrasound showing nephrocalcinosis is added.

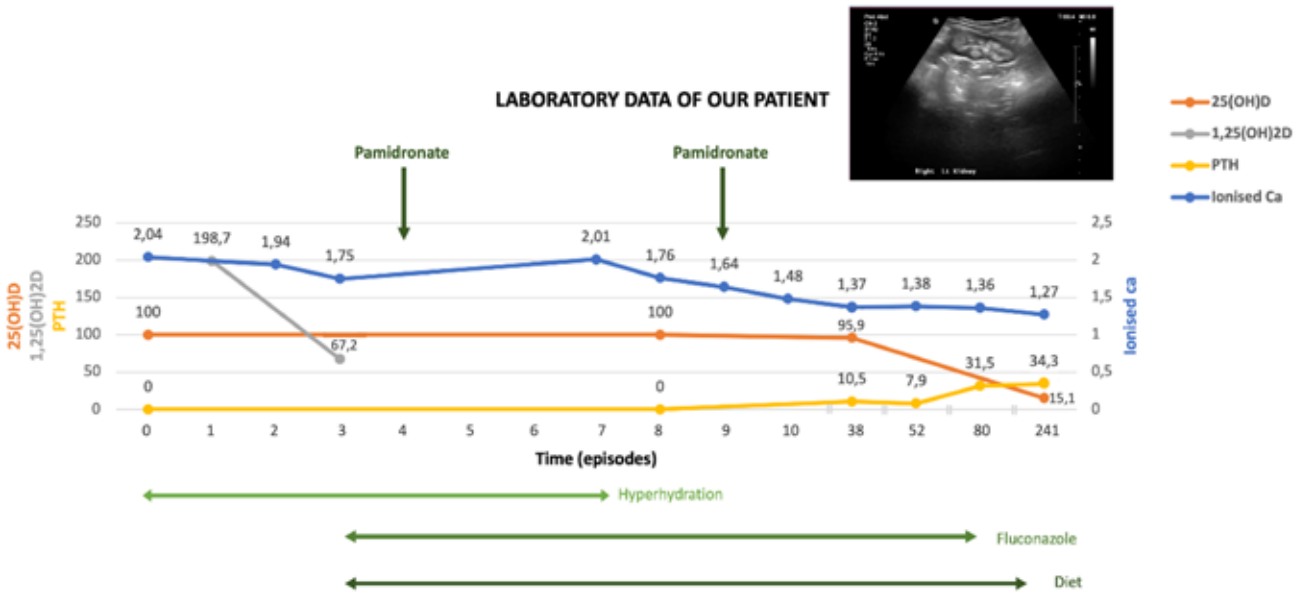


Figure 3: Diagnostic approach to hypercalcaemia in children. The flowchart is adapted from Stokes et al(2). Hypercalcaemia° is defined as a serum (adjusted for albumin or ionised) calcium concentration greater than two standard deviations above the normal mean. See table 1 for reference values of biochemical markers commonly used in the diagnostic approach to hypercalcaemia in children. *Differential diagnoses marked in italic are conditions affecting neonates.* Additional work-up is warranted to identify malignancy. *Some medications associated with hypercalcaemia include thiazide diuretics, lithium, excessive vitamin A, etc. If possible, any medication or supplement that may be causing hypercalcaemia should be discontinued.

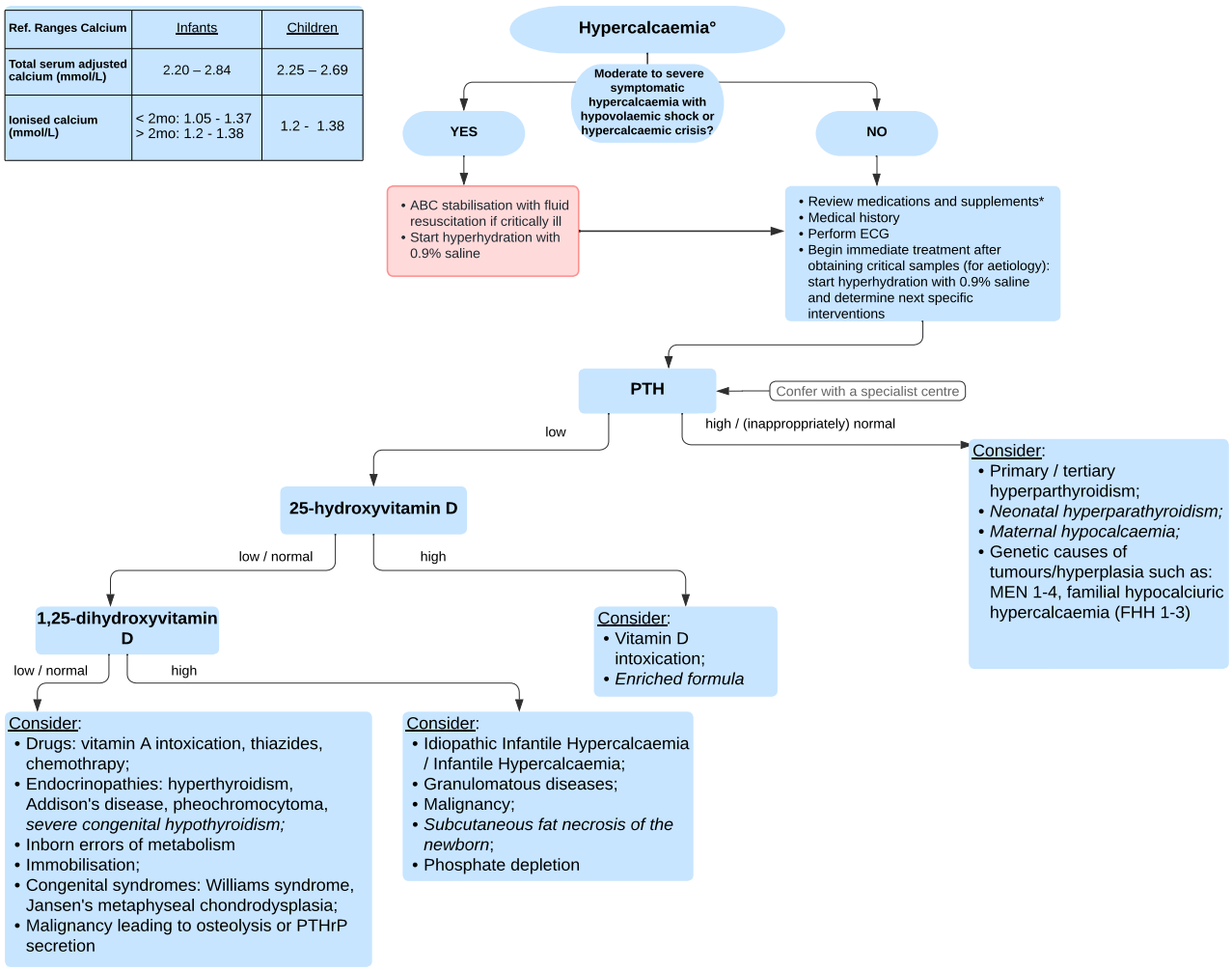


Figure 3 outlines a step-by-step guide for the diagnostic work-up of hypercalcaemia in childhood and is adapted from Stokes et al. (2). Initially, the severity and urgency of the presentation should be assessed. The presence or absence of symptoms of hypercalcaemia may indicate the urgency with which investigations should be pursued (2). If the child presents with a hypovolaemic shock due to a hypercalcaemic crisis, prompt management should be initiated (see treatment section).

Hypercalcaemia can be divided into disorders with inappropriately normal or high PTH and conditions with low or suppressed PTH (8). Primary hyperparathyroidism is rare in childhood (1% of cases), typically presenting with hypercalcaemia and high PTH. It is characterised by autonomous PTH secretion independent of circulating calcium levels, due to a parathyroid adenoma, parathyroid hyperplasia or rarely carcinoma (4, 11). Another disorder presenting with high PTH level is neonatal (severe) hyperparathyroidism. The majority present in the first few weeks of life. There is often severe hypercalcaemia (>4.5mmol/l), low plasma phosphate and very high PTH levels (1, 11). Familial hypocalciuric hypercalcaemia (FHH) (also termed familial benign hypercalcaemia (FBH)) is an autosomal dominant disorder with an inappropriate normal or marginally elevated PTH level despite hypercalcaemia (1, 4, 11). FHH is characterised by lifelong mild hypercalcaemia and very low levels of urinary calcium (4). The hypercalcaemia in FHH is generally benign, usually progresses asymptomatically, and thus does not always require treatment (2). As shown in Figure 3, conditions leading to hypercalcaemia with low or suppressed PTH levels encompass a wide differential diagnosis. In this subgroup, we recommend initiating a comprehensive evaluation, including 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 24:25-dihydroxyvitamin D3 ratio, serum phosphate, and serum magnesium, ideally prior to initial treatment (1). After collecting critical samples and starting the initial treatment, it is recommended to consult a paediatric specialist centre for further guidance. In addition, we suggest a skeletal survey, urinary tract ultrasound, and urinary spot calcium/creatinine ratio, and genetic evaluation to further guide the differential diagnosis (3, 6, 12). In children with hypercalcaemia and low PTH, it is important to consider secondary causes of hypercalcaemia due to immobilisation or medications like thiazide diuretics, lithium, and excessive vitamin A or vitamin D. If feasible, discontinue any medication or supplements that may contribute. Malignancies, such as leukaemia, lymphoma, rhabdomyosarcoma, Hodgkin and non-Hodgkin lymphoma, brain tumours and neuroblastoma, should also be considered in patients with hypercalcaemia and low PTH (4, 5, 13). Lastly, there are many other rare causes of hypercalcaemia that lead to elevated calcium levels by diverse mechanisms: chronic maternal hypocalcaemia, phosphate depletion, inborn errors of metabolism, infantile hypercalcaemia (see separate section), Williams-Beuren syndrome (deletion on chromosome 7), Jansen's metaphyseal chondrodysplasia, and subcutaneous fat necrosis (4, 11). Full-term newborns that have experienced perinatal stress, such as asphyxia, meconium aspiration, Rhesus incompatibility, hypothermia, or obstetric trauma, are at risk for developing subcutaneous fat necrosis (SCFN). It is

due to excessive 1,25-dihydroxyvitamin D production from over-activity of 1-alpha-hydroxylase. Symptoms of SCFN are often vague, including lethargy, irritability, failure to thrive, hypotonia, vomiting, and constipation (14). It is associated with a significant 15% mortality (4).

Treatment and prognosis

Investigation of the cause of hypercalcaemia and its management are often conducted simultaneously (6). The treatment approach focuses on normalising serum (adjusted) calcium levels and addressing the underlying disorder. Immediate treatment is essential in cases of symptomatic hypercalcaemia to prevent a hypercalcaemic crisis which is associated with significant neurological, cardiac and renal toxicity(6). Treatment should be individually tailored, taking into account the severity of the clinical manifestations, the patient's age, and the expected side effects of the proposed medication (15).

Most children presenting with symptomatic hypercalcaemia are dehydrated, primarily due to reduced fluid intake and the diuretic effect of hypercalcaemia (11). Children with symptomatic hypercalcaemia may present with hypovolaemic shock. ABC stabilisation is then recommended. The main treatment for the critically ill child with hypovolaemic shock is fluid resuscitation. Normal saline (0.9% NaCl) is used in this case because increasing sodium excretion enhances calcium excretion. During fluid administration, special attention should be paid to other electrolytes such as magnesium and potassium (16). Hyperhydration with isotonic sodium chloride is often effective in treating hypercalcaemia, yet is usually insufficient to normalise serum adjusted calcium levels in moderate to severe cases (2, 11). Other treatment options include decreasing calcium absorption from the gut by dietary adjustments, as well as avoiding vitamin D supplementation and prolonged sun exposure. In certain cases, bisphosphonates, loop diuretics, fluconazole (or ketoconazole), and calcitonin have been used (2, 4, 6, 7, 12, 13, 15). Fluconazole, as used in this case, inhibits the activity of vitamin D synthesising enzymes and thereby lowers 1,25-dihydroxyvitamin D levels and reduces calciuria. While fluconazole is not the most potent inhibitor of 1-alpha-hydroxylase, it is far less toxic and more widely available than ketoconazole. However, there is still little research on the use and efficacy of fluconazole in paediatric hypercalcaemia, and we are not convinced that it caused a significant decrease in serum calcium in this case either. Administration of intravenous bisphosphonates leads to a more sustained reduction in serum calcium levels, by suppressing osteoclastic activity and inhibiting 1-alpha-hydroxylase activity as well. Therefore, by decreasing the number of osteoclasts, the rate of calcium release from bone will be reduced. Pamidronate, the drug of choice in children and commonly used in these circumstances, provides a clinical response with a decrease in serum (adjusted) calcium in 2 to 4 days after administration and the effect may last for 2 to 4 weeks (2, 4, 5, 11, 12, 14, 17). Although a wide variety of potential side effects has been described, these appear to be uncommon (18). Comprehensive clinical trials on the safety and efficacy of bisphosphonates in children are lacking; however, several small studies have reported promising results for these agents in the treatment of young patients with hypercalcaemia (4, 12). Specific interventions such as cinacalcet (calcimimetic), denosumab (monoclonal antibody), or surgical intervention, are used depending on the underlying cause, but discussion of these is beyond the scope of this manuscript (2, 6, 11, 15). In a life-threatening crisis (e.g., in patients with renal failure), peritoneal dialysis or haemodialysis has been advocated (6, 11).

Hypercalcaemia in neonates and infants, although uncommon, can have serious long-term consequences, including nephrocalcinosis that may cause permanent kidney damage, bone mineralisation defects and neurodevelopmental impairments (1, 19). There is only limited published information on the natural history of this condition, and the long-term prognosis remains largely unknown (18). The main goal of long-term evaluation is the prevention of renal deterioration and its associated complications (12).

Infantile Hypercalcaemia

Infantile hypercalcaemia (IH), formerly known as idiopathic infantile hypercalcaemia (IIH), was diagnosed in our patient. It is an autosomal recessive disorder caused by inactivating variants in the *CYP24A1* gene encoding for 25-hydroxyvitamin D 24-hydroxylase(2, 6, 15, 17, 19, 20).This enzyme converts active vitamin D metabolites such as 1,25-dihydroxyvitamin D to their inactive form (13). It is expressed in many tissues including the kidney, bone, skin, and intestine (12).

It was first described when symptomatic hypercalcaemia developed in children after receiving high doses of vitamin D for the prevention of rickets in Great Britain in the 1950s (1, 12). However, high variability in the clinical and biochemical phenotypes emerges as a result of genetic and environmental interactions (12). IH is a rare condition and its prevalence in the general population is unknown (13). Its estimated incidence is 1:33 000 to 1:47 000 live births (12, 18). The underlying pathophysiology remained unknown until variants in *CYP24A1* (2011) (type 1) and later *SLC34A1* (type 2) were discovered (13, 15, 21). Despite the term “infantile”, the condition is not confined to infancy as it may also present in later childhood and even adulthood (12). Infants with IH may develop significant hypercalcaemia even when receiving standard vitamin D supplementation (22). Patients typically manifest symptoms between 4 and 12 months of age, have no characteristic dysmorphic features, and show failure to thrive, vomiting, and dehydration. Nephrocalcinosis is commonly detected at presentation (6, 8, 12, 13, 19, 23). Diagnosis of IH is characterised by increased serum (adjusted) calcium, normal or elevated 25-hydroxyvitamin D, elevated 1,25-dihydroxyvitamin D, and suppressed PTH. Particularly, loss-of-function variants in the *CYP24A1* gene result in increased levels of both 25(OH)D3 and 1,25(OH)2D3, which enhance intestinal calcium absorption and bone reabsorption (12). Persistently elevated levels of 1,25-dihydroxyvitamin D lead to increased intestinal calcium absorption and bone resorption (13). This sustained bone resorption could lead to bone mineralisation defects such as osteopenia or osteoporosis; however, this was not present in this case (12).

Although hypercalcaemia in IH usually resolves by age 2 to 3, some individuals may experience persistent hypercalcaemia into adulthood (1, 2, 6). If undiagnosed, IH can cause serious renal complications (13). Regular follow-up and genetic testing in siblings of IH patients are recommended due to the risk of progressive chronic kidney disease and nephrocalcinosis (12, 19, 24). Long-term follow-up through dietary modifications, biochemical evaluations, and renal ultrasound is recommended to prevent complications related to hypercalcaemia and to monitor nephrocalcinosis (12). In the absence of specific guidance in literature, we recommend monitoring these patients at least once every 6 to 12 months, or more frequently if calcium levels are not controlled (25).

Conclusion

In conclusion, we presented the case of a 5-month-old girl with hypercalcaemia due to a compound heterozygous pathogenic variant in the *CYP24A1* gene. This narrative review provides valuable insights into the clinical presentation, diagnostic approach, and differential diagnosis, as well as initial management strategies for hypercalcaemia in childhood. Determining the aetiology of hypercalcaemia is critical for successful treatment, the prevention of (long-term) complications and ensuring favourable outcomes.

The authors declare that they have no conflict of interest.

Informed consent was obtained from the parents of the patient for the publication of this case report and subsequent narrative review.

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Hypoallergenic preparations based on synbiotics:

new survey among parents and healthcare professionals confirms positive experiences

Studies have shown that hypoallergenic formulas (eHF/AAF) containing synbiotics favour the intestinal microbiota of infants, which is particularly relevant to children with CMPA. [7, 9, 11, 12, 18] **There is consistent evidence of the positive effects of synbiotics on immunity-related outcomes.** [7,9,11,12,18]

This reduces the children's dependence on healthcare and improves the quality of life for both the child and the family. New data from a survey conducted among professionals and parents confirms the results of clinical and practical studies on the positive impact on immunity. Cow's milk protein allergy is one of the most common food allergies in early life1. Its clinical manifestations are extremely varied, but the gastrointestinal tract is most frequently affected (vomiting, reflux, diarrhea, constipation, bloody stools, abdominal pain), followed by the skin (skin rashes, swelling of the lips and eyelids) and the respiratory tract (wheezing, coughing). Allergy to cow's milk protein is either IgE-mediated, with symptoms generally present within an hour after ingestion, It has long-term adverse consequences on overall health and well-being, on the quality of life of the infant and his or her family, and even on the wider healthcare system [3].

When breastfeeding is not possible

Breastfeeding should always be encouraged [4]. The composition of breastmilk is nutritionally rich in macronutrients and micronutrients. It includes a large number of bioactive compounds that are essential for infant growth and development [5].

In the event of allergy, when breast-feeding is not possible, the option is to switch to hypoallergenic formulas (eHF/AAF). Preferably a formula that goes

Table: **Benefits of formulas containing synbiotics in cow's milk protein allergy.**

Medication use

- Reduction of asthma medication at one-year follow up [10]
- Less digestive tract medication [7]
- Fewer infants requiring antibiotics [7, 9]
- Lower use of dermatological medication [11]
- Fewer prescriptions, including for antibiotics and anti-infectives [1]

Infections

- Fewer infections and gastrointestinal infections [15]
- Fewer ear infections [11]
- Lower rates of infections [1, 16]

Gastrointestinal

- Reduction in constipation and dry stools [12]
- Improvements in the severity of abdominal pain, burping, flatulence and constipation [8]
- Improvements or disappearance of gastrointestinal symptoms (e.g. stooling, flatulence) [13]
- Improved stool consistency and colour, closer to those of healthy breastfed children [14]

Cutaneous and ocular

- Further improvement of atopic dermatitis [12*]
- Improvement of atopic symptoms, including rhinitis and tingling eyes [8]
- Improvement of skin symptoms (e.g. dryness, erythema) [13]

Hospitalisations

- Reduction in hospital visits and medications at six-months follow up [8]
- Fewer hospitalisations due to infections [17]

Respiratory

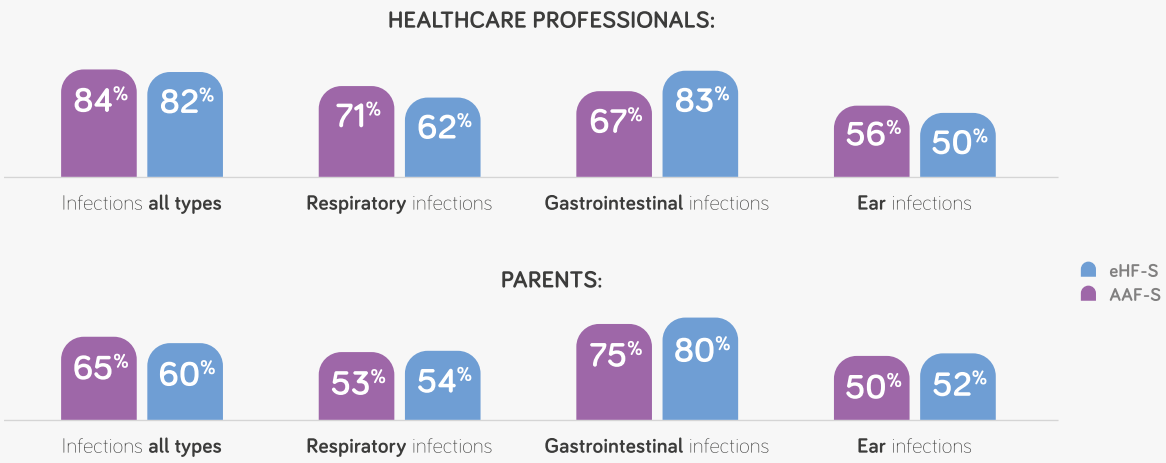
- Lower prevalence of asthma-like symptoms at one-year follow up [10]

Other

- Improvement in caregiver-reported quality of life [8]
- Improvement in the quality of life of children and parents [13]
- Lower rate of healthcare contacts [16]
- Potential healthcare cost-savings [1]

● eHF with short-chain galacto-oligosaccharides/long-chain fructo-oligosaccharides and Bifidobacterium breve.
● AAF with short-chain fructo-oligosaccharides/long-chain fructo-oligosaccharides and Bifidobacterium breve.
* Subgroup of children with IgE-associated atopic dermatitis.

Figure: **Percentage of parents and healthcare professionals observing a reduction in infections.**



eHF-S (formula extensively hydrolysed with synbiotics) / AAF-S (amino acid-based formula with synbiotics)

beyond the dietary treatment of allergy symptoms and contains ingredients that mimic the functions of certain bioactive components of breast milk, including synbiotics (combinations of prebiotics and probiotics).

The evidence - Clinical studies

To date, published research on hypoallergenic formulas, including extensively hydrolysed formulas containing synbiotics (eHF-S) and amino acid-based formulas (AAF-S), has shown them to have an excellent safety profile, to be well tolerated and to effectively support normal growth.[7,8] In addition, clinical studies have found that hypoallergenic formulas containing synbiotics are effective in cases of allergy and help restore the unbalanced microbiota of infants with an allergy9. Formulas containing synbiotics offer even more proven clinical benefits, as shown in the table below.

Opinions of professionals and parents

A survey of global experience of hypoallergenic formulas with synbiotics (eHF-S or AAF-S) was recently completed by 201 health professionals. These professionals included paediatricians, gastroenterologists, general practitioners, allergists and dieticians. 90 parents were also questioned about their experience of feeding their infants with these formulas. The survey took place in 6 countries: Australia, France, Germany, Spain, the United Kingdom and the United States. The aim was to verify whether this experiment reflected the data from randomised clinical trials (RCTs) and the results provided by "real-world evidence" (RWE) studies.

Results of the new user experience survey

In terms of reducing allergy symptoms, healthcare professionals reported high levels of acceptability (91%) with both types of formula. Among parents, the figure was 95%. More than 95% of parents whose children had been given another hypoallergenic formula as their first-line treatment recognised that formulas containing synbiotics were preferable to the previous formulas their child had been given.

They agree that they observed the expected improvement in allergy symptoms in their infant. The benefits of synbiotics go far beyond simply improving symptoms. Health professionals and parents reported an overall improvement in children's health, including a reduction in the number of infections among children and a reduction in the use of medication and health services. The figure summarises the professional and parent assessments, for eHF-S and AAF-S respectively.

In conclusion: confirmed benefits

Numerous randomised clinical trials (RCTs) and real-world evidence studies (RWEs) have been conducted into the benefits of hypoallergenic infant formulas containing synbiotics in the management of cow's milk protein allergy. The results of these studies showed improvements in gastrointestinal, respiratory and skin symptoms. What's more, they showed a reduction in the use of medication and healthcare, and a reduction in the number of hospital admissions, as well as an improvement in quality of life. This new assessment of the experiences of healthcare professionals and parents complements the data acquired through these studies. The health professionals were positive about their practical experience with eHF-S and/or AAF-S, and parents observed the expected improvement in the allergy symptoms of their infant.

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Vallecular Cysts as a Rare Cause of Failure to Thrive with Obstructive Breathing in Infants

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Keywords

Failure to thrive ; fibreoptic laryngoscopy ; infant ; upper airway obstruction ; vallecular cyst.

Abstract

A vallecular cyst is a rare cause of upper airway obstruction in neonates and infants. Symptoms include stridor, failure to thrive, obstructive breathing and respiratory distress. We present a case of a 2-month-old infant with poor weight gain and feeding difficulties. The diagnosis was initially missed due to a concomitant viral infection. The patient underwent transoral marsupialisation with complete resolution of symptoms. Vallecular cysts should be included in the differential diagnosis of children with stridor and dysphagia. Diagnosis is primarily by laryngoscopy. The preferred treatment is marsupialisation, which is less invasive than complete excision and has a low risk of recurrence.

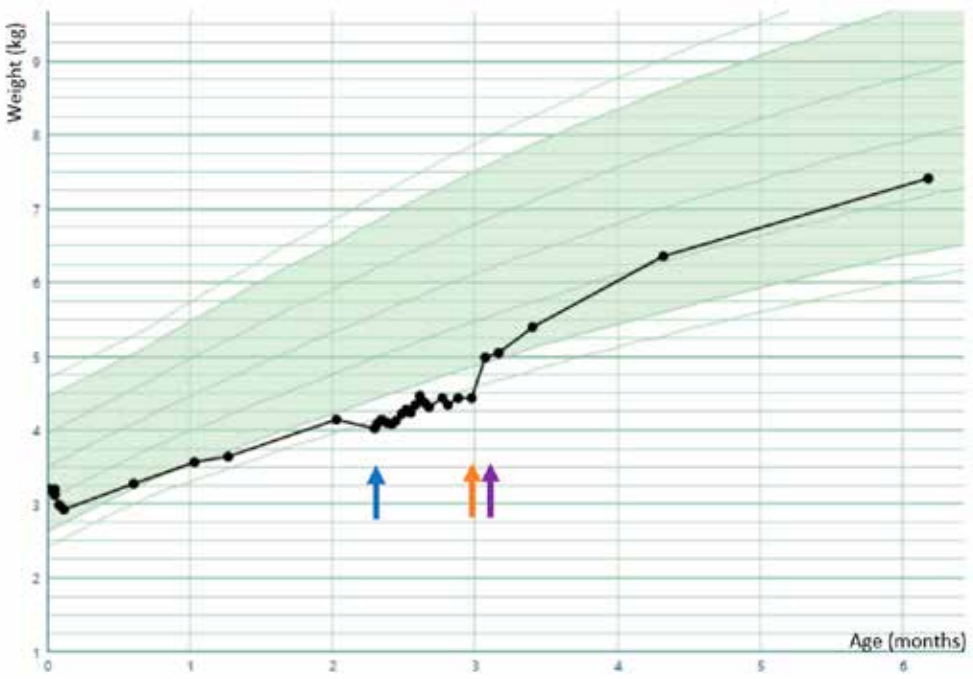
Introduction

A vallecular cyst is a unilocular cyst on the lingual surface of the epiglottis containing clear, non-infected fluid (1). Other terms used to describe the same lesion include mucus retention cyst, epiglottic cyst, base of tongue cyst and ductal cyst (2).They are thought to arise from obstructed ducts of submucosal glands in the vallecula (3). It is a rare cause of upper airway obstruction in neonates and infants. A vallecular cyst can cause stridor, dysphagia, failure to thrive, obstructive breathing, respiratory distress and, in rare cases, life-threatening upper airway obstruction (1, 4). The median age at diagnosis is one to two months, with a range of birth to 11 years reported in the paediatric literature (1, 4-7).The uncommon nature and often initially mild and non-specific symptoms often lead to delayed and misdiagnosis. We describe the case of an infant in whom the diagnosis was initially missed because of a concomitant viral infection thought to be responsible for the respiratory symptoms. Informed consent was obtained from the parents to publish the case.

Clinical report

A 2-month-old male infant presented to the paediatric outpatient clinic with poor weight gain and feeding difficulties since one month of age. The symptoms were previously attributed to cow's milk protein intolerance, for which a maternal diet was started. However, there was no improvement and the weight decreased from the standard deviation of -1 to -2 (Figure 1). He continued to drink very slowly and cried during feeding. When he returned to the outpatient clinic, he had a rhinitis and mild cough for a few days, with the appearance of diarrhoea. The mother had never reported any respiratory problems before. Clinically, we saw a thin, pale infant with signs of dehydration. He had nasal obstruction but no respiratory distress. He was admitted to hospital for additional tube feeding and oral rehydration solution to replace losses due to diarrhoea. A diagnosis of rhinovirus infection was made.

Figure 1: Growth chart.
Blue arrow: beginning of hospitalization, orange arrow: evacuation puncture, purple arrow: marsupialisation



However, he did not improve during hospitalisation but developed an obstructive breathing pattern with stridor. This was attributed to nasal congestion and viral laryngitis. Nasal decongestants and budesonide aerosols were started. However, the obstructive breathing worsened and weight gain remained suboptimal despite additional tube feeding. Episodes of desaturation with cyanosis were noted during drinking and deep sleep. Dexamethasone was given orally without improvement of stridor. The enteral feed was changed to an amino acid formula because of a suspected severe cow's milk protein intolerance (due to crying, convulsions, suboptimal weight gain and mild persistent diarrhoea). Additional investigations were carried out to search for an anatomical cause of the obstructive breathing.

Figure 2: Endoscopic view of the vallecular cyst during diagnostic laryngoscopy.

a: posterior displacement of the epiglottis (note: a nasogastric tube is in place), **b:** image of the cyst immediately before aspiration, **c:** image of the cyst at the end of the aspiration.

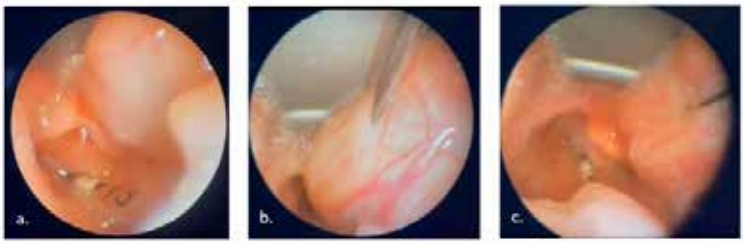
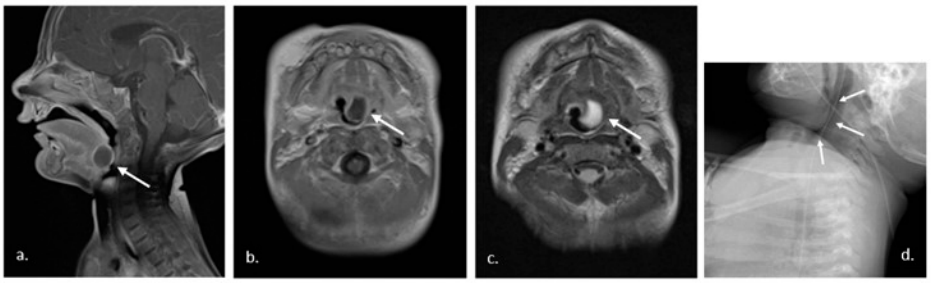


Figure 3: Radiologic findings

a-c: Magnetic resonance images (a : sagittal T1, b : coronal T1, c : coronal T2) showing a cystic mass at the left vallecula.
d: Lateral radiography showing a radiopaque mass in the laryngeal region.



Cardiac ultrasound showed no evidence of a vascular ring or arteria lusoria. An initial flexible laryngoscopy failed to show any evidence of laryngomalacia or laryngeal mass due to the presence of a nasogastric tube and poor cooperation. A lateral radiograph and barium oesophagography were reported as normal. Direct laryngoscopy under general anaesthesia revealed a cystic mass at the base of the tongue. A diagnostic evacuating puncture was performed with aspiration of 5 mL of clear fluid (Figure 2). Further radiological assessment by magnetic resonance imaging (MRI) was deemed necessary prior to removal of the cyst. Immediately after the evacuating puncture, an improvement in feeding technique and respiratory pattern was noted. The MRI showed a retention cyst of the left vallecula measuring 1.3-0.9m with a 50% reduction of the oropharyngeal surface (Figure 3 a-c). The thyroid gland had a normal appearance, so thyroid function tests were not performed. In retrospect, the cyst was already visible on the lateral radiograph (Figure 2d). Transoral marsupialisation was performed using a carbon dioxide (CO2) laser. Histopathology revealed a cyst lined by a non-keratinising stratified squamous epithelium. The patient left the hospital the following day with complete resolution of symptoms. Good weight gain was subsequently noted. Three months after the procedure, there has been no recurrence.

Discussion

A vallecular cyst is a rare cause of neonatal stridor, found in only 0.9-2% of infants with this presentation (6). Therefore, the condition is not always well known among paediatricians and ENT specialists and may be overlooked. It should be suspected when stridor is associated with failure to thrive, dysphagia and/or obstructive airway. Flexible laryngoscopy is the preferred primary screening technique in infants with stridor. The importance of good visualisation of the base of the tongue during the procedure should be emphasised. Often it is not possible to obtain a clear and reliable assessment with flexible endoscopy in infants. In this case, direct laryngoscopy under general anaesthesia should be performed to differentiate between laryngomalacia, subglottic stenosis, vocal cord paralysis, a laryngeal mass or a laryngeal web (6, 8). If the image is strongly suggestive of a vallecular cyst (a unilocular cystic mass on the lingual surface of the epiglottis containing clear fluid), it has been recommended to proceed immediately to direct laryngoscopy under general anaesthesia. The diagnosis can be confirmed by cyst puncture (1). The distinction between a solid and a cystic mass is not always immediately apparent on laryngoscopy and further investigations are required to differentiate between a thyroglossal duct cyst, dermoid cyst, adipose tumour, lymphangioma, haemangioma, lingual thyroid or teratoma before proceeding with therapy (1, 6).

Several investigations may contribute to the diagnosis. MRI is the preferred diagnostic modality, as it has the best ability to differentiate between the various laryngeal masses. However, it is sometimes difficult to obtain in a short period of time. Ultrasound is more readily available and can also differentiate well between cystic and solid masses. It can also confirm normal thyroid anatomy. However, it is important to remember that this examination is more operator dependent. The cystic mass can sometimes be seen on lateral radiographs, but these are difficult to interpret and do not allow differentiation between the different types of mass. Computed tomography cannot properly differentiate between a vallecular cyst, thyroglossal duct cyst, dermoid cyst, haemangioma and lymphangioma, all of which have a similar low-density appearance (6). Thyroid scanning should only be performed if the mass has a solid appearance and a normal thyroid position cannot be confirmed.

Associated conditions are found in a significant number of patients and should be considered in management strategies. In a retrospective chart review, 68/156 (43,6%) children with a vallecular cyst had concomitant laryngomalacia and 9/156 (5,8%) had gastroesophageal reflux (4). Another review found even higher figures, with two thirds of the children also having laryngomalacia, and one third having gastroesophageal reflux (7). Infants with laryngomalacia were younger at symptom onset, had more severe symptoms and were more likely to have residual symptoms after treatment. They were also more likely to be admitted to intensive care and to need mechanical ventilation (7).

There are several options for the surgical treatment of vallecular cysts, including needle aspiration, marsupialisation (deroofing) and complete excision. Simple needle aspiration has a high recurrence rate and is therefore not the preferred treatment (4).Marsupialisation is generally the preferred initial treatment option as it is less invasive than complete excision and has a low risk of recurrence. Marsupialisation can be performed using micro-instruments, electrocautery, coblation, KTP laser or CO2 laser. During the procedure, after marsupialisation, the larynx and epiglottic cartilage should be reassessed to diagnose concomitant laryngomalacia (4). In a retrospective study of 156 patients with vallecular cysts, only two patients had recurrence after marsupialisation (1.2%). Both children were over a year old. In older children, a thicker cyst wall

and more viscous cyst contents were observed, which may explain this increased risk of recurrence (4). Another study reported a recurrence rate of up to 15% (3/20) after marsupialisation, of which two patients required revision marsupialisation. The third patient was closely followed and showed no symptoms (3).In the event of recurrence, complete excision of the cyst can be performed transorally with a CO2 laser. In children with severe laryngomalacia (type I and II only) it has been suggested that supraglottoplasty be performed at the same time to improve the outcome of the operation (4).

Definitive diagnosis is made by pathological evaluation. Histopathology of the resected specimen shows an internal mucosal lining of non-keratinising squamous or respiratory epithelium and a fibrous wall (3).

Conclusion

A vallecular cyst is a rare cause of upper airway obstruction in neonates and infants. Clinical symptoms are similar to those of laryngomalacia, including stridor, failure to thrive, obstructive breathing and respiratory distress. Flexible laryngoscopy is the preferred primary screening technique, but has a high risk of missing the diagnosis. Therefore, direct laryngoscopy must be performed if the base of the tongue and larynx cannot be properly assessed. Several investigations can contribute to the diagnosis, with MRI being preferred as it has the best ability to differentiate between the various laryngeal masses. Many surgical treatments have been described, including needle aspiration, marsupialisation (deroofing) and complete excision. The preferred treatment is marsupialisation, which is less invasive than total excision and has a low risk of recurrence.

Conflicts of interest

None of the authors have a conflict of interest to disclose. No funding was received for this paper.

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Beckwith-Wiedemann Syndrome in a Three-Month-Old Child

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Keywords

Beckwith-Wiedemann syndrome ; macroglossia ; facial hemihypertrophy ; child.

Abstract

Beckwith-Wiedemann syndrome (BWS) is the most common pediatric overgrowth syndrome. The reported prevalence ranges from 1/10,000 to 1/13,700.

Most cases of BWS are sporadic with a recurrence risk of less than 1% in the family, but depending on the genetic mutation, the recurrence risk may be as high as 50%.

Patients with BWS have an increased risk of neonatal hypoglycemia and the development of embryonal tumors during childhood.

We present the case of a 3-month-old child who presented to the general pediatrics department with macroglossia and hemifacial hypertrophy. Molecular genetics revealed an abnormal methylation pattern at 11p15.5 region confirming the diagnosis of BWS.

Introduction

Beckwith-Wiedemann syndrome (BWS) is a complex medical condition characterized by a range of distinct clinical features. It is a genetic disorder marked by excessive tissue growth, predisposition to tumors, and congenital malformations.

The syndrome was first identified in 1963 by the American pathologist John Bruce Beckwith, who presented three postmortem cases exhibiting a range of anomalies including macroglossia, omphalocele, fetal corticoadrenal cytomegaly, renal medullary dysplasia, and visceromegaly. Concurrently, in 1964, the German geneticist Hans-Rudolf Wiedemann reported three siblings with similar clinical features, along with diaphragmatic anomalies and hypoglycemia (1).

This syndrome presents with typical manifestations, including neonatal hypoglycemia (present in 50% of cases), macroglossia, birth macrosomia, omphalocele, and anterior abdominal wall anomalies. Table 1 provides a summary of the frequency of major and minor manifestations observed in BWS (2) (5).

Table 1: Frequency of manifestations observed in Beckwith-Wiedemann Syndrome.

Clinical signs	Frequency
Macroglossia	90 %
Macrosomia	45 – 65 %
Ears anomalies (anterior earlobe creases or posterior helical ear pits)	63 %
Prenatal polyhydramnios	53 %
Facial nevus	52 %
Kidney anomalies	52 %
Neonatal hypoglycemia	30 – 60 %
Omphalocele	44 %
Visceromegaly	44 %
Umbilical hernia or diastasis recti	22 – 44 %
Hemihyperplasia	37 – 65 %
Embryonal tumor	8 %
Cardiac anomalies	13 %
Clef palate	3 %

The prevalence of this syndrome is low, estimated to be between 1/10,000 and 1/13,700 births. However, it is one of the most frequently encountered congenital overgrowth syndromes (3).

The overall prevalence is likely to be underestimated given the existence of undiagnosed individuals with milder phenotypes.

The majority of BWS cases are sporadic, with a recurrence risk of less than 1% within the family. However, depending on the genetic alteration (such as copy number variation at 11p15.5 or a *CDKN1C* pathogenic variant), the recurrence risk may be as high as 50% (4).

A greater prevalence of BWS has been observed in the population of children born through assisted reproductive technology (ART).It affects both boys and girls (5).

This genetic syndrome originates from an alteration in the expression of genes in the 11p15.5 region. This region encompasses two imprinting control regions: imprinting center 1 (IC1) and imprinting center 2 (IC2). Methylation occurs in the paternal allele of IC1 and in the maternal allele of IC2. Alterations in parental imprinting result in BWS (4). The clinical diagnosis is based on the association of at least 3 major criteria or 2 major criteria and 3 minor criteria (Table 2) (5).

Molecular analysis allows confirmation of the diagnosis (4).

Figure 1. Typical macroglossia of our patient with BWS

Table 2: Major and Minor Criteria Associated with Beckwith-Wiedemann Syndrome

Clinical signs	Minor Criteria
Major Criteria	
Abdominal wall defect : omphalocele or umbilical hernia	
Macroglossia	Pregnancy-related anomalies : polyhydramnios, hypertrophic placenta and/or thickened umbilical cord, threatened preterm labor
Macrosomia (birth weight greater than 90th percentile)	Neonatal hypoglycemia
Anterior lobe ear creases and/or posterior helical pits (bilateral or unilateral)	Port-wine stain
Visceromegaly of one or more intra-abdominal organs (liver, kidneys, spleen, pancreas, and adrenal glands)	Cardiac anomalies : cardiomegaly, cardiomyopathy
Embryonal tumor in childhood	Diastasis recti
Hemihyperplasia	Advanced bone age
Fetal adrenal cortex cytomegaly, typically diffuse and bilateral (pathognomonic)	
Renal anomalies (medullary nephrosclerosis)	
Family history of Beckwith-Wiedemann Syndrome	
Cleft palate	

Case report

A male infant was referred to the general pediatrics department at the age of three months due to macroglossia. (Figure 1). The infant was born at 31 weeks and 6 days of gestation, via vaginal delivery, following spontaneous rupture of the amniotic membrane, resulting in premature labor.

It was a dichorionic diamniotic twin pregnancy, resulting from in vitro fertilization with sperm donation. The patient is the second twin. Macrosomia had already been suspected antenatally, with no other ultrasound abnormalities observed.

The mother had pre-existing type 2 diabetes treated with insulin. At 27 weeks and 2 days gestation, she experienced threatened preterm labor, for which complete pulmonary maturation was performed.

At birth, the patient had a weight of 2360 grams (95th percentile), while his twin brother had a weight of 1820 grams. The patient was placed on non-invasive ventilation with continuous positive airway pressure for a period of two weeks due to the presence of hyaline membrane disease. His blood glucose levels remained within the normal range. However, he experienced feeding difficulties due to a large and asymmetrical tongue. Additionally a patent foramen ovale was identified, without hemodynamic repercussion. Hemihypertrophy gradually became apparent.

He was hospitalized at 3 months of age for a cyanotic spell in the setting of gastroesophageal reflux confirmed by pH-impedance monitoring. There have been no subsequent recurrences of spells.

The patient has a normal neurological development.

Tongue ultrasound and ophthalmologic examination were unremarkable. Abdominal ultrasound showed hepatomegaly without other organomegaly. Cardiac ultrasound revealed a structurally and functionally normal heart. Electrocardiogram was unremarkable. Laboratory tests (complete blood count, renal function, liver enzymes, coagulation, and thyroid function) were normal. Alpha-fetoprotein was 28.7 µg/L at the time of diagnosis confirmation when the patient was 10 months old.

Genetic testing included molecular karyotyping, which returned normal. Hypomethylation of IC2 at 11p15.5 confirmed the diagnosis of BWS.

The patient is currently 20 months old and has no major developmental abnormalities.

He experienced feeding difficulties related to macroglossia, which are now resolved. He has a growth delay with a weight below the 5th percentile. Alpha-fetoprotein was normalized (6.8 µg/L) at the last check-up (18 months old). Hepatomegaly remains stable on multiple ultrasound examinations. Macroglossia did not require surgical intervention.

Follow-up for this patient includes a multidisciplinary approach to monitor and manage potential complications associated with Beckwith-Wiedemann syndrome. Regular abdominal ultrasounds will continue every 3 months until 8 years of age to screen for abdominal tumors, particularly Wilms tumor and hepatoblastoma. Alpha-fetoprotein levels will be measured periodically until 4 years of age for early detection of hepatoblastoma. In addition, the patient will undergo regular assessments by a pediatric endocrinologist to monitor growth and metabolic parameters, and an orthopedic specialist will evaluate any progression of hemihypertrophy. Given the history of feeding difficulties, ongoing nutritional assessments and consultations with a dietitian are also planned. The patient's development will be closely monitored by a pediatric neurologist to ensure early intervention in the event of delays or abnormalities.

The patient's initial referral to the pediatrician was made by a stomatologist, who had identified and managed the macroglossia. A stomatologist will continue to play a crucial role in the follow-up care, with regular evaluations to monitor and address any dental or maxillofacial anomalies that may arise. This includes surveillance of the development of the teeth and jaw structure, as well as any necessary interventions to manage or correct abnormalities.

Discussion

Although rare, BWS remains the most common etiology of overgrowth with a prevalence of 1/10,000 to 1/13,700 births. This prevalence is increased in the population of children conceived through ART (6).

The severity of this condition correlates with the risk of hypoglycemia and the development of embryonal tumors (5 to 10% of cases), for which genotyping assists in screening (7).

In our case, there were no reported antecedents of BWS.

Epigenetic mechanisms play a key role in the regulation of gene expression. Genomic imprinting refers to the molecular processes that modulate gene expression depending on the parental origin of the gene. Several genes involved in embryonic and fetal growth are subject to genomic imprinting (8).

In the majority of cases, BWS results from epigenetic alterations that disrupt the parental imprinting of genes located at 11p15.5. These alterations are diverse, and some have been identified to be linked with different tumor risks (9).In our case, genetic analysis reveals hypomethylation of IC2 and a normal methylation of IC1 at the 11p15.5 locus.

The prevalence of BWS is increased in the population of ART children, as the methodologies used could have an influence on epigenetics (6). Prenatal genetic diagnosis is rarely performed because the majority of BWS cases occur sporadically. However, it can be beneficial in cases of

familial BWS with a known genetic alteration or when BWS is strongly suspected based on antenatal ultrasound findings (omphalocele, macrosomia, organomegaly, enlarged placenta, and polyhydramnios).

The challenge in establishing the diagnosis lies in the existence of milder forms, which may lead to delays due to certain clinical signs lacking pathognomonic features (8).

Patients with BWS have an increased risk of developing certain embryonal tumors, with Wilms tumor, neuroblastoma and hepatoblastoma being the most common (2). Precise identification of the genetic alteration can point towards certain tumors, mainly in case of paternal unidisomy 11p15.5 or hypermethylation of the imprinting center (4).

Surveillance is performed by abdominal ultrasounds. Other, less common tumors include rhabdomyosarcoma, and corticoadrenal carcinoma. The risk of these tumors is greatest in the first 8 years of life. Alpha-fetoprotein levels can be measured periodically up to 4 years of age for early detection of hepatoblastoma (4).

Multidisciplinary follow-up is recommended for patients with BWS.

When considering a diagnosis of Beckwith-Wiedemann syndrome, it is important to differentiate it from other overgrowth syndromes that may present with overlapping features. Differential diagnoses include Sotos syndrome, which is characterized by a distinctive facial appearance, advanced bone age, and learning disabilities; Simpson-Golabi-Behmel syndrome, which presents with congenital malformations and an increased risk of tumors; and Perlman syndrome, a rare condition associated with nephroblastomatosis and a high neonatal mortality rate. Other considerations might include mosaic overgrowth syndromes such as Klippel-Trénaunay syndrome, which involves vascular malformations and limb asymmetry, and Proteus syndrome, known for asymmetric overgrowth and skin abnormalities (5). Accurate genetic and clinical assessment is essential to differentiate BWS from these conditions, as management and surveillance strategies may differ significantly.

Conclusion

The diagnosis of BWS is challenging because of the existence of milder forms and because some clinical signs are not pathognomonic of the disease. However, it is essential to consider the condition because of its association with increased tumor risk. It requires an approach integrating clinical, genetic, and radiologic aspects. Close coordination between pediatricians, stomatologists, geneticists, radiologists, and other specialists is essential for optimal screening and management of patients with this syndrome.

Patient consent

Oral consent was obtained from the patient's parents for anonymized patient information to be published in this article.

Conflict of interest

The authors report no conflict of interest and no financial disclosures.

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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). Pour la liste complète des excipients, voir rubrique 6.1 du RCP complet. **FORME PHARMACEUTIQUE :** Suspension injectable. Suspension liquide blanche opalescente. **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 : Nourrissons de 2 à 5 mois[a]. Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** 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] - Primovaccination : Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** 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]. **Age lors de la première dose : Nourrissons de 6 à 11 mois. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose au cours de la deuxième année de vie avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 12 à 23 mois. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 2 à 10 ans. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • **Age lors de la première dose : Adolescents (à partir de 11 ans) et adultes*. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • [a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. - [b] En cas de retard, la dose de rappel ne devrait pas être administrée audelà de l'âge de 24 mois. - [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'autres doses 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, souscutanée 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. **Contreindications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **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 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 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 coadministré 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 hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. 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 gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : 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 musculosquelettiques 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 hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. Fréquence indéterminée : syncope ou réaction vasovagale 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 gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques 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. 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GSK

Brodie's Abscess in a 14-Year-old Boy. A Case Report

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Keywords

Brodie's abscess ; subacute osteomyelitis ; case report.

Abstract

We describe an adolescent boy who presented with insidious complaints of pain and swelling of the ankle and was subsequently diagnosed with Brodie's abscess of the distal tibia. From the literature we describe the prevalence, aetiology and management of this type of subacute osteomyelitis presenting as a bone abscess. The usual presentation is pain and swelling without fever and an insidious onset with elevation of C-reactive protein and other serum markers of inflammation in only a minority of patients. We aim to raise awareness of this subtle presentation, which is often associated with a significant delay in diagnosis.

Introduction

Brodie's abscess was first described by Sir Benjamin Collins Brodie in 1832 as a specific and rare form of subacute osteomyelitis, that presents as a collection of pus, usually affecting the metaphysis of long bones, most commonly the tibia (48.6%) followed by the femur (31.1%) (1, 2). It is more common in children and young adults and presents in an insidious manner (2-4). Pain is the most commonly reported presenting symptom (98%), followed by swelling (53%). Fever was reported in only 16% of the cases and serum markers of inflammation were mostly normal or slightly elevated (2-4). Staphylococcus aureus is by far the most common pathogen found (65%), however in 25% of the cases cultures remained negative (2). A systematic review showed an average time to diagnosis of 12 weeks (2). In the literature, possible aetiologies are often either not described or unclear, yet a history of minor trauma has been described in 25 out of 56 cases (2). Haematogenous spread appears to be the main cause of infection but is often difficult to prove due to the long delay in diagnosis (2). The diagnosis of Brodie abscess is confirmed by radiological imaging with X-ray, computed tomography (CT) or magnetic resonance imaging (MRI) and perioperative cultures (2-4). Surgery remains the cornerstone of the treatment and is usually followed by a prolonged course of antibiotics.. The outcome is usually favourable but is poorly documented in the literature.

Case report

A 14-year-old boy presented to the emergency department with a 1-week history of right ankle pain and swelling. There was no clear history of trauma, no local wounds or systemic symptoms.

Initial biochemistry revealed a mildly elevated C-reactive protein (CRP) of 32 mg/L [N≤5.0 mg/L]. Ultrasound showed extensive periarticular inflammation around the right ankle with a limited amount of intra-articular fluid. Treatment with systemic non-steroidal anti-inflammatory drugs (NSAIDs) was started for 2 weeks with a presumptive diagnosis of arthritis. During follow-up the patient had a maximum temperature of 38.0°C and a complete resolution of his symptoms was observed under the initiated therapy.

Figure 1: FMRI scan of the Brodie abscess in the right distal tibia with surrounding oedema and penetration of the growth plate.

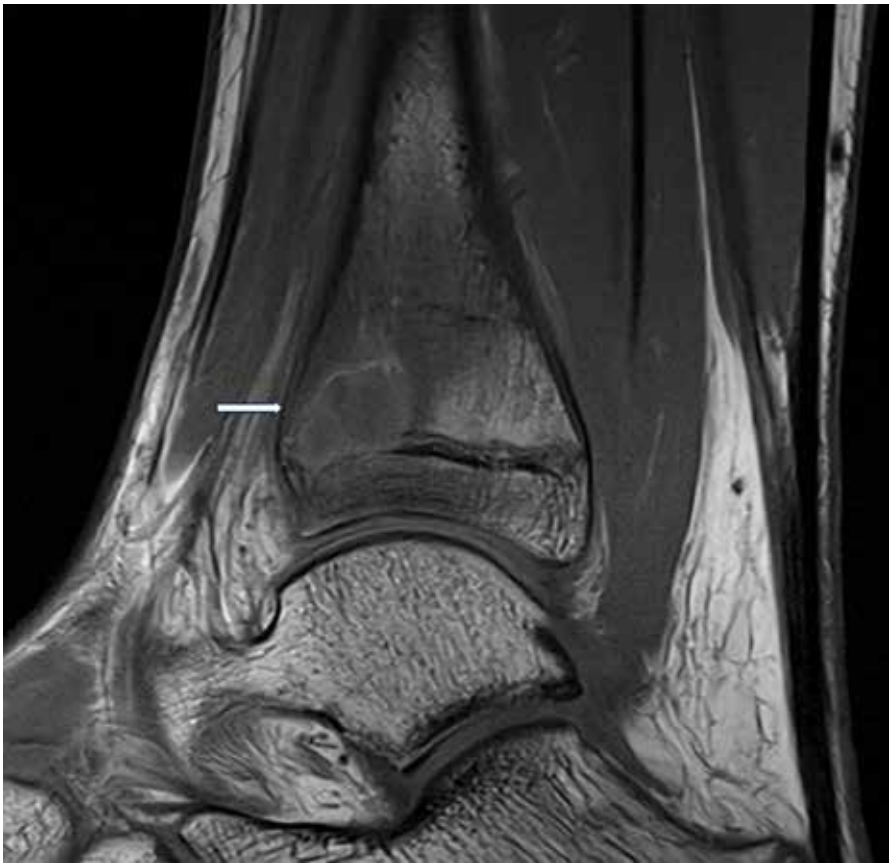
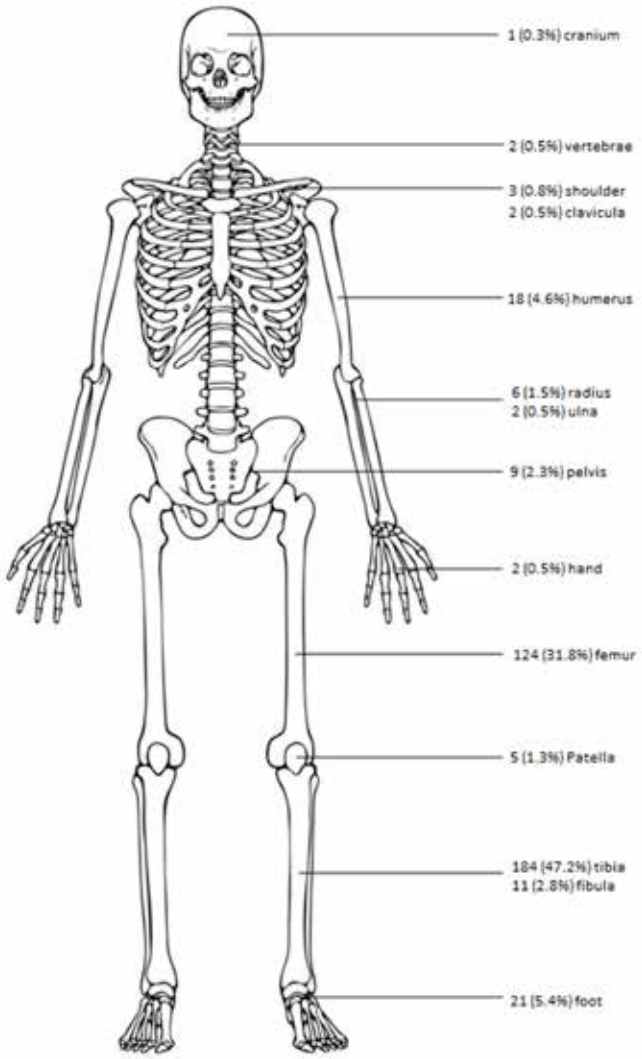


Figure 2: Brodie's abscess localisation reported in literature.



However, after discontinuation of the treatment, his symptoms rapidly returned. Following reassessment by the general practitioner, an MRI of the ankle was ordered. This confirmed the presence of a bone abscess in the right distal tibia with surrounding bone oedema, with extension into the growth plate and oedematous infiltration of the surrounding soft tissues (Figure 1). This confirmed the diagnosis of a Brodie abscess, for which elective surgical debridement was planned. After obtaining cultures, empirical antibiotic treatment was started with intravenous flucloxacillin. Perioperative cultures became positive for *S. aureus.* After 72 hours, treatment was switched to oral flucloxacillin and continued for 4 weeks. Given the patient's age, current height and the location in the distal tibia, the chances of a significant leg length difference were expected to be minimal.

Discussion

Epidemiology

Van der Naald et al. found that a Brodie abscess is more common in males (male: female ratio 2.1:1) with a median age of presentation of 17 years (2).

Aetiology

Brodie's abscess is usually defined as a collection of pus in bone after suspected haematogenous spread of bacteria, without a history of open trauma or surgery (2). As mentioned above, case reports have described recent minor trauma, leading to the hypothesis that bruising may increase the susceptibility of the affected bone to infection (2).

Diagnosis

As mentioned above, Brodie's abscess can be easily misdiagnosed due to its insidious onset with absent or mild systemic symptoms. Therefore, in the setting of atraumatic limb pain in children, clinicians should maintain a high index of suspicion. Rapid and accurate imaging is needed to avoid a major delay in diagnosis, with its possible complications (2, 3, 5). Therefore, in the setting of atraumatic limb pain in children, clinicians should maintain a high index of suspicion. Conventional radiography remains the most commonly used examination due to its high and easy availability (2). The lesion typically presents as a well-demarcated radiolucent lesion predominantly in the metaphysis of a long bone (Figure 2) (5). However, one has to be aware that it can take 10 to 21 days for an osseous lesion to become visible on conventional radiography, making it a poor diagnostic tool in the early stages of infection (5). In the case of an atypical presentation, diagnosis in the early stages or in difficult anatomical locations, CT-scans and/or MRI are required. MRI remains the most sensitive technique to evaluate Brodie's abscess, especially to differentiate this pathology from bone tumours (2, 5). T1-weighted images show a lower signal intensity than fatty bone marrow. CT scan is superior to conventional radiography and MR imaging for the detection of sequestra (5).

Treatment

The cornerstone of Brodie abscess treatment is surgical intervention (2, 6). The primary objective of debridement is to remove all infected and necrotic tissue, which is crucial for effective infection control and bone healing. Current practice recommends thorough surgical exploration and debridement before starting antibiotic therapy, so that cultures can be obtained for subsequent targeted antibiotic treatment.

Although there are reports for surgical treatment alone, the administration of antibiotics is often critical to the management of the bacterial infection (2). Empirical antibiotic therapy should be initiated based on the most frequently associated pathogens: *S. aureus*, methicillin-resistant *S. aureus* (MRSA), *Salmonella* spp., *Kingella kingae* and *Pseudomonas* spp. After obtaining cultures and antimicrobial susceptibility, antibiotic therapy should be tailored to the specific pathogen. However, in 25.6% of the cases no pathogen can be identified (Figure 3) (2). In these cases, PCR detection of *K. Kingae* cab be an additional diagnostic tool. Slinger et al. have already demonstrated its effectiveness in cases of septic arthritis with negative cultures (7).

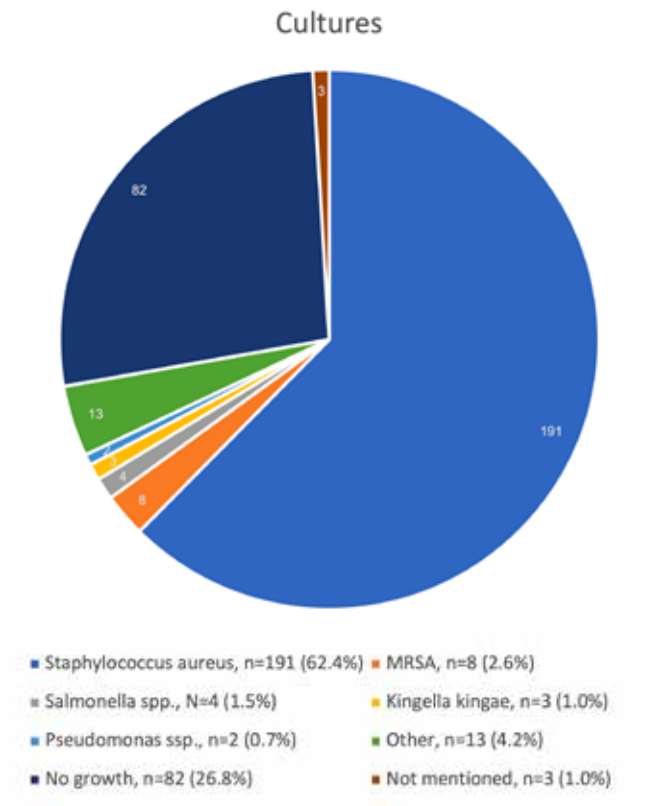
The optimal duration of antibiotic therapy for chronic osteomyelitis is poorly studied (2, 8). The available literature shows a wide range of duration of therapy, usually between 4 and 6 weeks, but one study even described a patient treated with antibiotics for over 2 years (6, 9). Intravenous versus oral antibiotic treatment of bone infections also remains a matter of debate. The duration of intravenous treatment for bone infections has shortened significantly over the years, and this does not seem to affect the rate of disease remission in case of susceptible pathogens (8). Further research is needed, yet for now, a personalised approach guided by clinical response and ongoing assessment is essential to optimize antibiotic therapy.

Follow up and prognosis

Follow-up visits are usually scheduled every few weeks to assess the healing process and any persistent symptoms, such as pain or swelling (2, 3). Conventional x-rays can be used for regular follow-up to assess the decreasing size of the bone lesion. CT or MRI scans can be used if indicated (5).

Overall a Brodie abscess has a very good prognosis but it can lead to several complications if not managed effectively.. These may include

Figure 3: Microbiological results of cultures from Brodie's abscess reported in literature.



chronic pain and mobility issues as the abscess can damage surrounding bone and soft tissue, or in some cases limb length discrepancy due to growth plate lesions (2).

Conclusion

In this case, the diagnosis of a Brodie abscess was made within 3.5 weeks of initial presentation, despite mild symptoms, through a rapid MRI analysis. The patient had an excellent recovery with no residual symptoms after surgery and tailored antibiotic treatment.

Take home message: as paediatricians we are familiar with the presentation of acute arthritis and osteomyelitis. However, this case highlights the need to consider the possibility of Brodie's abscess or subacute osteomyelitis in a child/adolescent presenting with atraumatic limb pain and subtle clinical symptoms, as a high index of suspicion is needed for diagnosis. Further research is needed, particularly regarding the optimal antibiotic treatment options.

The authors have no conflict of interest to declare.

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Fear-Anxiety-Phobia of the Dentist: Development and Analysis of a Federating Instrument about the Different Material and Behavioral Techniques for Ideal Patient Management: Clinical Studies

Joint PhD ULB-VUB presented on November 28, 2023 at the ULB, Brussels, Belgium

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Keywords

Dental anxiety ; behavior ; children.

Abstract

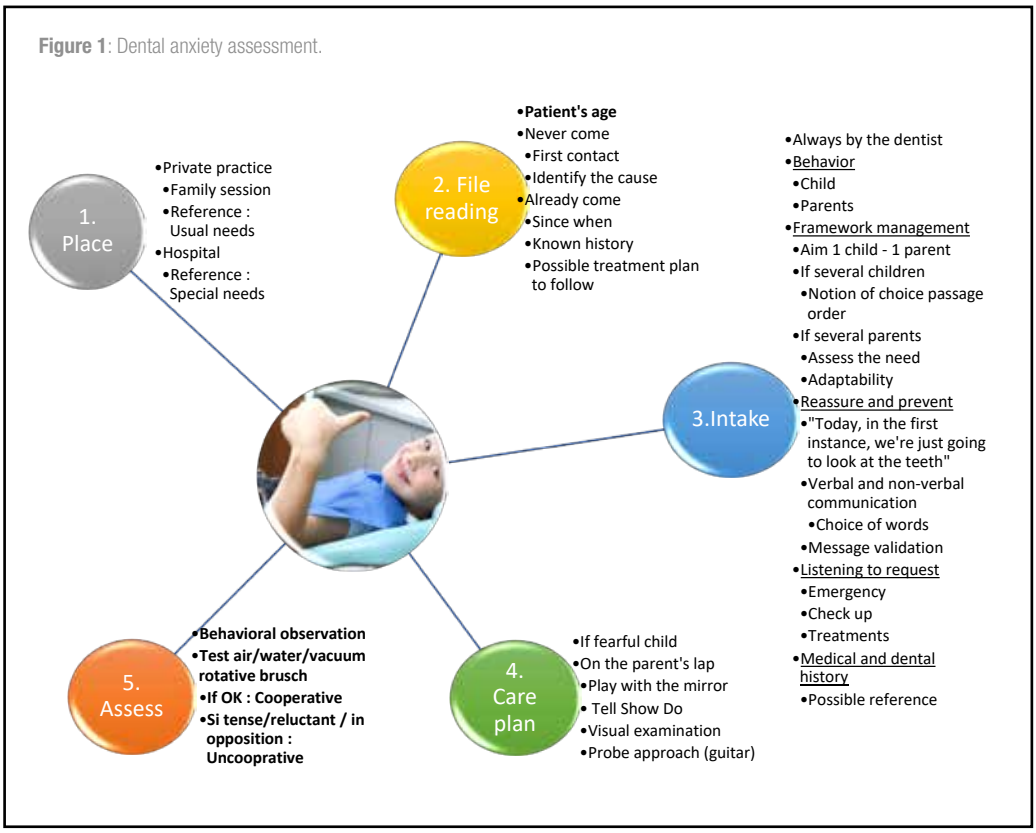
Dental anxiety remains an understudied problem, despite the fact that it is one of the major barriers to dental care for patients. The work done in this dissertation has brought to light several dimensions of this problem. "Do not frighten" is comparable to "Do no harm" in the Hippocratic oath. The specificity of the dentist, similar to the family doctor, is to maintain a long-term therapeutic relationship with his patients. It is up to us, dentists, to do everything we can to ensure a good therapeutic relationship. Other health care professionals should encourage patients to see a dentist early for preventive care before problems arise.

For many years, the concerns to improve dentistry have been of a technical nature: the management of dental pathologies and their complications. Then came the preservation of the tissues surrounding the tooth, periodontium conservation and biofilm management. In order to meet the technical requirements and to treat patients with the greatest possible comfort, the technologies were improved with more complex protocols. In just over a century, we have gone from the itinerant dentist to the modern dentist whose offices are equipped with a very high level of technology (1). In addition, pain management through the introduction of local anesthetics allows for very little or no pain (2). The psychological approach to care, on the other hand, has a much less visible place in teaching compared to the technological approach.

However, in spite of all these technological advances, a large part of the population still does not visit the dentist because of fear. In the epidemiological study commissioned by INAMI-RIZIV between 2012 and 2014, 18.1% of respondents stated that fear was one of the main reasons for avoiding dental care (3). This trend was described by Armfield in 2007 as a vicious circle: dental anxiety leads to the postponement of consultations, which leads to the worsening of lesions. These larger lesions require more extensive treatment and are therefore more difficult to tolerate, leading to an increase in patient dental anxiety (4).

The prevalence of moderate to high dental anxiety ranges from 13.1% to 19.8% of the population and dental phobia from 3% to 7.1%. It affects

Figure 1: Dental anxiety assessment.



all age groups and all regions of the world (5).

When patients enter the dental office, one of the first subjects to be addressed is anxiety: "I don't like the dentist", "Nobody likes going to the dentist", "Doctor, I'm scared", ... This fear is so common that it has become a part of habit, a part of the norm. It is quite possible for anyone to express their fear of going to the dentist.

Dental anxiety is still an under-researched problem, although it is one of the main obstacles for patients to go to the dentist. Through the work done in this dissertation, several dimensions of this problem have been brought to light.

Having more information about the stimuli of dental anxiety according to age allows the dentist to adapt his care. In a survey, we found that for 3 to 6 year olds, the representation of the acts that frighten them is more important than the act itself (seeing the syringe, seeing blood, etc.). From the age of 7 to 12, the pure representation is replaced by a mixture of sensations, probably due to their own experiences (tooth extraction, tooth decay, etc.). In adolescence, the procedure becomes more important than the local anesthetic. One item that was largely missing, however, was the dental dam item, with a percentage of missing data of 75% (6).

This observation confirmed the importance of highlighting a clinical observation felt by practitioners using the dental dam: the dam relaxes the patient. This system of dental operating field is a real asset in our practice, both technically and behaviorally. It helps both cooperative and non-cooperative patients. Significant results in patient relaxation have been achieved both awake and under conscious sedation. Unknown to patients and underutilized by practitioners, the dental dam is a very interesting tool that completes the therapeutic arsenal in the management of fear at the dentist (7).

Another very interesting tool is conscious sedation by inhalation of a mixture of nitrous oxide and oxygen (CS). Regardless of the system used, the observed success rate is very high (94.5%). This system deserves to be further developed because it represents a real improvement in patient care, regardless of the gas distribution system used (8).

However, this system is not suitable for all patients because it has limitations. It is a light sedation and the patients observed in the study corresponded to a population resulting from a preoperative consultation that allowed its indication. In order to better understand the profile of uncooperative patients, in rupture of care, a retrospective study was carried out to describe certain objective characteristics of these patients that could guide the practitioner towards one or the other therapeutic option. Young children presenting in CS are on average just over 4 years old and have an average caries index of 6.68, whereas young children presenting in general anesthesia (GA) are younger, less than 4 years old and have an average caries index of 11.97. Therefore, these patients often present with severe polycaries in early childhood (9).

As pediatric dentists, we have an important role to play in caring for these patients who are lost to care. The support we provide to these patients can have an impact on their dental future, as well as their overall health.

Figure 2: Decision tree for managing dental anxiety in children under 4 years old.

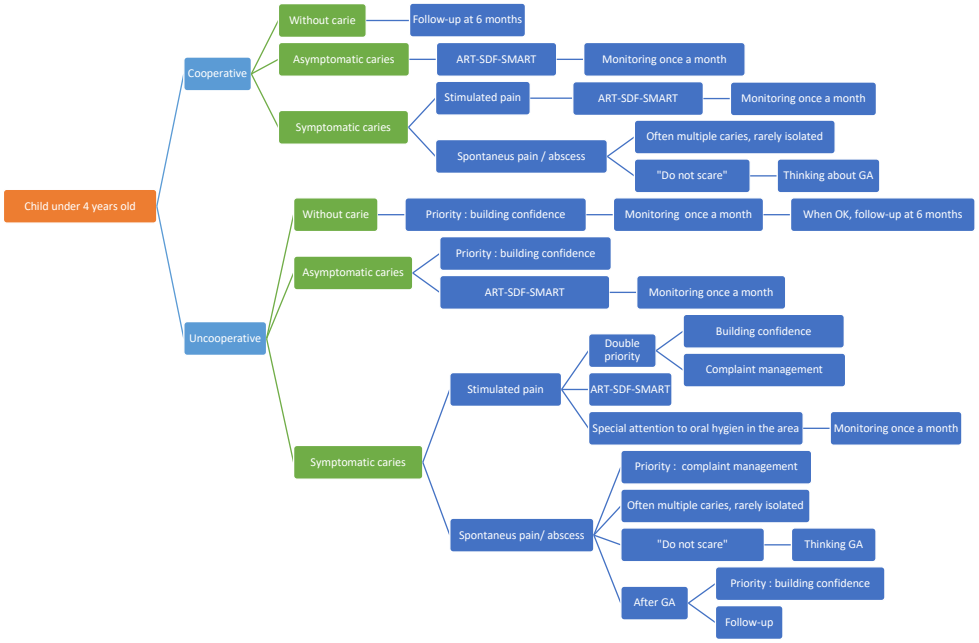
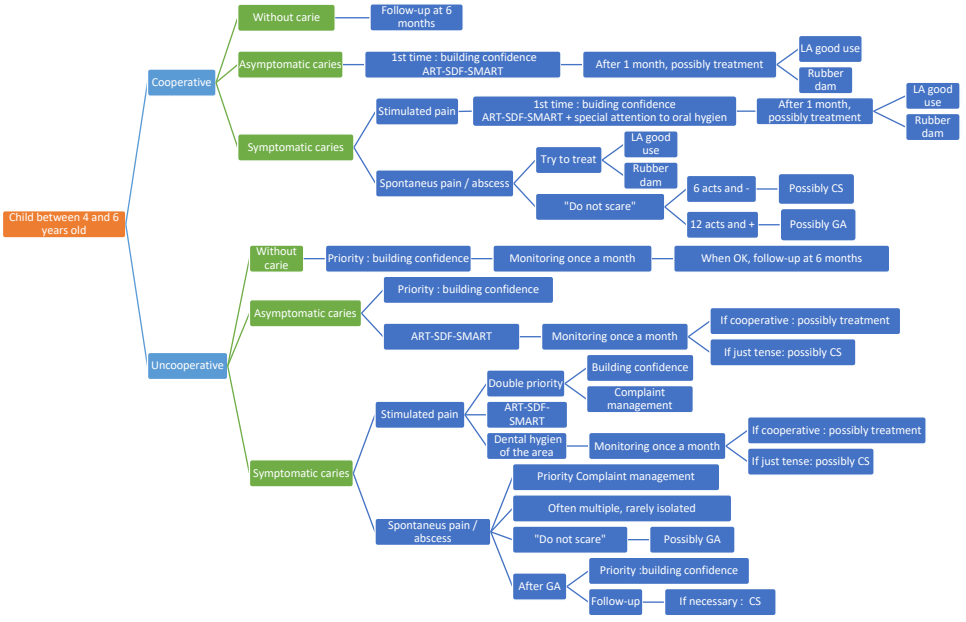


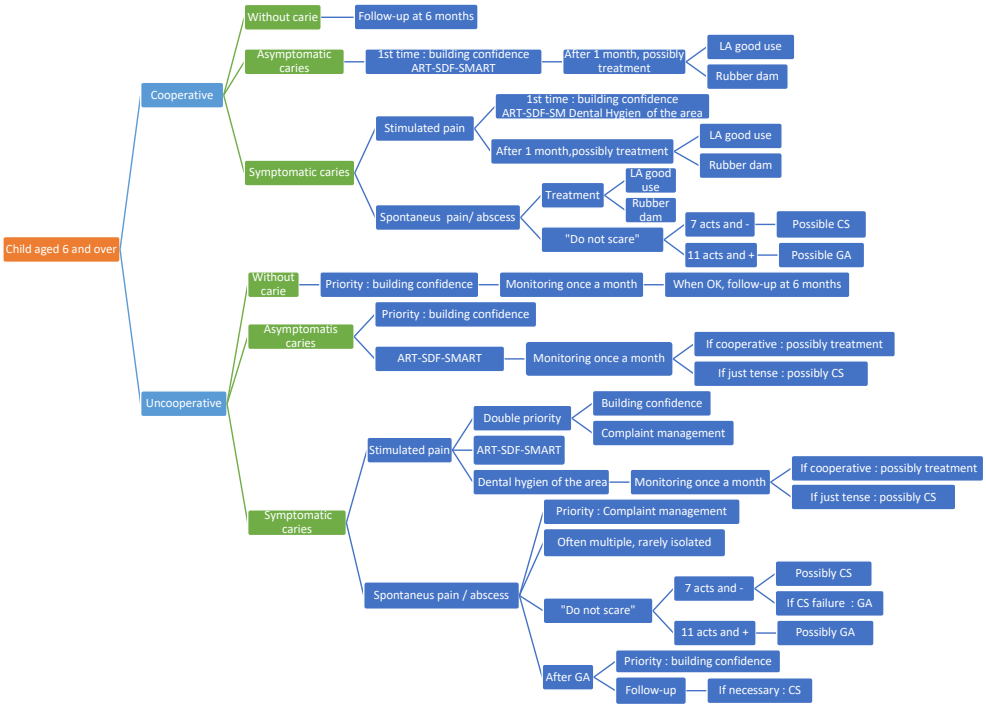
Figure 3: Decision tree for managing dental anxiety in children between 4 and 6 years old.



Pediatric dentistry is a teamwork that reaches its highest level when all participants in the therapeutic relationship are equally committed to the well-being of the patient. If the dentist and the patient are obvious members of this team, the parents are an essential and unavoidable part of the therapeutic triad.

We have many tools to evaluate patient behavior, but sometimes we lack a scale that allows us to measure exactly what we want. This was the case when we wanted to compare the behavior of the children with that of the accompanying parents. Analysis of the data from our study showed that a scale with important descriptors, such as the modified Venham scale and the corresponding scale we created for parents, is valid in the context of a scientific study by observers trained in its use, but less so by observers without sufficient training. In the context of daily practice, the use of a less detailed scale may provide better concordance (10).

Figure 4: Decision tree for managing dental anxiety in children aged 6 years and over.



Behavior is a good indicator in the choice of care for the child, but it is not everything. In fact, the therapeutic relationship that has been established is crucial to the choice. This choice is also influenced by the level of dental involvement, particularly in the case of multiple infections due to dental abscesses, which can lead to serious complications with repercussions on the patient's general health.

In all studies conducted, age is an important objective criterion. Cooperation, surgery time, and level of autonomy are directly related to the age of the patient. The older the child, the better he/she can understand the provided care, communicate with the practitioner, tolerate longer sessions and participate in his/her care. His autonomy also increases.

The different elements described in this thesis form a real therapeutic arsenal that can be considered as a unifying fear management tool accessible to any dentist. This tool allows the assessment of dental anxiety in the form of a mind map (Figure 1) and provides support for therapeutic choices in the form of 3 decision trees, one for each age group (Figure 2-4).

"Do not scare" is similar to "Do no harm" from the Hippocratic Oath. The specificity of the dentist, much like the family doctor, is to maintain a long-term therapeutic relationship with his patients. It is up to us, as dentists, to do everything we can to ensure a good therapeutic relationship. It is equally important that early dental care is promoted not only by dentists but also by other health professionals such as pediatricians, obstetricians, nurses and midwives.

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The Belgian Journal of Paediatrics (Belg J Paediatr) is the Official Journal of the Belgian Society of Paediatrics.

The Belgian Journal of Paediatrics publishes peer reviewed original research articles, review articles, short communications, case reports and images on all aspects of paediatrics. In addition, all official reports of the Belgian Academy of Paediatrics are published in the journal.

The Belgian Journal of Paediatrics aims to connect all Belgian paediatricians with stimulating, scientifically sound, peer-reviewed articles.

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When resubmitting a manuscript after review the authors should indicate clearly their responses to the reviewers' comments. A document in which the reviewers' comments are answered point by point should be provided with the revised manuscript and include a copy of the original manuscript with track changes displaying the changes made. All co-authors should approve the revised manuscript version. The corresponding author should confirm approval in the point-by-point answer document. All components of the manuscript (point-by-point response letter, clean revised manuscript, manuscript with track changes, figures, tables, etc.) must be resubmitted even if no changes have been made at revision. To submit a revision, go to https://belgjpaediatrics.com/index.php/bjp/login and log in as an Author. Your submission record can be found by clicking on "View" → "Revisions" → "Upload file".

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Corresponding authors will receive electronic page proofs to check the copy-edited and typeset article before publication. Portable document format (PDF) files of the typeset pages and support documents will be sent to the corresponding author by e-mail. It is the author's responsibility to ensure that there are no errors in the proofs. Changes that have been made to conform to journal style will stand if they do not alter the authors' meaning. Only the most critical changes to the accuracy of the content will be made, no substantial changes can be made at this point. The publisher reserves the right to deny any changes that do not affect the accuracy of the content. Proofs must be checked carefully, and corrections returned within 1 week of reception. Any errors found after this time will result in an erratum and not an article correction.

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Instructions for peer reviewers

Review of a submitted manuscript by at least two external and independent reviewers who are solicited by the editors. The reviewers' names will be blinded to the authors. Authors' identities are not blinded to the reviewers.

Reviewers should only agree if they feel qualified to review a manuscript and are able to return the review within a reasonable time-frame of maximum three weeks. If they cannot review, it is helpful to make suggestions for alternative reviewers.

Reviewers must refuse to review a manuscript in case of any potentially conflicting or competing interest.

Reviewers are requested to maintain confidentiality about the manuscripts and the information they contain.

Reviewers must provide a fair, honest, and unbiased assessment of the strengths and weaknesses of the manuscript. Reviewers should offer thoughtful suggestions to help authors enhance the quality of the manuscript, doing so in a respectful, constructive, and actionable manner.

Comments to the authors will be passed in full to authors. The reviewers can also provide additional confidential comments to the editors, which will not be passed to the authors.

If the reviewer has concerns about misconduct during the elaboration or submission of the manuscript, he must notify the editor. This also applies to the case where the reviewer notices important similarities between the manuscript and a published article.

Instructions for invited editors

Each year, a number of issues address a special chapter dedicated to a particular topic. Two guest editors, a Dutch-speaking and a French-speaking, are responsible for the content of these chapters.

A number of six manuscripts per chapter is expected. If more than six articles are needed to elaborate the topic of the chapter correctly, the editors can decide to spread the chapter over two issues.

The tasks of the invited editors are:

- To make choices of topics
- To invite authors
- To supervise the manuscripts in terms of content
- To protect the expected deadline for publication
- To write an editorial introducing the chapter

Editorial review and solicitation of peer reviewers will be done by the editorial team of the BJP.

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(nirsévimab)

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Prix remboursé (AO)	12.10 €
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NOUVEAU

Beyfortus® est remboursé pour les bébés dans le cadre de la prévention du VRS

Le pouvoir de réduire le chaos lié au VRS.

Beyfortus® est le **premier** anticorps direct à action prolongée conçu pour **tous les bébés**.[1]

Beyfortus® réduit le risque d'infections des voies respiratoires inférieures et **diminue les hospitalisations** liées au VRS avec un bon profil de **sécurité** et de **tolérance**.[1]

Une seule injection **protège durant toute la saison** de circulation du VRS.[1]

Scannez le QR code pour plus d'informations sur l'immunisation des bébés avec Beyfortus®.

▼ Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de la santé déclarent tout effet indésirable suspecté. Voir rubrique 4.8 pour les modalités de déclaration des effets indésirables. DÉNOMINATION DU MÉDICAMENT Beyfortus 50 mg solution injectable en seringue préremplie. Beyfortus 100 mg solution injectable en seringue préremplie. COMPOSITION QUALITATIVE ET QUANTITATIVE Beyfortus 50 mg solution injectable en seringue préremplie : Chaque seringue préremplie contient 50 mg de nirsévimab dans 0,5 mL (100 mg/mL). Beyfortus 100 mg solution injectable en seringue préremplie Chaque seringue préremplie contient 100 mg de nirsévimab dans 1 mL (100 mg/mL). Le nirsévimab est un anticorps monoclonal humain de type immunoglobuline G1 kappa (IgG1κ) produit dans des cellules d'ovaires de hamster chinois (CHO) par la technologie de l'ADN recombinant. Pour la liste complète des excipients, voir rubrique 6.1. FORME PHARMACEUTIQUE Solution injectable. Solution limpide à opalescente, incolore à jaune, de pH 6.0. INDICATIONS THÉRAPEUTIQUES Beyfortus est indiqué pour la prévention des infections des voies respiratoires inférieures dues au virus respiratoire syncytial (VRS) chez les nouveau-nés et les nourrissons au cours de leur première saison de circulation du VRS. Beyfortus doit être utilisé conformément aux recommandations officielles en vigueur. POSOLOGIE ET MODE D'ADMINISTRATION Posologie La dose recommandée est une dose unique de 50 mg administré par voie intramusculaire pour les nourrissons dont le poids est <5 kg et une dose unique de 100 mg administré par voie intramusculaire pour les nourrissons dont le poids est ≥5 kg. Beyfortus doit être administré avant le début de la saison d'épidémie à VRS, ou dès la naissance chez les nourrissons nés au cours de la saison d'épidémie à VRS. La posologie chez les nourrissons dont le poids est compris entre 1,0 kg et 1,6 kg est basée sur une extrapolation, aucune donnée clinique n'est disponible. L'administration du traitement chez les nourrissons de moins de 1 kg est susceptible d'entraîner une exposition plus élevée que chez les nourrissons pesant plus de 1 kg. Par conséquent, les bénéfices et les risques de l'utilisation du nirsevimab chez les nourrissons de moins de 1 kg doivent être soigneusement évalués. Les données disponibles sont limitées chez les enfants extrêmement prématurés âgés de moins de 8 semaines (âge gestationnel [AG] < 29 semaines). Il n'y a pas de données cliniques disponibles chez les nourrissons dont l'âge post-menstruel (âge gestationnel à la naissance + âge chronologique) est inférieur à 32 semaines (voir rubrique 5.1). Chez les nourrissons devant subir une chirurgie cardiaque avec circulation extracorporelle, une dose supplémentaire peut être administrée dès que le nourrisson est stable après l'intervention, afin de garantir des taux sériques de nirsévimab adaptés. Si l'intervention a lieu dans les 90 jours suivant l'administration de la première dose de Beyfortus, la dose supplémentaire doit être de 50 mg ou 100 mg selon le poids. Au-delà de 90 jours, la dose supplémentaire peut être une dose unique de 50 mg indépendamment du poids, afin de couvrir le reste de la saison de circulation du VRS. Il n'y a pas de données disponibles sur la sécurité et l'efficacité d'une administration répétée. La sécurité et l'efficacité du nirsévimab chez les enfants âgés de 2 à 18 ans n'ont pas été établies. Aucune donnée n'est disponible. Mode d'administration Beyfortus doit être administré uniquement par voie intramusculaire. Il doit être administré par voie intramusculaire, de préférence dans la partie antérolatérale de la cuisse. Le muscle fessier ne doit pas être utilisé systématiquement comme site d'injection en raison du risque de lésion du nerf sciatique. Instructions relatives à l'administration Beyfortus est disponible sous la forme d'une seringue préremplie de 50 mg et d'une seringue préremplie de 100 mg. Vérifier les étiquettes collées sur l'emballage extérieur et sur la seringue préremplie pour vous assurer d'avoir choisi la présentation correcte requise de 50 mg ou de 100 mg. Seringue préremplie de Beyfortus 50 mg (50 mg/0,5 mL) avec tige de piston violette. Seringue préremplie de Beyfortus 100 mg (100 mg/1 mL) avec tige de piston bleue clair. Étape 1 : En tenant le Luer Lock d'une main (éviter de tenir la tige du piston ou le corps de la seringue), dévisser le capuchon de protection de la seringue en le tournant dans le sens antihoraire avec l'autre main. Étape 2 : Fixer une aiguille sur la seringue préremplie en tournant délicatement l'aiguille, dans le sens horaire sur l'embout Luer Lock de la seringue préremplie, jusqu'à rencontrer une légère résistance. Étape 3 : En tenant le corps de la seringue d'une main, tirer délicatement sur le capuchon protecteur de l'aiguille avec l'autre main pour l'enlever. Ne pas tenir la tige du piston pendant le retrait du capuchon protecteur de l'aiguille, au risque de déplacer la butée en caoutchouc. Ne pas toucher l'aiguille et ne pas la mettre en contact avec une surface. Ne pas remettre le capuchon protecteur sur l'aiguille et ne pas retirer l'aiguille de la seringue. Étape 4 : Administrer tout le contenu de la seringue préremplie en injection intramusculaire, de préférence dans la face antérolatérale de la cuisse. Le muscle fessier ne doit pas être utilisé systématiquement comme site d'injection en raison du risque de lésion du nerf sciatique. CONTRE-INDICATIONS Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1. EFFETS INDÉSIRABLES Résumé du profil de tolérance L'effet indésirable le plus fréquent était les éruptions cutanées (0,7 %) survenues dans les 14 jours suivant l'administration. La majorité des cas étaient d'intensité légère à modérée. De plus, une pyrexie et des réactions au site d'injection ont été rapportées à un taux respectif de 0,5 % et 0,3 % dans les 7 jours suivant l'administration. Les réactions au site d'injection étaient non graves. Liste des effets indésirables La liste ci-dessous présente les effets indésirables rapportés chez 2 966 nourrissons nés à terme et prématurés (AG ≥29 semaines) ayant reçu du nirsévimab dans le cadre d'essais cliniques. Les effets indésirables rapportés au cours des essais cliniques contrôlés sont répertoriés par classe de systèmes d'organes (SOC) MedDRA. Au sein de chaque SOC, les termes préférentiels sont présentés par fréquence décroissante puis par gravité décroissante. La fréquence de survenue de chaque effet indésirable est définie 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) et fréquence indéterminée (ne peut être estimée à partir des données disponibles). Affections de la peau et du tissu sous-cutané • Peu fréquent - Eruptions cutanées1 1 L'éruption cutanée était définie par les termes préférentiels groupés suivants : rash, rash maculopapuleux, rash maculeux. Troubles généraux et anomalies au site d'administration • Peu fréquent - Réaction au site d'injection2 ; Pyrexie 2 La réaction au site d'injection était définie par les termes préférentiels groupés suivants : réaction au site d'injection, douleur au site d'injection, induration au site d'injection, oedème au site d'injection, gonflement au site d'injection. Nourrissons avec un risque plus élevé d'infection sévère par le VRS La sécurité d'emploi a également été évaluée dans l'essai MEDLEY chez 918 nourrissons à risque plus élevé d'infection sévère par le VRS, dont 196 très grands prématurés (AG <29 semaines) et 306 nourrissons porteurs de maladie pulmonaire chronique ou d'une cardiopathie congénitale hémodynamiquement significative pendant leur première saison d'épidémie à VRS, qui ont reçu du nirsévimab (614) ou du palivizumab (304). Le profil de sécurité était comparable à celui du comparateur palivizumab et cohérent avec le profil de sécurité chez les nourrissons nés à terme et prématurés d'AG ≥29 semaines (essais D5290C00003 et MELODY). Immunogénicité Comme avec toutes les protéines thérapeutiques, il existe un potentiel d'immunogénicité. Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via : Belgique: Agence Fédérale des Médicaments et des Produits de Santé – Division Vigilance – Boîte Postale 97 – 1000 Bruxelles Madou – Site internet: www.notifieruneffetindesirable.be – e-mail: adr@afmps.be Luxembourg: Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé – Site internet : www.guichet.lu/pharmacovigilance TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly, France NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ EU/1/22/1689/001 50 mg, 1 seringue préremplie à usage unique EU/1/22/1689/002 50 mg, 1 seringue préremplie à usage unique avec aiguilles EU/1/22/1689/003 50 mg, 5 seringues préremplies à usage unique EU/1/22/1689/004 100 mg, 1 seringue préremplie à usage unique EU/1/22/1689/005 100 mg, 1 seringue préremplie à usage unique avec aiguilles EU/1/22/1689/006 100 mg, 5 seringues préremplies à usage unique DATE DE PREMIÈRE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION Date de première autorisation: 31 octobre 2022 DATE DE MISE À JOUR DU TEXTE Date d'approbation : 11/2023 Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu

Référence:
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