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Use of complementary and alternative medicine in children with asthma

To the Editor:

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation and accompanied by respiratory symptoms such as wheezing, shortness of breath, chest tightness, coughing, and airflow limitation that vary over time and in intensity.¹ The goals of asthma therapy are to achieve optimal symptom control, to prevent asthma exacerbations, and to reduce airflow limitation and the side effects of treatment. The majority of asthma patients achieve the status of clinically controlled asthma with specific interventions, that is, inhaled corticosteroids (ICS), short- or long-acting beta₂ agonists, and leukotriene receptor antagonists.¹ Due to the chronic nature of asthma, children and adolescents with asthma and their families may turn toward complementary and alternative medicine (CAM). The World Health Organization (WHO) has defined CAM as a "broad spectrum of healing methods which are not part of the country's tradition".² Knoeller and colleagues have recently reported an association between CAM usage and poor asthma control among adults with work-related asthma.³ The results highlight the importance of assessing the extent of CAM usage among asthmatic patients; as such usage might potentially diminish the adherence to evidence-based recommendations or even replace standard care. The aim of this study was therefore to assess the use of CAM among children and adolescents who have been diagnosed with asthma and to discover whether parents confer with their doctor about using CAM.

Our study included children between >6 and <18 years of age who had been diagnosed with asthma by a doctor according to current guidelines of the Global Initiative of Asthma (GINA) and with written informed consent by the parents and children.¹ The asthma diagnosis was based on symptoms (wheeze, shortness of breath, chest tightness, and cough) with an asthma-specific pattern (ie, generally ≥1 symptom; variability over time and in intensity; and worse at night or on waking; triggered by exercise, allergens, and viral infections) and a confirmed variable expiratory airflow limitation.¹ Exclusion criteria were as follows: pre-term delivery (<37 weeks); no active/passive

understanding of German; known inborn or perinatal pulmonary disease or airway malformation (ie, diagnosis of cystic fibrosis; primary ciliary dyskinesia; heart failure; and interstitial lung disease); oxygen therapy after birth for a duration of more than 24 hours; and ventilator support or mechanical ventilation after birth. Clinical examination was performed by a doctor (A.H. or M.V.K.). A standardized questionnaire, which was adapted from "The International Study of Asthma and Allergies in Childhood" [ISAAC] questionnaire, was used to collect information on asthma status, respiratory and atopic symptoms, infections, sociodemographic variables, and use of medication over the past twelve months. A routine lung function test using spirometry and plethysmography was performed to assess limited airway function (MasterScreen Body, Care-Fusion, Wuerzburg, Germany). Assessments of airway inflammation were performed using fractional exhaled nitric oxide (FENO; NO Vario Analyser, FILT GmbH, Germany) measurement. Assessment of asthma control status was based on symptoms (daytime symptoms, if yes = 1 point; symptoms at night = 1 point), limitation of any activities due to asthma (1 point) and use of rescue medication, as suggested by the GINA guidelines.¹ "Well controlled" asthma was defined as none of these symptoms, "partly controlled" as 1-2 and "uncontrolled" as 3-4 points on this scale. For statistical analysis, Fisher's exact test for categorical data and Mann-Whitney *U* test were applied. *P*-values <.05 were considered to be statistically significant.

We invited *n* = 163 children and their parents and recruited *n* = 147 asthmatics (response rate 90.2%; 63.1% males; age 9.9 years; SD ± 4.4 years). Among the participants, *n* = 35 used CAM (23.8%; CAM+) and 112 did not (CAM-). Multiple answers were possible. Classical homeopathy (*n* = 28 out of 64 nominations; 43.8%), Schüssler salts (*n* = 14; 21.9%), osteopathy (*n* = 9; 14.1%), and bioresonance (*n* = 6; 9.4%) were the most commonly used CAMs, followed by acupuncture (*n* = 3; 4.7%), traditional Chinese medicine (*n* = 2; 3.1%), kinesiology (*n* = 1; 1.6%), and other, non-specified CAMs (*n* = 1; 1.6%). Only 54% (*n* = 19) reported that they had talked with their doctor about the use of CAM. We then

TABLE 1 Comparison of clinical and sociodemographic variables of children with doctors diagnosed asthma using CAM (CAM+) and not using CAM (CAM−)

	CAM+	CAM−	P-value
N (%)	35 (23.8)	112 (76.2)	
Males (n, %)	23 (65.7)	69 (61.6)	.667
Age (years; mean, SD)	9.91 (+4.69)	9.95 (+4.33)	.982
Height (cm; mean, SD)	131.85 (+29.09)	132.83 (+26.76)	.799
Weight (kg; mean, SD)	34.25 (+19.7)	38.89 (+32.15)	.433
FEV 1% predicted (mean, SD)	99.1 (+15.2)	95.76 (+13.9)	.446
FeNO (ppB; mean, SD)	26.3 (+23.2)	24.4 (+22.8)	.35
Use of ICS (n, %)	19 (54.3)	55 (49.1)	.69
Asthma status: controlled (n, %)	18 (51.4)	55 (49.1)	.924
Additional atopic comorbidities (n, %)	22 (62.9)	61 (54.5)	.368
Positive family history for asthma (n, %)	15 (42.9)	55 (50.9)	.82
Age of the mother (years; mean, SD)	41.03 (+6.03)	39.77 (+7.07)	.413
Age of the father (years; mean, SD)	44.97 (+7.32)	45.32 (+7.1)	.802
Educational level ^a (mean, SD)	6.17 (+1.6)	4.33 (+2.2)	<.001
Origin			.005
Both parents from Germany (n, %)	32 (91.4)	96 (85.7)	
Mother or father from Germany (n, %)	3 (8.6)	10 (8.9)	
Both parents not from Germany (n, %)	0	5 (4.5)	

SD, standard deviation; ppB, parts per billion.

^aEducational level: The "educational level" was calculated based on the cumulative school-leaving qualification of father and mother: 0 = no school-leaving qualification; 1 = junior high school; 2 = secondary compulsory education; 3 = vocational baccalaureate diploma; and 4 = graduation baccalaureate diploma.

compared children with asthma who used CAM with children with asthma who did not (Table 1). There was no difference between the two groups with respect to age, gender, asthma control status, lung function, FENO, atopic comorbidity, or the use of ICS. However, parents of children with asthma who used CAM had a significantly higher level of education, and more were of German descent. We asked the supporting pediatricians to estimate how many of their asthmatic patients used CAM. Overall, *n* = 45 pediatricians supported our study population of *n* = 147 asthmatics, with *n* = 21

(46.6%) responding to our questionnaire. The respondents estimated that an average of 26.6% of their patients with asthma used CAM, and 25.6% of the patients had talked to them about CAM use.

In our study population, which included asthmatic children in Luebeck, Germany, nearly every fourth family (23.8%) reported using CAM. Of these, only half of the families had talked to their doctor about using CAM. The most obvious factors associated with using CAM compared to not using CAM were a higher level of education among the parents and the origin of the parents from Germany. We identified no other determinants associated with the use of CAM, that is, asthma control status, use of ICS, or gender.

Published data about the use of CAM show a wide variability, which might mirror cultural influences and different national backgrounds. Moreover, other studies have used different definitions of CAM. The reported prevalence of use among pediatric cohorts has ranged from 13% to 66%.^{4,5} We therefore aimed to collect data from our own outpatient department and to compare the results with those of other countries. In the United States, for example, a very similar proportion of 26.7% of children with asthma reported CAM use, with breathing techniques (58.5%), vitamins (27.3%), and herbal products (12.8) being the three most commonly used therapies.⁶ However, in contrast to our findings, the authors of this study observed that children with poorly controlled asthma are more likely to use CAM, even when their parents' education was checked as a potential factor. This might be due to differences in our health-care systems, which provide different access to medical resources. Similarly, in a population-based study among adult asthmatics from Canada, 36.8% reported CAM use over the last 12 months. Again, uncontrolled asthma, as well as female gender, was associated with a higher likelihood of using CAM in this population. The most popular CAM again comprised breathing exercises (17.7%), herbal medicines (10.1%), and vitamins (9.7%), while homeopathy was used by only 3.3%.⁷ The prevalence of CAM use among asthmatic children in Canada in a slightly younger study population was 13%,⁴ with supplementary vitamins (24%), homeopathy (18%), and acupuncture (11%) as the preferred CAMs. Children younger than six, those of Asian origin, and children with poor asthma control were associated with a significantly increased likelihood of using CAM.

Our study has several strengths, but also some limitations. Asthma diagnosis and control status were highly standardized according to the current GINA guidelines¹ and thoroughly assessed by two doctors, who performed the physical examination and interpreted the lung function measurements. The participation rate of 90% was high, reducing the risk of selection bias. Information about asthma symptoms and medication intake was obtained by one and the same study nurse, who also performed the lung function testing. However, the data about CAM usage were based on self-reports in the questionnaire and are therefore subject to recall bias. We provided seven pre-specified examples of CAMs to our patients to increase the accuracy of the received information. Therefore, individuals might be less likely to report alternative forms of CAMs not listed in our questionnaire, which might result in a slightly under-reported number of CAM users.

Despite these limitations, our findings have important clinical implications. The benefit of CAM for asthma patients is uncertain. Systematic reviews of CAM for asthma showed “no evidence” (chiropractic and kinesiology), “not enough evidence” (acupuncture and homeopathy), or “somewhat promising but insufficient evidence” (herbal medicine and breathing techniques) [reviewed by⁸]. Therefore, the side effects and possible drug interactions of CAMs have to be addressed. This is of particular importance regarding the use of herbal medicine, which might in some cases interact with the prescribed drugs or cause hepatotoxicity.⁹ However, adverse effects were also noted after the use of some homeopathic drugs that evidently were not produced respecting the rules of good manufacturing practice. In a systematic review, Posadzki reported allergic reactions, intoxications, and even four fatalities following homeopathy.¹⁰ The US Food and Drug Administration has recently announced that its “laboratory analysis found inconsistent amounts of belladonna (...) in certain homeopathic teething tablets, sometimes far exceeding the amount claimed on the label,” and warned that tablets containing belladonna “pose an unnecessary risk to infants and children” [https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm538684.htm (visited on 30th of November 2017)].

Besides these potentially adverse effects, the indirect risk of using CAM is an additional health issue. Besides patients who are using CAM as an adjuvant therapy, this might lead in some CAM users to replace their conventional treatment, leading to loss of asthma control, reduced lung function, and increased asthma exacerbation. However, our use of a cross-sectional design did not allow us to assess prospectively the role of CAMs in changes to asthma control.

We conclude from our data that an open, unprejudiced discussion about the use of CAM among asthmatic children and adolescents is important to improve compliance and adherence.

We observed that CAM use among the German population is strongly associated with parents with a high level of education and is particularly prevalent among parents of German origin. Doctors should routinely ask their patients about the use of CAM in every consultation.

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CONFLICT OF INTEREST

Author MVK has received a speaker honorarium or consultant fees from the following companies: Abbvie, ALK-Abello, Allergopharma, Chiesi, Infectopharm, Meda, Novartis Pharma, and Nutricia. Author IR, MHE, and AH declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Written Informed consent was obtained from the parents of all individual participants included in the study.

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Tolerability and palatability of donkey's milk in children with cow's milk allergy

To the Editor,

The therapy of cow's milk allergy (CMA) consists of eliminating cow's milk protein from cow's milk (CM)-allergic children's diet.¹ They consequently need a milk substitute that should ideally be hypoallergenic, not cross-reactive with CM, palatable and nutritionally adequate. The selection of formula depends on the clinical manifestations of the CMA. The current guideline² extensively recommends hydrolysed formulas (eHFs) as a first choice of IgE-mediated CMA treatment except for cow's milk (CM) anaphylaxis where free amino acid formulas (FAAFs) are preferred over eHF. Unfortunately, eHFs and FAAF are hampered by their unpleasant taste.

Soya bean formulas are easily available and have an acceptable taste. However, they are not recommended as a first choice for CMA treatment, especially in infants under the age of 6 months with gastrointestinal symptoms because of the risk of sensitization over time.³

The possibility of using milk from other mammalian species for children with CMA has been examined: Goat's milk (GM) and sheep's milk are contraindicated due to cross-reactivity between their proteins and cow's milk proteins.⁴

Donkey's milk (DM) appears to be promising as an alternative: it has been used in clinical studies of children with CMA and it has been found to be well tolerated, providing both nutritional adequacy and good palatability⁵⁻⁷ although the limit is its high cost.

The aim of our study was to assess the clinical tolerability and palatability of DM in children with CMA.

Seventy children (45 males, 25 females; age-range 6 months-18 years, mean age 5.2 ± 5.3 years), referred to the Allergy Unit of Anna Meyer Children's Hospital of Florence, Italy, with a proven CMA were recruited from 1 February 2015 to 31 October 2017.

As recommended by the DRACMA guidelines,² the diagnosis of CMA was made on the basis of clinical history and/or the outcome of the oral food challenge (OFC).

All patients underwent CM-OFC except those (13 children) with a recent history (within 6 months) of anaphylaxis and with positive CM IgE tests.

Before beginning the study, approval was obtained from the ethics committee and informed consent from the parents. The DM was provided by a certified farm where donkeys are raised outdoors and the DM was certified to have good nutritional and nutraceutical components without any health or hygiene risks.

Skin prick tests (SPT) were conducted in all of the children with CMA [prick by prick (PbP) with fresh CM], CM proteins (α -lactalbumin, β -lactoglobulin, casein), DM (PbP with fresh DM), soya,

GM, PbP with eHF and FAAF. The cut-off point for positivity was set at 3 mm of wheal diameter.

Specific serum IgE (s-IgE) to CM, CM proteins (α -lactalbumin, β -lactoglobulin, casein), DM and GM were measured in children with CMA (Immunocap-FEIA, Uppsala, Sweden). The cut-off point for positivity was set at 0.10 KU/L.

After confirming the diagnosis of CMA from the clinical history and/or OFC with CM, patients underwent an open DM challenge. The OFCs with DM were performed in hospital with all available resuscitation facilities. Fresh DM was administered at increasing doses up to 150-200 mL. The time interval between each dose was 20 minutes. After completing the OFC, the children were kept under observation for at least 2 hours and then discharged. The OFC was considered to be positive if any objective skin, respiratory and/or cardiovascular, neurologic or gastrointestinal symptoms were recorded.

In children ≥ 3 years of age, DM palatability was assessed through a "liking scale." We used the Wong-Baker-modified pain scale (6 faces with different expressions [from smiling to crying] corresponding to different degrees of taste [delicious, good, normal, not good, bad taste, disgusting]). In children < 3 years of age, the DM palatability was assessed according to the physician's opinion.

The data were analysed using a commercially available statistical software package (SPSS, Chicago, IL, USA).

The demographic and allergy profiles of the 70 patients are summarized in Table 1.

Table 2 contains the means and standard deviations (SD) of SPT to cow's milk proteins, GM, soya and PbP to FAAF and eHFs and s-IgE to CM, cow's milk protein, DM and GM.

SPT and s-IgE to CM were positive in 100% of the children; 9 of 70 (12.8%) children had positive SPT to DM. S-IgE to DM was measured in 41 out of 70 patients (58.6%): 37 of 41 (90.2%) children had positive results. Forty-four of 70 (77.1%) children had positive SPT or s-IgE to GM, and two of 70 patients (2.8%) had positive SPT to soya. No patients had positive SPT to eHFs or FAAF.

Sixty-seven of 70 patients underwent DM-OFC. The parents of 2 of 9 patients with positive DM SPT (SPT > 6 mm) and the parents of 1 of 37 patients with positive DM s-IgE (s-IgE > 100 KU/L) refused to give their consent to the DM-OFC. Only 1 patient of 67 (1.5%) had positive DM-OFC (SPT to DM with a diameter of 5 mm). In particular, 20' after the ingestion of 1 mL of DM the patient presented rhinorrhoea, sneezing and bronchospasm, treated with oral antihistamine and bronchodilator and with resolution of symptoms in an hour.