Overdiagnosis of cow's milk allergy with home reintroduction

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To the Editor,

Cow's milk allergy (CMA) may present with IgE-mediated or non–IgE-mediated symptoms.[1] In the Netherlands, non–IgE-mediated CMA in infants is more common (3.5%) than IgE-mediated CMA (1%).[2-4]

For many years, it has been a matter of debate which challenge is best for the diagnosis of food allergy: home reintroductions (HR), supervised open food challenges (OFC) or double-blind, placebo-controlled food challenges (DBPCFC).[5,6] In 2012, an evidence-based Dutch guideline for the diagnosis of CMA was developed[6] in which, in most cases, for initial diagnosis HR is not recommended, the use of the OFC is recommended to reject the diagnosis of CMA, while the DBPCFC is recommended to establish the diagnosis of CMA. These recommendations were based on the available evidence, although scarce, and the observed tendency in the Netherlands to overdiagnose CMA.[7] Features, advantages and disadvantages of home and supervised challenges are shown in Box 1, adapted from.[8]

In the Netherlands, all infants are routinely screened during well-child visits throughout the first four years of life in Preventive Child Healthcare centres (PCH centres) of the Dutch primary care national health service.[7] Infants of 0-12 months of age suspected of CMA presenting with mild/moderate and likely non–IgE-mediated symptoms may either be diagnosed in these PCH centres or in secondary or tertiary care. Infants with more severe and/or likely IgE-mediated symptoms of CMA and children older than 12 months of age are referred to secondary or tertiary care.

Until 2012, in PCH centres the diagnosis of CMA was established by elimination and subsequent OFC (first dose at PCH centre, followed by HR) or complete HR. From 2012 onwards, according to the newly developed Dutch guideline, including evidence-based questionnaires on symptoms and protocols for the diagnosis of CMA, the DBPCFC for the diagnosis of CMA in infants has been implemented in PCH centres in certain regions of the Netherlands, such as in Eindhoven, a large city in the south of the Netherlands. Medical staff was trained in performing DBPCFCs by experienced regional paediatricians with expertise in allergy.

The aim of this study was to evaluate the efficacy of the DBPCFC for the diagnosis of CMA in bottle-fed infants with mild-to-moderate symptoms in comparison with HR in PCH centres in Eindhoven. Medical records were retrospectively analysed for the results of the last 50 HRs performed *before* the implementation of the DBPCFC and the first 50 performed DBPCFCs *after* implementation. Since the implementation of the DBPCFC in Eindhoven, the diagnosis of CMA was not established by HR anymore; thus, all infants underwent a DBPCFC since its implementation.

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According to the guideline, mild-to-moderate symptoms of CMA were defined as flares of mild-to-moderate atopic dermatitis, rash, vomiting or reflux, cramp, diarrhoea, constipation, crying/distress and food refusal. HRs or DBPCFCs were preceded by replacement of standard infant feeding by an intensively hydrolysed formula (eHF) during 4 weeks with clinically relevant symptom reduction. The HR consisted of 3 doses: 10, 60 and 120 mL of standard infant formula (equivalent to 130, 780 and 1560 mg milk protein and a total of 2470 mg of milk protein) mixed through the eHF. All doses were administered at home during three days, followed by complete replacement of all eHF by standard infant formula. The DBPCFCs were performed in the PCH centres under supervision of the medical staff. Placebo and milk challenges were administered in random order during two separate days, with at least 1 week in between. Dose increments with 30 minutes interval consisted of 4 doses of 100, 300, 1000 mg and 1000 mg (infants 1-2 months) to 3000 mg (6-12 months of age) milk protein. In total, 2400 to 4400 mg milk protein was administered, respectively. Late-onset symptoms as reported by the parents until 48 hours after the last challenge dose were considered as valid in HR as well as in DBPCFC.

Ready-to-use provocation kits were used to facilitate the performance of DBPCFCs in primary care. The provocation kits were produced and provided for free by the manufacturers of commonly available hypoallergenic formulas in the Netherlands: Nutrilon Pepti, (whey based), Nutramigen and Hero Baby Allergy Care (casein based), and Neocate (amino acid based). These kits consisted of the following: (a) ready-to-use sachets containing either hypoallergenic formula powder for the placebo challenge, or hypoallergenic formula powder with added pasteurized cow's milk powder for the cow's milk challenge; (b) a closed envelope with the code for placebo and cow's milk challenge; and (c) dosing instructions according to the Dutch National Guideline.[6]

The last fifty infants with suspected CMA who reintroduced cow's milk by HR between January 2011 and December 2012, and the first 50 infants who underwent DBPCFCs between January 2012 and June 2013 were included. Patient characteristics at baseline, before dietary intervention, are given in Table 1. Both groups did not differ in gender and age. In the DBPCFC group at baseline, more infants presented with ≥3 symptoms (P = .000), whereas in the HR group at baseline more infants presented with 1 symptom (P = .000).

In the HR group, test results were negative in 12/50 (24%), inconclusive in 2/50 (4%), and positive in 36/50 (72%) infants. Skin symptoms (rash, flare of atopic dermatitis, itch) were reported in 24/36 (67%), gastro-intestinal symptoms (vomiting or reflux, cramp, diarrhoea, constipation) in 13/36 (36%), upper airway symptoms (itchy or watery runny nose, sneezing) in 3/36 (8%), and change in behaviour (crying or distress/irritability, food refusal) in 11/36 (31%) of these infants.

BOX 1 Features, advantages and disadvantages of home and supervised challenges

	Unsupervised challenge	Supervised challenges	
	Home reintroduction	Open food challenge (OFC)	Double-blind, placebo-controlled food challenge (DBPCFC)
Application	Frequently used in primary care for diagnosis and monitoring for symptom resolution	Most frequently used in clinical practice for diagnosis, monitoring for symptom resolution and educational purposes	Most frequently used in research settings Best challenge to establish or reject diagnosis and determination of symptom resolution
Advantages	Cheap Easy to perform Convenient for patient Minimal work load	Less labour intensive than DBPCFC Food is administered in natural state. Blinding and randomization not needed	Gold standard for diagnosis. Minimal bias due to randomization, placebo and disguise of test food in food matrix
Disadvantages	Highly prone to bias Highly prone to confounding factors in home environment	Prone to bias by patient and medical staff. No placebo challenge	Labour intensive Requires more complex logistics for randomization and disguise of test food Requires two separate test sessions Possible matrix effects

Adapted from.[8]

TABLE 1 Patient baseline characteristics of infants who underwent an open food challenge/home reintroduction (n = 50) or a double-blind, placebo-controlled food challenge (n = 50)

Patient characteristics	DBPCFC	OFC/Home Reintroduction	*P* value
Gender: male (n/N, %)	33/50 (66)	32/50 (64)	n.s.
Age in months: mean; (range)	4; (1-11)	4,3; (1-14)	n.s.
No of baseline symptoms per patient			
1 symptom	9	31	.000*
2 symptoms	23	16	n.s.
≥3 symptoms	18	3	.000*

Note: The following symptoms were counted separately: Skin symptoms: Rash or atopic dermatitis; Gastro-intestinal symptoms: Vomiting or reflux; cramp; diarrhoea; constipation; Upper airway symptoms: Itchy or watery runny nose, sneezing; Change in behaviour: Crying or distress/irritability, food refusal.
*$P < .05$.

In the DBPCFC group, test results were negative in 33/50 (66%), questionable in 4/50 (8%), and positive in 13/50 (26%). 4/33 infants with a negative DBPCFC did not reintroduce cow's milk due to disbelief or reported symptom recurrence. Skin symptoms were reported in 7/13 (54%), gastro-intestinal symptoms in 10/13 (77%), upper airway symptoms in none, and change in behaviour in 13/13 (100%) of the infants. The number of positive tests in the DBPCFC group was reduced by 46% and was significantly lower than in the HR group ($P = .01$). In the DBPCFC group, placebo reactions were reported in 7/50 (14%) of infants. Of these, four infants reacted to placebo only while three infants reacted to both challenges.

Although this was not a randomized study, these data suggest that the DBPCFC in infants with mild-to-moderate CMA reduces the overdiagnosis of CMA considerably, while HR strongly overestimates the diagnosis of CMA (Box 1). This study describes the results of HR versus DBPCFC in similar patient groups in a successive time period. Because the diagnosis of CMA was exclusively established by DBPCFC since its implementation (and not by HR anymore), the risk of bias was strongly reduced. However, a more methodologically sound study is needed for definite conclusions. In addition, when adhering to the guideline, staff was more critical in their suspicion of CMA, given the significant lower number of infants in the DBPCFC group with only one symptom in comparison with the HR group.

Unjustified CMA diagnosis may have major medical, nutritional and economic consequences.[7] Guidelines advocating HR for the diagnosis of mild-to-moderate non–IgE-mediated CMA in infancy should be aware of high probability of false-positive rates of diagnoses. We realize that performing DBPCFCs on a large scale in hospital settings would impose a substantial impact on the work load of the medical staff. In our study, the availability of ready-to-use provocation kits made the performance of DBPCFCs logistically more feasible. Moreover, a decreased number of CMA diagnoses would reduce costs. In 2010, the costs of one infant with CMA in the Netherlands and the UK were calculated at €2574 and €1381, respectively, during

the first year following initial consultation,[9,10] predominantly due to high costs of hypoallergenic and amino acid–based formulas. These costs may outweigh extra costs of DBPFCs in hospital settings.

CONFLICT OF INTEREST

BVB received research grants from Nutricia Advanced Medical Nutrition and Nutricia Early Life Nutrition. BVB is Consultant of Marfo Food Groups, producer of commercially available food challenge materials in the Netherlands. ABS received research grants from Nutricia Advanced Medical Nutrition. The other authors declared no conflicts of interest.

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Adverse events in patients with hen's-egg-allergy who passed scrambled egg challenge

To the Editor,

The 2017 Japanese Guidelines for Food Allergies (JGFA2017) defined the dosage of the oral food challenge (OFC) to evaluate allergic tolerance to hen's egg (HE) as a single cooked egg.[1] However, individuals passing the OFC may not necessarily be capable of unrestricted egg intake at school or kindergarten lunches, as the allergenic activity is altered during heat degeneration of HE protein.[2] The JGFA2017 has no clearly defined criteria for lifting restrictions

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