

CORRESPONDENCE

Common colic, gastroesophageal reflux and constipation in infants under 6 months of age do not necessitate an allergy work-up

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To the Editor,

Gastrointestinal disorders such as colic, constipation, and gastroesophageal reflux (GER) are frequently diagnosed in early life. In the literature, epidemiologic data are sparse. Iacono et al. (1) report a relatively high prevalence, e.g. in up to 55% infants <6 months old in an Italian birth cohort of 2800 infants (23% with reflux, 20% with colic, 17% with constipation, and 15% with poor weight gain). Of note, in this study, infants with mild symptoms were included, probably explaining the apparently high prevalence. In fact, gastrointestinal symptoms in this age group are usually rather mild and transient. Nevertheless, cow's milk (CM)-free diets are frequently prescribed in such a clinical context, without positive diagnostic tests for food allergy or intolerance. Excessive prescription of avoidance diets impacts health and quality of life and leads to increased medical costs.

In this study, we aimed to evaluate the potential causal role of CM in infants with common gastro-intestinal symptoms in the first 6 months of life, by using a placebo-controlled, cross-over CM exclusion diet with two 3 week phases. Recruitment criteria were based on accepted diagnostic criteria (2–4) based on severity and persistence of symptoms. The rationale of using the above mentioned criteria was to avoid recruitment of infants with short lasting, spontaneously resolving gastrointestinal symptoms, most likely linked to functional disorders. Once screened, infants were asked to undergo a CM-free diet followed by re-exposition to prove causality.

Using a prospective study design, infants between 0 and 6 months of age presenting with specific gastrointestinal pathologies (colic, GER, constipation), partially or completely bottle-fed, were screened in three outpatient settings at the Geneva Children's Hospital: the allergy clinic, the gastroenterology clinic or the emergency department. In addition, patients were recruited through a large network of primary care pediatricians in private practice in Geneva, Switzerland, including one pediatric gastroenterologist. As mentioned above, recruitment criteria were based on known and accepted clinical criteria to selectively include infants with persistent symptoms potentially attributable to an underlying CM allergy (Table 1). We used Wessel's criteria for colic (2), Rome III criteria for constipation (3) and the combined recommendation from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) for GER (4).

Subjects presenting a concomitant infectious or other specific gastrointestinal disease were excluded from recruitment. It was determined that 120 subjects needed to be

recruited to avoid a β -type statistical error. The trial was registered in ClinicalTrials.gov under number NCT01684319.

During the first phase of the study, infants were sought for recruitment as described above. However, no single subject did meet the recruitment criteria during a 6-month period.

Based on these observations, we initiated a second phase of the study lasting 3 months (March to June 2013), during which we aimed to identify the frequency of all infants <6 months old with complaints of colic, GER, or constipation, regardless of severity and duration. The results of the 3-months population screening are shown in details in Figure 1. A total of 6208 children (0–16 years of age) were seen in all four sites during this 3-months period. We identified thirty-four (34) infants 0–6 months old who consulted for colic, constipation or symptoms suggestive of GER. Only 8 infants met standard diagnostic criteria, but all of them had exclusion criteria (3 were exclusively breastfed, 1 had concomitant infectious disease, 2 had diagnosis of allergic enterocolitis and finally 2 improved spontaneously or with standard treatments). Therefore, no infant with persistent gastrointestinal symptoms could be identified and enrolled in the study.

Infants <6 months of age meeting standard diagnostic criteria for colic, constipation, or GER without improvement with standard treatment and though potentially due to an underlying food allergy are infrequent in our population. Indeed, during a 9 months period totaling more than 18,000 visits to pediatricians, no infant met the study criteria. This is in strong contradiction with a general feeling among pediatricians who spontaneously report "many cases" of gastrointestinal "milk allergy".

The role of CM in infantile colic, constipation and GER is still debated, and studies show controversial results. The most convincing evidence has been reported for constipation. In an interesting double cross-over study comparing CM and soy milk in 65 Italian children with constipation, Iacono et al. (5), showed initial improvement on CM-free diet and relapse of symptoms after challenge with CM in 68% of these children. Inclusion criteria for this study were bowel movements every 3–15 days and lack of improvement on laxative treatments. Median age of children was 34.6 ± 171 months, that is, older subjects than the population reported here.

The same author also described an improvement in 41.8% in infants younger than 12 months suffering from symptoms of GER after initiating a CM protein-free diet (6). Nevertheless, only children with concomitant symptoms suggestive of an associated CM allergy (alterations of bowel habits, rhinitis or atopic dermatitis) or positive allergy testing were selected for

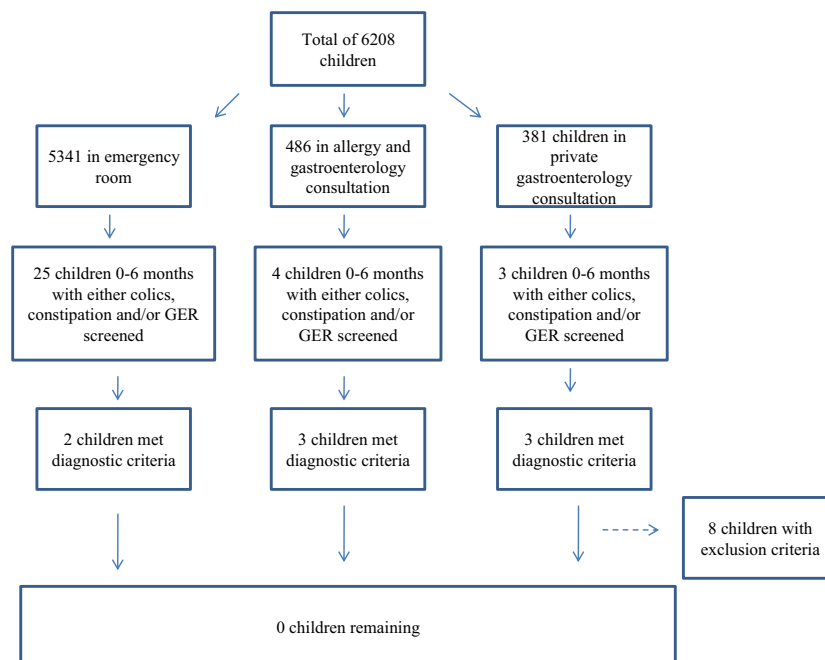
Table 1 Diagnostic criteria used for analyses

	Colic	Constipation	GER
Diagnostic criteria	Wessel's criteria* Crying/fussing more than 3 hours a day, more than 3 days a week for more than 3 consecutive weeks	Rome III criteria (adapted to age)† Less than a bowel movement every third day and/or Crying/pain during defecation and/or Palpable stool in left colic quadrant	Based on NASPGHAN/ESPGHAN recommendations‡ At least one of the following symptoms: Recurrent episodes of regurgitations and/or vomiting Irritability Episodes of rumination Hematemesis Wheezing or stridor in relation with GER and Standard treatment failure during 2 wk

*Wessel et al. (2).

†Rome et al. (3).

‡Vandenplas et al. (4).

**Figure 1** Results of our the second phase of the study (frequency trial 3 months).

an avoidance diet followed by a food challenge, thus potentially overestimating the true prevalence.

For infantile colic, data are available only in exclusively breastfed infants. In a double-blind cross-over trial, Jakobsson and Lindberg showed improvement of colic on a maternal CM-free diet in 35 of 66 infants, with a relapse in 23 of these infants after challenge (7). Similar to previous studies, standard diagnostic definitions were not used leading to an overestimation of the prevalence. In a similar randomized double-blind cross-over study performed by Evans et al. (8), no improvement

in infantile colic was identified in 20 exclusively breastfed infants.

Based on a large cohort of prospectively recruited patients, we found that the large majority of young infants have short lasting, benign symptoms. This group of patients could not be properly investigated for possible CM allergy as the duration of a proper diagnostic CM-free diet would have exceeded the duration of the symptoms. We suggest that milk allergy *stricto sensu* seems not to play a role in a large group of young infants presenting with colic, constipation or GER. Indeed, the

diagnosis of milk allergy, implying a CM free diet, should only be considered in a minority of infants with persistent symptoms, meeting standard diagnostic criteria, which represent a minority of patients in this age group. A diet could even be detrimental, as in a recent paper, Al Dhaheri et al. (9) have described the cases of 2 infants with colic who developed a IgE-mediated CM allergy after a CM-free diet.

We acknowledge that by excluding exclusively breastfed infants, we restricted patient recruitment. However, symptoms caused by minute amounts of CM proteins in breast milk potentially are addressing other immunologic mechanisms (10). IgE and non-IgE mediated CM allergy, occurring through exclusive breastfeeding are uncommon, with the exception of allergic proctocolitis, a benign form of non-IgE-mediated allergy to CM characterized by isolated bloody stool during the first year of life.

In conclusion, we strongly disagree with the common practice of restricting CM in young infants with common short-lasting gastro-intestinal symptoms. Only a very restricted group of infants with persistent and severe symptoms might need allergy testing and a diagnostic CM-free diet.

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