

# Constipation and Cow's Milk Allergy: A Review of the Literature

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## Key Words

Constipation · Cow's milk allergy · Food allergy

## Abstract

The causal association between cow's milk allergy (CMA) and constipation is not well established. Some guidelines describe constipation as a possible symptom of CMA, while others do not mention it. We conducted a literature review and found 10 prospective clinical trials. In all of them, an oral food challenge was performed, and 2 of them were randomized. These studies reported that a cow's milk (CM) protein-free diet has a beneficial effect on constipation, with a rate of successful outcomes ranging from 28 to 78%. The hypothetical pathogenic mechanism lies in increased anal pressure at rest, probably caused by allergic inflammation of the internal sphincter area due to mucosal eosinophil and mast cell infiltration. Eighty percent of patients reach tolerance within 1 year after the diagnosis of CMA-related constipation. We believe that a CM-free diet for 2–4 weeks should be proposed for children with chronic functional constipation, even if it is not severe or resistant to laxatives.

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## Clinical Scenario

Babette is 7 years old and has been suffering from functional constipation since she was 4. Roma III diagnostic criteria [1] are met. The child's diet includes significant amounts of fiber-rich foods and an adequate water intake. She also practices exercise thrice a week and regularly takes polyethylene glycol without any benefit for her constipation. The mother reports that one of Babette's schoolmates, also suffering from constipation, was prescribed a cow's milk (CM)-free diet and this resolved the problem. Could a CM protein-free diet be a useful therapeutic option also for Babette?

Prescribing a CM-free diet is not an easy decision for the clinician to take, because many of Babette's favorite foods (especially cakes and desserts) are made with CM and the diet would affect her quality of life. Nonetheless, this could be a cost-effective therapeutic option to resolve her constipation.

## Introduction

Is it possible that Babette's severe constipation is caused by CM allergy (CMA)? To confirm this hypothesis, in a recent retrospective survey, 437 children affected

**Table 1.** Clinical studies on the causal association between CMA and constipation, available on MEDLINE (up to March 10, 2014)

| First author (year)   | Study design             | Children, n | Constipation                  | Food (time of food elimination in weeks) | Children with symptom resolution, % | Major features in responders          |
|-----------------------|--------------------------|-------------|-------------------------------|------------------------------------------|-------------------------------------|---------------------------------------|
| Iacono (1995) [7]     | before-after case series | 27          | resistant or not to laxatives | CM (4)                                   | 77                                  | anti-BLG IgG, elevated IgE            |
| Iacono (1998) [8]     | DB crossover RCT         | 65          | resistant to laxatives        | CM (2)                                   | 68                                  | anal fissures, specific IgE           |
| Daher (2001) [9]      | before-after case series | 25          | resistant or not to laxatives | CM (4)                                   | 28                                  | none                                  |
| Turunen (2004) [10]   | before-after case series | 35          | resistant to laxatives        | CM (4)                                   | 34                                  | none                                  |
| Iacono (2006) [11]    | before-after case series | 36          | resistant to laxatives        | CM, MFI (4)                              | 47                                  | AD, asthma, IgG anti-BLG specific IgE |
| Borrelli (2009) [12]  | before-after case series | 33          | resistant to laxatives        | CM, soy, wheat (4)                       | 54                                  |                                       |
| El-Hodhod (2010) [13] | before-after case series | 27          | resistant to laxatives        | CM (4)                                   | 78                                  | specific IgE                          |
| Irastorza (2010) [14] | before-after case series | 69          | resistant or not to laxatives | CM (3)                                   | 39                                  | none                                  |
| Syrigou (2011) [15]   | before-after case series | 48          | resistant to laxatives        | Eggs, wheat (8)                          | 60                                  | APT positive                          |
| Dehghani (2012) [16]  | open RCT                 | 140         | resistant to laxatives        | CM (4)                                   | 34                                  | none                                  |

RCT = Randomized controlled trial; DB = double-blind; MFI = multiple food intolerance; AD = atopic dermatitis; BLG =  $\beta$ -lactoglobulin; APT = atopy patch test.

by non-IgE-mediated food allergy (FA) with gastrointestinal involvement were observed and constipation was reported in 44.6% of the cases [2]. Conversely, constipation is not included in the list of symptoms described in the National Institute of Allergy and Infectious Diseases (NIAID) guidelines (GL) on FA management [3]. Moreover, important authors such as Sicherer and Sampson [4] do not consider constipation as a possible clinical manifestation of a FA. On the other hand, World Allergy Organization (WAO) [5] and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [6] GL on CMA outline constipation in their classification of symptoms. Only 2 of the official documents we have mentioned [3, 5] were written following the GRADE (Grading of Recommendations Assessment, Development and Evaluation approach; <http://www.gradeworkinggroup.org/>) method, and they are controversial. So, after evaluating the discrepancies found in the GL, we decided to conduct a review of the literature.

### Research Strategy

To achieve the aims of our literature review, we set the following eligibility criteria for clinical studies: (a) enrollment of patients younger than 14 years, (b) prospective

nature, (c) having a population of at least 10 patients at the end of the observation, and (d) being randomized, or at least having a control group, or having performed an oral food challenge after the benefit obtained with the restricted diet. A literature search was performed on PubMed (MEDLINE) up to March 10, 2014. The search terms were 'constipation AND (milk allergy OR cow's milk allergy OR food hypersensitivity OR milk hypersensitivity)'. The terms 'constipation' and 'milk hypersensitivity' were searched also as Medical Subject Headings (MeSH terms). We identified 110 studies and 10 [7–16] were eligible for our review. Their most relevant features are showed in table 1.

### Summary of the Most Significant Studies

In 1984, Chin et al. [17] described for the first time a case of constipation with CMA as the only symptom and well demonstrated the causal relationship between these two entities. The child had been bottle-fed since birth, and at 6 months of age he started to have constipation; no benefit was obtained with a fiber-rich diet and laxatives (senna glycoside, lactulose). When the child was 2 years old, he was prescribed a CM protein-free diet (milk was substituted with an extensively hydrolyzed casein formu-

la), and the constipation resolved itself in a week. The child underwent 3 oral food challenges and every time he presented constipation within a few days and the symptoms disappeared within 48 h after avoidance of CM. A rectal biopsy was performed during constipation and it showed massive eosinophilic mucosal infiltration; also serum CM-specific IgE were weakly positive. We mention this study because it is the first case described in the literature and it contains several key points for our discussion. However, it did not meet our eligibility criteria.

The study of Iacono et al. [8] is the only double-blind randomized study evaluating the causal role of CMA in the pathogenetic mechanism of constipation. However, no strict blinding procedure was followed: CM and soy milk were supplied in identical bottles, but nothing was done to equate the organoleptic properties of the two products. Sixty-five children (mean age: 35 months) with chronic constipation (mean duration of illness: 9 months) not responding to lactulose were enrolled into this cross-over study. Sixteen children had a personal history of CMA. The children were randomized to either a CM protein-free diet (receiving soy milk) or CM for a 2-week period. After a 1-week washout period during which the diet was unrestricted, the patients were switched to the other type of milk for another 2 weeks. Forty-four of the 65 children (68%) responded while following a CM protein-free diet (responders). All 44 children who responded to the CM-free diet underwent a double-blind, placebo-controlled challenge with CM in the hospital after following the restricted diet for another month. None of those taking placebo (soy milk) had adverse reactions. On the other hand, all 44 children taking CM presented constipation after 5–10 days. Responders were significantly more likely to have anal fissures, serum CM-specific IgE positivity, and eosinophilic infiltration at the rectal biopsy. No patients lost to follow-up were reported.

The Iranian study of Dehghani et al. [16] is the second and last randomized study on the association between CMA and constipation. One hundred forty children with functional constipation, according to Roma III diagnostic criteria [1], not responding to polyethylene glycol were enrolled into this open study. The mean age was 55 months and the mean duration of illness was 26 months. The children were randomly assigned to either a CM-free diet (70 patients) or an unrestricted diet (70 patients) for a period of 4 weeks. All children underwent skin prick tests with CM. At the end of the 4-week period, resolution of constipation was obtained in 80% of the children on a CM-free diet and in 46% of the children in the other group. The 56 responders to the restricted diet were re-

challenged with CM for another 2 weeks, and 24 of them showed constipation again. In conclusion, 34% (24/70) of the children assigned to a CM-free diet benefited from it. No specific features were described for responders and nonresponders; the children with a positive skin prick test were very few (only 1 in the responder group). No patients lost to follow-up were reported.

The study of Irastorza et al. [14] was not randomized and can be considered a 'before-after' case series. Sixty-nine children with chronic functional constipation (not necessarily resistant to laxative treatments) were enrolled. The mean age was 60 months and the mean duration of illness was 16 months. The children were observed during 1 week of an unrestricted diet and afterwards were prescribed a CM protein-free diet for a period of 3 weeks. Children younger than 2 years received extensively hydrolyzed formula, while older children were given rice milk. Soy milk and soy proteins (SP) were not allowed in the diet. Constipation resolved in 27 patients (39%); their condition worsened when CM was reintroduced into the diet for 3 weeks and improved again when the restricted diet was followed for another 3 weeks. The authors described that responders were not different from nonresponders in many features (e.g. a personal history of atopy, serum CM-specific Ig-E, and anal lesions). Nevertheless, the number of children affected by mental retardation was significantly higher in the responder group (29 vs. 6%). No patients lost to follow-up were reported.

### Pathogenetic Theory

The cause of constipation induced by CMA could be an increased anal sphincter pressure at rest. The pressure increase is probably caused by allergic inflammation of the rectal mucosa. Indeed, the lack of noninvasive diagnostic exams with sufficient accuracy does not allow easy demonstration of the presence of an immunologic mechanism in constipation or distinguishing between allergy and a more generic hypersensitivity, characterized by non-immunological mechanisms [18]. However, some authors [9–12] have observed that patients with constipation who are responsive to a CM-free diet have a higher pressure at anorectal manometry and evidence of lymphocytes, eosinophils, and mast cell infiltration at rectal biopsy. The number of mast cells was significantly higher in children responding to the diet compared to nonresponders [12]. Moreover, Iacono et al. [11] and Borrelli et al. [12] described that these findings were resolved during a restricted diet. Eosinophils, lymphocytes, and mast

cell infiltration of the digestive tract have already been associated with clinical evidence of food hypersensitivities [19, 20] and can be considered as the expression of an immunologic mechanism causing CM-related constipation, even if specific serum IgE are not present.

In a recent review, Murch [21] outlined the role of FA, mast cells, and eosinophils in the pathogenesis of intestinal dysmotility, and many data were obtained from animal models. Rats sensitized to ovalbumin showed disturbed motility, with intense clusters of contractions followed by intestinal inactivity. The changes induced by food sensitization were chronic, related to the persistence of mast cells even after the antigen was withdrawn. Allergen-induced gastric dysmotility in ovalbumin-sensitized mice did not develop when the eosinophil chemokine eotaxin-1 was absent, showing the importance of eosinophil recruitment. Other animal models have provided evidence that mucosal allergy may induce a visceral nociceptive trigger that chronically sensitizes the neurons of the anterior cingulate cortex which respond specifically to colorectal distension. However, as Murch [21] says, it is true without any doubt that '... clear evidence of causal linkage for specific diseases may await better clinical stratification of cases of functional bowel disorders, to identify those subgroups where allergic responses are unequivocally responsible for symptoms ... The challenge is to identify these patients amongst the many presenting with functional bowel disorders. The lack of detectable systemic IgE responses or measurable biomarkers makes this a challenging area of clinical practice.'

### Acquisition of Tolerance

In 1995, Iacono et al. [7] reported that reintroduction of CM was performed in 16 infants 6–9 months after the diagnosis of CMA-related constipation. Fifty percent of those patients (8/16) suffered from constipation within 2–3 days after reintroduction. In 1998, the same authors [8] reported that 15 out of 44 responders suffered from constipation when CM was reintroduced after 8–12 months of a restricted diet. El-Hodhod et al. [13] found that tolerance to CM was achieved after 6 months in 22.2% of patients versus 88.8% after 12 months of a CM-free diet. Similarly, Syrigou et al. [15] observed that tolerance to food allergens was achieved in only 6 out of 28 patients after 6 months, in 25 out of 28 patients after 12 months, and in all of their patients after a 2-year period of food elimination.

Thus, patients have a good chance of achieving tolerance when CM (or another food) is reintroduced after 12 months of a restricted diet.

### Discussion

The causal association between constipation and FA is not universally accepted. Allen et al. [22] described CMA-related constipation as controversial, and in 2013 Morita et al. [23] did not include this entity among the gastroenterological manifestations of FA. However, the most authoritative GL on CMA [5] (written following the GRADE method) considers constipation to be, without a doubt, one of the possible clinical manifestations of CMA. How can these different points of view be explained? And which opinion should we consider in the clinical management of our patients (e.g. Babette)?

We reviewed clinical trials and only a few of them were conducted following a strict methodology. Moreover, of the 2 randomized trials [8, 16] only 1 was a double-blind study, but its blinding procedure is questionable. The remaining 8 studies were before-after case series. Nonetheless, in all of them an oral food challenge was performed and the results are consistent: constipation can resolve after a CM protein free diet. What varies between the studies is the percentage of responders, ranging from 28% [9] to 78% [13]. Moreover, evidence of increased eosinophil and mast cell infiltration at rectal biopsy, which improves after a restricted diet [11, 12], is suggestive of the causal association between CMA and constipation. The study of Simeone et al. [24] and other published studies do not agree with this hypothesis, but they are few and the populations of observed children are poor.

Another issue to consider in the evaluation of causal relationships between CMA and constipation is the late onset of symptoms in children without other previous clinical manifestations of CMA. For example, in the best study available, i.e. that of Iacono et al. [8], 65 children were enrolled, with a mean age of 35 months and a mean duration of illness of 9 months; the mean age of constipation onset was 26 months. Since 16 out of 65 children already had a personal history of CMA, in that study 75% of patients (49/65) had constipation as the first clinical manifestation of CMA and the age of onset was more than 2 years; this late onset seems to be unusual. A late onset of constipation was a common finding in the studies we evaluated.

Another slight incongruence to consider is that CMA-related constipation resolved in children receiving soy

milk during a restricted diet; that is what Iacono et al. [8] described in their population in 1998. We did not expect these results since in 1998 the American Academy of Pediatrics (AAP) stated that: 'Infants with documented CM protein-induced enteropathic enterocolitis frequently are sensitive also to SP and should not be given SP-based formula routinely. They should be provided hydrolyzed or synthetic amino acid formula.' [25] The same recommendation was reaffirmed in the updated document of 2008 [26]. Furthermore, it was recently shown that CM-sensitized mice without previous exposure to SP elicited hypersensitivity signs immediately after the oral administration of SP, suggesting that immunochemical cross-reactivity might be clinically relevant [27]. Consistent with these indications, Irastorza et al. [14] did not allow their patients to ingest soy. However, in 2009, Australian GL on the diet management of CMA [28] suggested soy milk as the first choice for children older than 6 months without failure to thrive, in order to resolve constipation (and, more generally, gastrointestinal syndromes such as gastroesophageal reflux disease, allergic eosinophilic gastroenteritis, food protein-induced enteropathy, and colics). Thus, the points of view are numerous and quite varied.

## Conclusion

The demonstration of a causal association between CMA and constipation presents some problems, first of all because the methodological quality of the available studies is scarce, with two exceptions. However, these studies all go in the same direction, i.e. they coherently show improvement of constipation (in a variable percentage of cases) in children on a CM-free diet; consistency between studies is one of the factors to be taken into account when evaluating the strength of an association. Also, we have to consider that the attempt to follow a restricted diet for 2–4 weeks is not a big sacrifice. Moreover, the probability of acquiring tolerance in a short period of time (around 12 months) is high. A restricted diet can also be given to those who complain of constipation not necessarily resistant to laxatives; in 3 studies [7, 9, 14], constipation unresponsive to laxative therapies was not mentioned in the inclusion criteria.

So what about Babette? We are not very sure the girl would benefit from a CM-free diet, but we think that, based on the scientific literature available, it is worth an attempt. In the future, if following a restricted diet is too difficult for the child, we must look for other solutions.

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