Article Type: Review Article

Algorithms for managing infant constipation, colic, regurgitation and cow’s milk allergy in formula-fed infants

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Short title: Algorithms for gastrointestinal symptoms

Key-words: algorithms, constipation, colic, cow’s milk protein allergy, regurgitation

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apa.12962
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Abstract
Gastrointestinal symptoms, such as constipation, regurgitation and infant colic, occur in about half of infants. These symptoms are often functional, but they may also be caused by cow’s milk protein allergy. We developed three algorithms for formula-fed infants, which are consensus rather than evidence-based due to the limited research available in the existing literature.

Conclusion. We believe that these algorithms will help primary healthcare practitioners to recognise and manage these frequent gastrointestinal manifestations in infants.

Key Notes
- Gastrointestinal symptoms, such as constipation, regurgitation and infant colic, frequently affect infants and these can be functional or caused by cow’s milk protein allergy.
- The authors developed three algorithms for formula-fed infants, which are consensus rather than evidence-based due to the limited research available in the existing literature.
- We believe that these algorithms will help primary healthcare practitioners to recognise and manage these frequent gastrointestinal manifestations in infants.

Conflict of Interest: Yvan Vandenplas is a consultant for Biocodex and United Pharmaceuticals.

The other authors have no conflicts of interest relevant to this article to disclose.

Abbreviations:
CMPA: cow’s milk protein allergy
GORD: gastro-oesophageal reflux disease
IgE: immunoglobulin E

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Introduction

About 50% of infants present with functional gastrointestinal symptoms, such as colic, regurgitation and constipation, and many infants experience a combination of these symptoms (1). Each of these three conditions account for roughly 20 to 25% of all cases (1). The Rome III criteria propose diagnostic criteria for these symptoms, but do not propose management techniques (2). These symptoms are almost never a reason to stop breastfeeding, but functional GI symptoms very frequently lead to formula changes by parents and healthcare providers. A descriptive study published 30 years ago quantified this frequency, by showing that these moderate digestive problems led to formula changes in 35% of cases (3) and these findings have repeatedly been confirmed.

Most algorithms propose different approaches for each separate functional GI symptom, but many infants present with a combination of these problems (1). Cow’s milk protein allergy (CMPA) is not a functional gastrointestinal problem, but it is a similar condition since symptoms of CMPA are unspecific and functional. CMPA in infants presenting with gastrointestinal manifestations, is normally non-Immunoglobulin E (IgE) mediated. Therefore, laboratory tests such as specific IgE tests, skin prick tests and patch tests are not helpful as they are, at best, indicative of a diagnosis of IgE mediated CMPA (4) and the management of IgE and non-IgE mediated allergy is identical.

This study presents state-of-the-art practical algorithms for the management of these functional gastrointestinal symptoms, providing a follow-up to the algorithms that were published in 2013 (5). The goal was to further simplify the proposed approach. Like guidelines or recommendations, they need to be challenged and adapted over time. The authors met face-to-
face twice and held email discussions to reach a consensus. They didn’t receive any financial contribution or other kind of help.

### Constipation

Feeding plays a key role in the stool pattern of infants younger than four months. Healthy breast-fed babies may defecate as frequently as seven times per day or as infrequently as once a week (2,5,6). Extremes of up to 12 times a day or once in three or four weeks have even been reported (2,6). Hard stools occur in only 1% of exclusively breast-fed infants, compared to 9.2% in standard formula-fed infants, without prebiotic or probiotic supplementation (7). Firm or hard stools are often seen when breast milk is switched to infant formula or after the introduction of solids. Harder stools are frequent in infants fed with formulas containing palm olein oil or palm oil as the main source of fat (8).

### Diagnosis

A thorough medical history and physical examination are the cornerstones for establishing the diagnosis and aetiology of infant constipation. Failure to pass meconium during the 24 to 48 hours after birth should raise suspicion of Hirschsprung’s disease or cystic fibrosis (6,9). Functional constipation is constipation without an underlying causal organic disease.

It is important that healthcare professionals are aware of the normal defecation pattern of infants so that they can differentiate between abnormal and normal defecation, educate and advise parents adequately and avoid unnecessary treatment. It is crucial to understand what parents mean when they use the term constipation. Information should be gathered regarding the duration of the condition, the frequency of bowel movements, the consistency and size of the...
stools, whether defecation is painful and the presence of pain and blood. This information will help to make the distinction between functional constipation and constipation due to organic disease. The Amsterdam stool scale may provide a more objective description of stool consistency (10). The definition proposed by Biggs et al for infant constipation - of “difficult or rare defecation lasting for at least two weeks” - has been well accepted and recommended by experts (9). No laboratory or radiographic testing is necessary if there are no reasons to suspect an organic cause (6). The younger the infant, the higher the risk of an anatomical or organic cause, although functional constipation remains the most frequent condition at any age. Anorectal examination should evaluate perianal sensitivity, anal position and tone, the size of the rectum and the presence of an anal wink (5,6). Specific tests must be performed if other clinical data are present, such as failure to thrive, intermittent diarrhoea or abdominal distension (6).

Although CMPA has been shown to be a cause of constipation in a subset of children, the exact proportion is unclear and the pathophysiological mechanisms have remained elusive (6).

**Management**

The first step in managing functional constipation is to educate and reassure the parents by addressing the myths and fears around constipation and pointing out that functional constipation is one of the most common manifestations in infants (1,5,6). Infantile dyschezia - crying and straining during defecation - is considered to be normal behaviour in young infants and should not be medicalised (2). Dietary recommendations may help. If the probability of an organic condition is low, reassurance and close follow up should be sufficient. In some regions, it is common to use magnesium-rich mineral water to prepare infant formula. However, there is no evidence to support this practice and mineral intake will be above the recommended limit if only
this water is used (6). Juices containing sorbitol, such as prune, pear and apple juices, can decrease constipation, but the risk is that infants may drink more fruit juice than formula and, therefore, become malnourished. Glycerine suppositories can be helpful if rectal emptying is necessary to provide acute relief. However, evidence does not support the use of mineral oil, which could lead to a risk of lipoid pneumonia due to aspiration, or enemas such as phosphates, in young infants. Infant formulas offer a good alternative for managing functional constipation if they contain partially or extensively hydrolysed proteins, fortified with prebiotics and, or, probiotics, and do not contain palm oil as the main source of fat in the oil blend (11,12). There are some formulas advertised as anti-constipation formulas, but some of them have a high magnesium content, albeit within the regulatory limits (13). An Italian study suggested that Lactobacillus reuteri (L. reuteri) was effective in preventing constipation (14). The literature about the efficacy of probiotics in infant constipation is very limited, since only one trial has been performed that shows encouraging results (15), but supplementing infant formulas with probiotics and prebiotics is regarded as safe. Several studies have been performed with a partial hydrolysate, supplemented with a prebiotic and β-palmitate, and this showed some beneficial results (16,17).

**Regurgitation**

The prevalence of daily regurgitation in three to four-month-old infants is estimated to be around 50 to 60% (5,18). More than four episodes of regurgitation per day, which occurs in about 20% of all infants, is considered to be troublesome by parents and leads them to seek medical help (18-21).
Diagnosis

Regurgitation is the passage of refluxed contents into the pharynx or mouth or from the mouth. Vomiting is defined as a central nervous system reflex involving both autonomic and skeletal muscles. Most episodes of gastro-oesophageal reflux and regurgitation occur during the post-prandial period and cause few or no symptoms (18). According to the Rome III criteria, the diagnosis of regurgitation in a healthy infant between the age of three weeks and 12 months should include: regurgitation two or more times per day for at least three weeks or more and absence of nausea, haematemesis, aspiration, apnoea, failure to thrive, difficulty in feeding or swallowing and abnormal posture (2). More than 50% of all infants fit these criteria and we feel that there needs to be a stricter definition. In our view, infants should present with at least four episodes of regurgitation a day for at least two weeks and, according to the epidemiologic data, this corresponds to 20% of all infants (5,18). Gastro-oesophageal reflux disease (GORD) is a condition in which the reflux of gastric contents causes a decreased quality of life and, or, complications (18). The management of GORD, which is seldom used in this age group, includes lifestyle changes as well as pharmacological therapy - mainly acid reducing medication - and, in few cases, surgery (5,18,22). In infants younger than three weeks and older than six months, the differential diagnoses should be more strictly excluded, since physiologic regurgitation rarely starts before the age of three weeks or after the age of six months.

Management

Regurgitation is physiological in this age group and occurs in normal healthy infants. However, a complete medical history and physical examination are warranted in infants with troublesome and frequent regurgitation involving more than four episodes a day, to rule out organic disease.
Since physiological regurgitation should not be diagnosed in an infant with vomiting and poor weight gain (5,18), anthropometry is of major importance. The management of regurgitation starts with reassuring the parents and providing information on the natural history of regurgitation, correct formula preparation and how overfeeding may exacerbate regurgitation. In infantile regurgitation, thickened formula or anti-regurgitation formula decreases the frequency and the volume of regurgitation, but does not decrease gastro-oesophageal reflux (18). The prone anti-Trendelenburg position cannot be recommended because of the risk of sudden infant death syndrome (23). An anti-regurgitation bed with an angle of 40 or 50 degrees has been studied (24). Sleeping the infant on their side has also been recommended (25), but this sleeping position is associated with an intermediate risk for sudden infant death syndrome between prone and supine sleeping positions. Many studies have failed to show any benefits of anti-secretory drugs or prokinetic agents in this situation (5,18,22). A subset of infants with therapy resistant regurgitation may suffer from CMPA (4,5,22,22) as detailed in the CMPA algorithm.

The nutritional management of regurgitation consists of correcting the frequency and volume of feeds if necessary (5,18,22,28). Because of its increased viscosity, thickened anti-regurgitation formula reduces both the volume and frequency of regurgitation and crying and improves sleep and supports weight gain (5,18,22). The commercial anti-regurgitation formulas contain different thickening agents, such as processed rice, corn or potato starch, guar gum or locust bean gum (5,18,22). In-vitro laboratory tests have found that bean gum has a negative effect on the absorption of vitamins and minerals (26), but this has not been confirmed in clinical trials (27). If a commercial anti-regurgitation formula is not available, a thickening product may be added to the formula. Cereals increase the caloric intake, possibly inducing excessive weight gain, and
Locust bean gum does not increase the calorific density, but may cause gassiness. Home-thickening of a regular formula always increases the osmolarity, which may induce reflux and regurgitation by increasing the number of lower oesophageal sphincter relaxations. This may induce reflux and regurgitation. Infants with persistent regurgitation or vomiting should be referred to a paediatric specialist (18).

There is limited literature suggesting that some specific probiotics (L. reuteri DSM 17938) and prebiotics prevent functional GI symptoms such as regurgitation (14,17). L. reuteri may accelerate gastric emptying (28). CMPA should be suspected in an infant with persistent and recurrent regurgitation and, or, vomiting, particularly if this is associated with other manifestations of allergic disease, such as eczema and, or, wheezing, as seen in the CMPA algorithm. There are also studies that need to be replicated that suggest that formulas that do not contain palm olein or palm oil as the main source of fats in the oil blend are associated with less regurgitation (29) or that a thickened partial hydrolysate formula may be slightly more effective than a thickened standard infant formula (30), possibly because it is easier to digest partial hydrolysates (31). Partial hydrolysates empty the stomach faster than standard protein, which may contribute to a decrease in regurgitation (32).

**Infantile colic**

Infantile colic was originally defined by Wessel in 1954 as crying lasting three or more hours a day, at least three days a week and for at least three weeks (33). In 2006, the Rome III criteria defined it as “episodes of irritability, fussing, or crying that begin and end for no apparent reason and last at least three hours a day, at least three days a week, for at least one week” (2). The
incidence of infantile colic varies between 5 and 30% (34,35) and it is reported to occur equally frequent in breast and bottle-fed infants and in both sexes. The aetiology of colic is multifactorial and is unknown. Multiple hypotheses have been proposed, including altered gastrointestinal function, food intolerance, transient low lactase activity, CMPA, gastro-oesophageal reflux and intestinal microflora imbalance. (5). Parents being able to cope is of major importance for reporting and managing colic, more so than in any other functional gastrointestinal manifestation.

**Diagnosis**

The cardinal manifestation of infantile colic is excessive and persistent loud crying, mostly late in the afternoon. During each episode the child appears irritable, distressed and fussy and contracts the legs, becomes red-faced and has frequent episodes of borborygmi. CMPA and GORD should be considered in patients with severe colic. Very limited literature suggests that a transient low lactase activity could also cause excessive crying (36,37).

Attention should always be focused on how the parents are coping, including their anxiety levels, signs of depression, the absence of mother–child reciprocity and the risk of child abuse.

**Management**

There are no uniform criteria for a specific therapeutic approach. The first recommended step is to look for potential symptoms that indicate a possible organic disease (see algorithm). If these are not present, the feeding technique should be evaluated and the parents should be reassured and supported. Parents should be informed about how to recognise signs of hunger and fatigue and how they can offer their infant offering structure, regularity and a calm environment. General advice emphasising the self-limiting nature of the condition is important. Clinicians

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should advise mothers who are breastfeeding to continue doing so. If there are reasons to consider CMPA, advising the mother to avoid cow’s milk proteins for a minimum of two weeks can be considered. The most validated treatment for infant colic is to substitute cow’s milk with an extensively hydrolysed formula in a highly selected population of infants (5). In formula-fed infants, eliminating CMP and replacing it with an extensively hydrolysed protein formula has been reported as an effective treatment (5,35). However, this information is mainly derived from studies in highly selected patients from tertiary care level centres. Experience, but not evidence, has shown that partially hydrolysed formulas can be a useful option when extensive hydrolysate would be too expensive and CMPA is not a potential cause of infant colic (31,35). In many cases, these formulas have reduced lactose or are lactose free and have added prebiotics or probiotics and this results in a reduction in the number of crying episodes per week and total crying time with varying levels of evidence (31). However, the role of lactose can be questioned, as soy formula has not been associated with any benefits (34). According to one review (36), soy formulas seemed to be effective, but soy milk can induce allergy and is, therefore, not recommended. In a recent meta-analysis, which included data from 40 studies, the weighted prevalence of soy allergies was no more than zero to 0.5% in the general population (38). But the negative results of studies evaluating the efficacy of lactase strongly suggest that low lactase activity can cause infant colic (36). Patient selection is likely to be a major bias in these studies. Several studies have been performed with proton pump inhibitors in distressed infants, but they all failed to show any benefit (39). Allopathic drugs, such as simethicone and lactase, have not proved to be effective and some of them, such as dicyclomine, can cause potentially serious adverse reactions (36,40). Fennel extract and sucrose solutions have shown some benefit (36). Medications such as dicycloreverine or cimetropium have also been tested in infant colic.
Cimetropium has shown a high rate of lethargy, motion sickness and, or, somnolence. Other randomised controlled trials have studied glucose or saccharose solutions, showing varying effects on crying time (41). In a double-blind, placebo-controlled trial, a partial hydrolysate with high β-palmitate and a specific prebiotics mixture with galacto and fructo-oligosaccharides, resulted in a significant decrease in colic within one week of intervention (42). One clinical trial demonstrated the safety and efficacy of L. reuteri in preventing infant colic (14). Two randomised double-blind trials showed that L. reuteri effectively reduced crying time in breast-fed infants (43,44). A recent study with the same probiotic strain, L. reuteri DSM 17938, in a community sample of breast-fed and formula-fed infants with infant colic failed to show any benefit (45). In fact, at one-month-old, the probiotic group actually cried or fussed 49 minutes more than the placebo group (95% confidence interval eight to 90 minutes, P=0.02) (45).

Studies have evaluated the role of additional family support, counselling therapies, car rides during colic episodes, reduced stimulating actions, such as changing nappies, spinal massages by chiropractors and even the use of herbal options. None of these trials has been of sufficient methodological quality to allow any recommendation (22,36,40). There is also insufficient evidence to systematically recommend swaddling, although the technique has been reported to be of some benefit in infants younger than eight-weeks-of-age (46).

Infant colic is a multi-factorial condition and it is, therefore, unlikely that a single intervention will reduce it significantly in an unselected patient population. According to all the systematic reviews to date, there is some evidence of a beneficial effect of hydrolysed formula in patients with infant colic due to CMPA.
Cow’s milk protein allergy (CMPA)

Cow’s milk is the most common cause of food allergy in infants and occurs in 3-5% of formula-fed infants and in 0.5% of breast-fed infants (4). CMPA often presents with gastrointestinal manifestations, such as regurgitation, vomiting and abnormal defecation. Avoiding cow’s milk protein can resolve the symptoms. However, dietary restrictions and elimination diets need to be avoided if they are not needed because they may induce impaired growth or malnutrition and cause unnecessary costs for the family.

Classification and clinical features

According to the definition proposed by the World Allergy Organization, CMPA is a hypersensitivity reaction caused by specific immunological mechanisms to one or more of the proteins in cow’s milk (4). CMPA can be classified in different categories: IgE-mediated, non-IgE mediated and a mixture of IgE-mediated /non-IgE-mediated.

IgE-mediated CMPA is caused by an immediate hypersensitivity to CMP, which is often associated with atopic conditions such as atopic eczema, asthma and, or, allergic rhinitis. Gastrointestinal symptoms, such as regurgitation, vomiting, colic and diarrhoea, accompany systemic manifestations of the skin, such as urticaria and angioedema, and respiratory tract symptoms such as rhinitis, wheezing and stridor. Symptoms such as pallor or flaccidity (hypotension) also occur soon after allergen exposure, usually within an hour. Anaphylaxis is the most serious manifestation of IgE-mediated CMPA, but is rare (4). Mixed IgE/non-IgE-mediated CMPA and non-IgE-mediated CMPA constitute a mixed group of disorders that have been well defined clinically, although their immunological mechanisms are not well understood. In
individual infants, it may be very difficult to distinguish reflux from CMPA symptoms. The conditions that might be caused by CMPA are not confined to CMPA and may also be triggered by other food allergens.

**Diagnosis and management**

The central principle in managing patients with food allergies is avoiding the food known to cause the reaction. In some parts of the world there is a tendency for medical practitioners to over-diagnose CMPA and prescribe elimination diets that are not adequately supervised. In other parts there is a tendency to under-diagnose CMPA. Both practices could have an adverse impact on the child’s growth (47). An elimination diet should be recommended for infants with symptoms that suggest an IgE-mediated reaction. Skin prick or specific IgE tests can be performed, but are not recommended (4) and atopy patch testing is not a recommended procedure (48). Recently, the Cow’s Milk Related Symptom Score was developed as an awareness tool to facilitate appropriate diagnosis of CMPA (49). Total IgE has a poor specificity for the diagnosis of CMPA, but does provide information on the prognosis: the higher the IgE, the longer it will take to develop tolerance. (50). A cow’s milk challenge is the diagnostic gold standard, but does not provide proof that the immune system is involved. IgE sensitisation without a clinical history does not conclusively show CMPA.

Children with CMPA should also be monitored for the development of tolerance. Most children with IgE-mediated CMPA will ultimately achieve tolerance (51) and children that have an IgE negative allergy become tolerant at a younger age. However, our knowledge of the natural
evolution of CMPA is likely to be biased since most data has come from tertiary care level centres and focused on the most severe cases.

Regarding formula replacement, all guidelines recommend an extensive hydrolysate as the first option (4). There is limited evidence that the addition of prebiotics or probiotics to an extensive hydrolysate offer any additional benefit (50,52). An open study suggested that probiotics induced a more rapid tolerance (50). Soy is the second option, when the extensive hydrolysate is not available, too expensive or if the child refuses to drink it (4). Rice hydrolysates, which are on the market in a growing number of countries, will soon play a role in these recommendations since the evidence of their efficacy is growing (53,54). Extensively hydrolysed rice protein formulas are free of CMP allergens, and thus have a low residual allergenicity, and they are cheaper than extensive cow’s milk-based hydrolysates. The World Allergy Organization Diagnosis and Rationale for Action against CMPA (WAO-DRACMA) guidelines recommend amino acid-based formulas rather than extensive hydrolysates for infants at high risk of anaphylactic reactions (55). WAO-DRACMA recommends extensive hydrolysates over soy formula in IgE-mediated CMPA, but stresses the need for more data by stating that “there is very sparse evidence suggesting a possible benefit from using eHF compared to soy formula”. Although soy protein has been used in infant feeding for more than 100 years, the popularity of soy infant formula varies substantially in different parts of the world. The world is divided into those countries where is it popular, such as the USA, and those where it is avoided, such as France (56). The Agence Française de Sécurité Sanitaire des Aliments has underlined the limited knowledge and uncertainties regarding the presence of isoflavones in soy formulas (57). However, a recent meta-analysis concluded that soy infant formula was safe (58).
A literature review by The American Academy of Pediatrics concluded that about 10% to 14% of infants with CMPA will become sensitised to soy and that this happens more frequently in non-IgE mediated CMPA (59). In a prospective cohort study of 13,019 infants by Katz et al, the incidence of IgE-mediated CMPA was 0.5%. Interestingly, none of the 66 had a documented allergy to soy and 64 of these infants could tolerate soy (60). A recent meta-analysis found that the prevalence of allergy to soy and IgE sensitisation to soy infant formula was less than reported and that there was insufficient evidence to hypothesise that the risk would be increased in infants younger than six months (59, 60).

**Conclusion**

Infants presenting with functional gastrointestinal problems often go through a series of unnecessary investigations and medical treatments. The practical algorithms presented in this paper will help general practitioners and paediatricians to diagnose and manage these functional disorders and CMPA, focusing on reassurance, education and dietary intervention. The diagnosis and management of CMPA is challenging because there is no specific symptom or diagnostic test other than exclusion or provocation. Overall, medication has failed to provide significant improvements in these conditions. Although there is some evidence that functional gastrointestinal disorders and CMPA may be accompanied by dysbiosis, the proof on the efficacy of therapeutic interventions with prebiotics and probiotics is very limited.
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**Figure 1.** Algorithm for the management of constipation in formula-fed infants.

**Figure 2.** Algorithm for the management of regurgitation in formula-fed infants.

**Figure 3.** Algorithm for the management of colic in formula-fed infants.

**Figure 4.** Algorithm for the management of cow’s milk protein allergy.
Cow Milk Protein Allergy (CMPA)

- CMPA based on symptoms? +/- specific IgE / SPT

Breastfed baby
- Continue BF, mother on CM-free diet for 2-4 weeks
- Symptoms improve or disappear?
  - No: Reconsider compliance, Consult dietitian & medical specialist
  - Yes: Consider Cow’s milk challenge

Formula fed baby
- Anaphylaxis (specific IgE positive or pos SPT)
  - 2-4 weeks AAF
  - Symptoms improve or disappear?
    - No: Not CMPA
    - Yes: Consider Cow’s milk challenge

Formula fed baby
- No anaphylaxis
  - EHF 2-4 weeks
  - Symptoms improve or disappear?
    - No: Not CMPA
    - Yes: Consider Cow’s milk challenge

SPT: skin prick test
BF: breastfed
AAF: amino acid-based formula
EHF: extensively hydrolyzed formula (CM/Rice), Soy formula, AAF

Long-term management
- Elimination of cow milk sources
- Consider: Breast milk as the first option
  - Extensively hydrolyzed formula (CM/Rice), Soy formula, AAF
  - for at least 6 months or until 9 to 12 months of age
- Monitor for tolerance

May not be undertaken if clinical diagnosis is obvious or symptoms are life threatening.