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SPECIAL ISSUE: *Prebiotics and probiotics in paediatrics*

Updated algorithms for managing frequent gastro-intestinal symptoms in infants

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REVIEW ARTICLE

Abstract

Regurgitation, constipation, excessive crying/fussiness, infantile colic and gassiness are frequent GI manifestations in young infants and result in numerous visits to paediatricians and in many cases in unnecessary change of formulas. The aim of this study was to offer paediatricians consensus based and simple algorithms for the management of the most frequent GI symptoms in infants. Paediatric gastroenterologists processed practical algorithms to assist general practitioners and general paediatricians. Four such practice recommendations were developed, based on the in 2013 published algorithms after an updated literature review. These algorithms cannot be considered as an 'evidence based guideline'. To date, these algorithms are the result of a consensus based on the available literature and the algorithms published in 2013.

Keywords: constipation, colic, crying, functional disorder, formula, gastrointestinal symptom, regurgitation

1. Introduction

Functional gastro-intestinal (GI) symptoms such as regurgitation, constipation, excessive crying and colic are very frequent in infants (Hyman *et al.*, 2006). The Rome III criteria propose diagnostic criteria for these functional GI symptoms, but do not discuss their management (Hyman *et al.*, 2006). Functional GI symptoms are almost never a reason to stop breastfeeding. However, functional GI symptoms are a frequent reason for formula change. Already 30 years ago, 35% of parents report moderate digestive problems leading to a change in infant formula (Forsyth *et al.*, 1985).

Although algorithms attempt to separate the different GI functional symptoms, in real life many infants do present with a combination of these symptoms. About half of the infants present with one or more functional GI symptoms, with regurgitation, constipation and colic (prolonged crying fits) each accounting for roughly 20 to 25% (Iacono *et al.*, 2005). If consulted for such manifestations general practitioners and family paediatrics very often change the formula.

The authors present practical algorithms for the management of functional GI symptoms. Since double-blind placebo controlled prospective intervention trials are very limited in this field, our algorithms are based on consensus using the evidence wherever it was available. This paper is the follow-up publication that was already announced in the abstract of the original publication, since it was written that 'the authors are convinced that challenging these proposals will result in updated and improved versions' (Vandenplas *et al.*, 2013).

2. Regurgitation

The prevalence of daily regurgitation in 3-4 month old infants is estimated to be around 50 to 60% (Osatakul *et al.*, 2002). It is hypothesised that regurgitation is related to the volume of food ingested: the greater the volume ingested, the longer the gastric emptying time and the higher the intragastric pressure, and the more frequent transient spontaneous relaxations of the lower oesophageal sphincter, which predispose an infant to gastro-oesophageal reflux (GER) (Khoshoo *et al.*, 2000). However, the evidence for this (very logic) way of thinking is very limited, since only 6 infants were included in the only paper evaluating this hypothesis (Khoshoo *et al.*, 2006).

Diagnosis

GER is a physiological process occurring several times per day in all healthy individuals. Regurgitation is defined as the passage of refluxed contents into the pharynx or mouth, or from the mouth (Sherman *et al.,* 2009). Vomiting is defined as a central nervous system reflex involving both autonomic and skeletal muscles. Most GER episodes occur during the postprandial period and cause few or no symptoms (Vandenplas *et al.*, 2009). According to the Rome III criteria, the diagnosis of regurgitation in a healthy infant between three weeks and 12 months of age should include: regurgitation two or more times per day for three weeks or more and absence of nausea, hematemesis, aspiration, apnoea, failure to thrive, difficulty in feeding or swallowing, and abnormal posture (Hyman *et al.*, 2006). More than 50% of all infants respond to these criteria. More than 4 episodes of regurgitation per day, what occurs in about 20% of all infants, is considered by parents as a troublesome condition for which they seek medical help (Hegar *et al.*, 2009; Martin *et al.*, 2002; Nelson *et al.*, 1997; Vandenplas *et al.*, 2009). This definition of 'troublesome regurgitation' (≥4 episodes/day for ≥2 weeks, in infants >3 weeks and <6 months) was used in our algorithm (Figure 1).

Management

The great majority of infants that regurgitate are normal healthy infants. Regurgitation is physiologic in infants. However, in the infant with troublesome and frequent regurgitation, a complete medical history and physical examination are mandatory in order to rule out red flags that may suggest a pathological condition. An important parameter is the evolution of the child's anthropometric percentiles. Physiological regurgitation should not be diagnosed in an infant presenting with regurgitation/vomiting and/or poor weight gain (Stroud *et al.*, 2009). The management of regurgitation starts with parental education and reassurance. Parents need to be informed on how overfeeding may exacerbate regurgitation. In infantile regurgitation, thickened formula or 'anti-regurgitation formula' (AR-formula) decreases the frequency and the volume of regurgitation (Vandenplas *et al.*, 2009). Although AR-formula may not decrease the number of reflux episodes, the reduction in episodes and volume of regurgitation is a welcome improvement in quality of life for the caregivers (and the infants) (Vandenplas *et al.*, 2009). Prone (anti-trendelenburg) position cannot be recommended because of the risk of sudden infant death syndrome (SIDS) (Stroud *et al.*, 2009). Studies failed to show any benefit of anti-secretory drugs or prokinetic

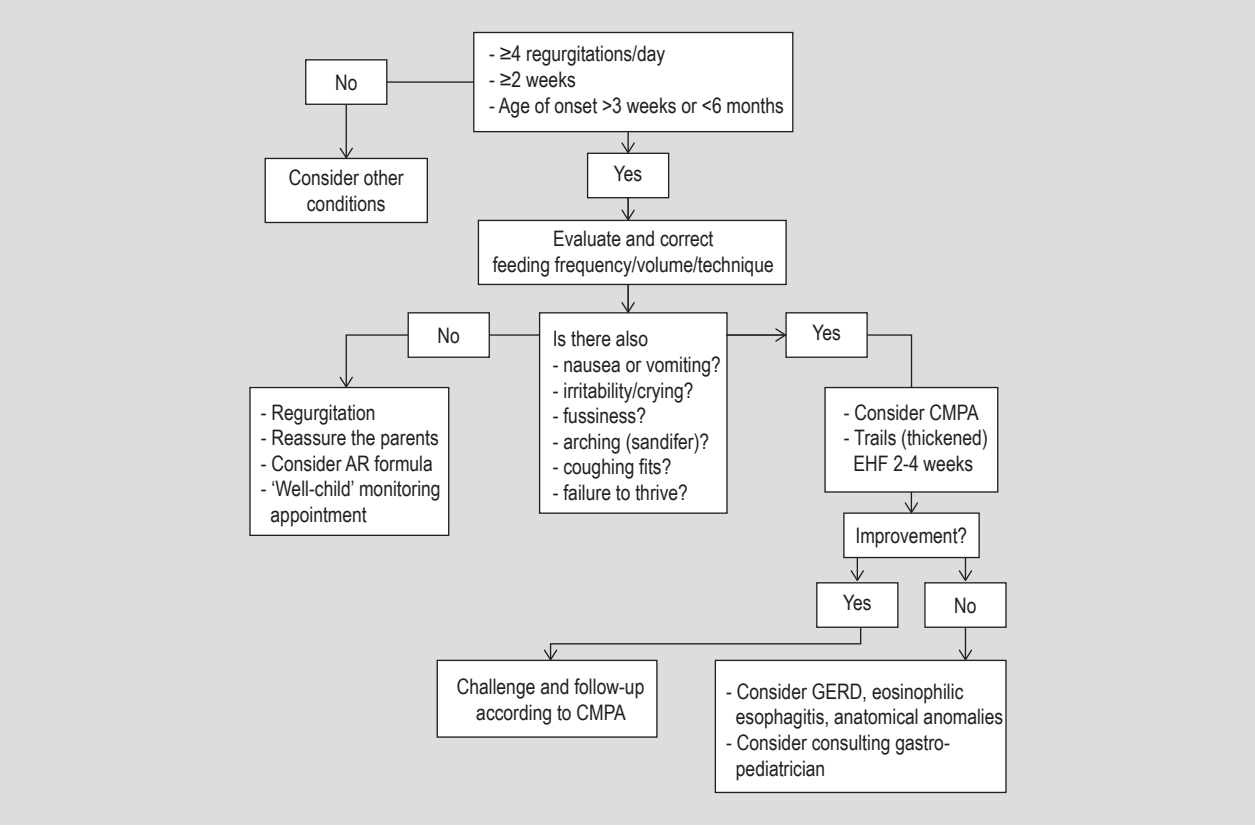

Figure 1. Algorithm for the management of regurgitation in formula-fed infants. AR = anti-regurgitation; CMPA = cow's milk protein allergy; EHF = extensive hydrolysate formula.

agents in this situation (Horvath 2008). A subset of infants with regurgitation that do not respond to traditional management may in fact suffer cow's milk protein allergy (CMPA) (Vandenplas *et al.*, 2009). Elimination of cow's milk protein decreases regurgitation and/or vomiting significantly within 2 weeks in these infants (Vandenplas *et al.*, 2009). Re-introduction causes recurrence of symptoms. Studies support the use of extensively hydrolysed formula in formula-fed infants with bothersome regurgitation and vomiting (Vandenplas *et al.*, 2009).

In contrast, gastro-esophageal reflux disease (GERD) is present when the reflux of gastric contents causes a decreased quality of life and/or complications (Vandenplas *et al.*, 1998). Obviously, there is a grey zone between troublesome regurgitation and GERD. The management of GERD includes besides lifestyle changes pharmacological therapy, mainly acid reducing medications (Vandenplas *et al.*, 2009).

The nutritional management of regurgitation consists of correcting the frequency and volume of the feedings if necessary. Thickened AR-formulas – also known as a 'anti-spitting up' formulas – have an increased viscosity and relieves not only the volume and frequency of regurgitation, but also reduces crying, improves sleep, and improves weight gain (Vandenplas *et al.*, 2009). AR-formulas contain different thickening agents: processed rice, maize or potato starch, guar gum or locust bean gum (Vandenplas *et al.*, 2009). A negative effect of the thickener on absorption of vitamins and minerals has been hypothesised *in vitro* (Aggett *et al.*, 2002), but has not been demonstrated *in vivo* (Levtchenko *et al.*, 1998). If commercial AR-formula is not available, a thickening agent may be added to the formula. However, cereals increase the caloric intake, possibly causing excessive weight gain. Locust bean gum does not increase the caloric density, but may cause gassiness. 'Home thickening' of a regular formula increases the osmolarity, which in turn may increase the number of lower oesophageal sphincter relaxations (Vandenplas *et al.*, 2009), which may cause more reflux and regurgitation. Patients with regurgitation/vomiting and persistent failure to thrive should be referred to a paediatric specialist (Vandenplas *et al.*, 2013).

There is limited literature suggesting that some specific probiotics (*Lactobacillus reuteri* DSM 17938) do prevent functional GI symptoms, among which regurgitation (Indrio *et al.*, 2014). *L. reuteri* has also been shown to accelerate gastric emptying and therefore to improve regurgitation (Indrio *et al.*, 2011). However, more studies are needed to provide any specific recommendations.

As mentioned above, CMPA should be suspected in an infant with recurrent regurgitation and/or vomiting, certainly if associated with eczema and/or wheezing. In this case, elimination of CMP should start with an extensive hydrolysate based on whey, casein or another protein source such as rice, and by amino acid-based formulas (American Academy of Pediatrics, 2000; Vandenplas *et al.*, 2014b). A thickened extensive hydrolysate offers interesting therapeutic options (Vandenplas *et al.*, 2014a). A pilot-study suggest that a hydrolysate, thickened or not, is equally effective in infants with a positive cow's milk protein challenge and that only the thickened hydrolysate is effective in those with a negative challenge test (Vandenplas *et al.*, 2014a). There are also publications that need to be replicated suggesting that formulas without palm olein or palm oil as the main source of fats in the oil blend are associated to less regurgitation (Alarcon *et al.*, 2002) or that a thickened partial hydrolysate formula may be slightly more effective than a thickened standard infant formula. Partial hydrolysates empty the stomach faster than standard protein, what may contribute to a decrease in regurgitation (Vandenplas *et al.,* 2014c).

3. Constipation

In infants younger than four months, the type of feeding has a key role in the stool pattern. Healthy breast-fed babies may defecate as frequently as seven times per day or as infrequently as once per week (Hyman *et al.*, 2006; Tabbers *et al.*, 2014). Extremes up to 12 times per day or once in three or four weeks have even been reported (Hyman *et al.*, 2006; Tabbers 2014). In this age group, hard stools are found only in 1.1% of exclusively breast-fed vs 9.2% in standard formula-fed (without prebiotic or probiotic supplementation) infants (Tunc *et al.*, 2008). Firm or hard stools are often seen with the change from breast milk to infant formula or after introduction of solid food. Harder stools are frequent in infants fed with formulas containing palm olein oil or palm oil as the main source of fat (Tunc *et al.*, 2008).

Diagnosis

A thorough medical history and physical examination are the cornerstones for establishing the aetiology of infant constipation. Failure to pass meconium within 24 to 48 h after birth should raise suspicion of Hirschsprung's disease (Biggs and Dery, 2006; Tabbers *et al.*, 2014). The normal defecation pattern of infants must be known by the health care professional in order to differentiate between abnormal and normal to properly educate and advise parents and to avoid unneeded treatments. It is crucial to establish what the parents mean when using the expression 'constipation': the length of time the condition has been present, the frequency of bowel movements, the consistency and size of the stools, whether defecation is painful, whether blood has been present in the stool, and whether the child seems to experience abdominal pain (Figure 2). The Amsterdam stool scale may be a useful tool to get more objective

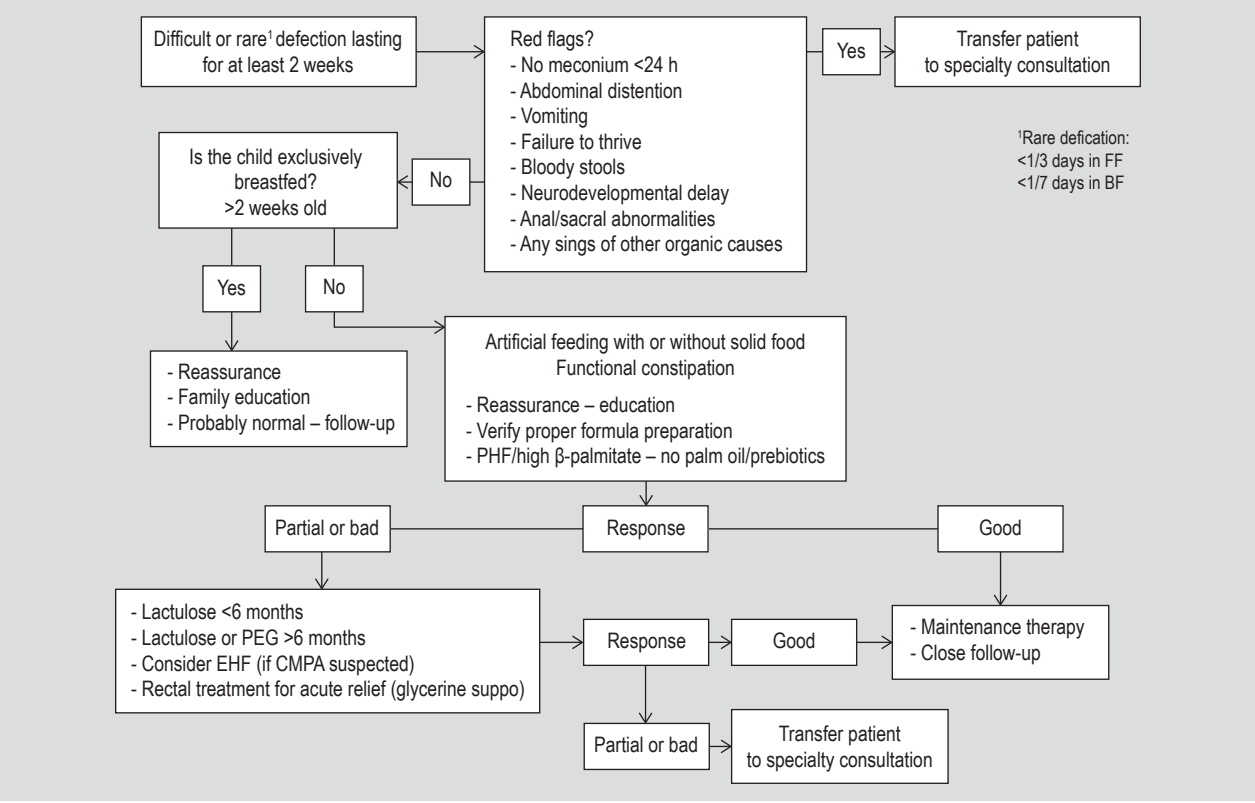

Figure 2. Algorithm for the management of constipation in formula-fed infants. BF = breast-feeding; CMPA = cow's milk protein allergy; EHF = extensive hydrolysate formula; FF = formula feeding; PEG = polyethylene glycol; PHF = partial hydrolysate formula.

description of stool consistency (Ghanma *et al.*, 2014). For infants, many experts recommend using the definition proposed by Biggs: 'difficult or rare defecation lasting for at least two weeks' (Biggs and Dery, 2006). The diagnosis of functional constipation (FC) is made by history and physical examination (Tabbers *et al.*, 2014). No testing is necessary if there are no arguments for an organic cause (Tabbers *et al.*, 2014). The younger the infant, the higher the risk of anatomical or organic cause, although FC remains the most frequent condition at any age. Anorectal examination should evaluate the perianal sensations, anal position and tone, the size of the rectum, the presence of an anal wink, the amount and consistency of stool, and its location within the rectum (Vanderplas *et al.*, 2013). Specific tests must be performed if other clinical data are present (i.e. pain, failure to thrive, intermittent diarrhoea, abdominal distention) (Tabbers *et al.*, 2014). 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 (Koo *et al.*, 2006; Tabbers *et al.*, 2014).

Management

The first step in the treatment of FC is parental education. Doctors should address the myths and fears and point out that FC is one of the most common, non-dangerous problems in paediatrics and that it usually disappears (Tabbers *et al.*, 2014; Vandenplas *et al.*, 2013). Dietary recommendations may help. If the probability of any organic condition is low, reassurance and close follow-up should be enough. In some regions, it is popular to use magnesium-rich mineral water to prepare the infant formula. However, there is no evidence to support this practice, and mineral intake is in these circumstances above international recommendations (Vandenplas *et al.*, 2013). Juices that contain sorbitol, such as prune, pear, and apple juices, can decrease constipation, but the risk exists that the infant is drinking fruit juice instead of formula. Glycerin suppositories can be helpful if acute relief by rectal emptying is wanted. Evidence does not support the use of mineral oil (risk of lipoid pneumonia due to aspiration) or enemas (e.g. phosphate) in young infants. Infant formulas containing partially hydrolysed proteins, fortified with prebiotics and/or probiotics and high in sn-2 palmitate or without palm oil as the main source of fat in the oil blend, offer a good alternative for managing FC (Koo *et al.*, 2006; Moro *et al.*, 2003). In fact, several studies were performed with a partial hydrolysate, a prebiotic supplementation and high β-palmitate, with quiet positive results (Bongers *et al.*, 2007; Moro *et al.*, 2003; Vivatvakin *et al.*, 2010). Also, there are some formulas commercialised as 'anti-constipation formulas'; some of them are rich in lactose and have a high – but within the regulatory limits – content of magnesium

(Chao *et al.*, 2007). An Italian study showed that *L. reuteri* is effective in the prevention of constipation (Indrio *et al.*, 2014). The literature about the efficacy of probiotics in infant constipation is ambiguous, since about half of the studies are negative and half are positive (Banaszkiewicz and Szajewska, 2005; Bekkali *et al.*, 2007; Bu *et al.*, 2007; Coccurullo *et al.*, 2010; Guerra *et al.*, 2011; Tabbers *et al.*, 2011). In favour of probiotics is their safety profile. Stool pattern (i.e. consistency and frequency) can be modulated by the type and dose of prebiotics. Fortifying formulas with galacto-oligosaccharides (GOS) alone or GOS/fructo-oligosaccarides (FOS) are associated with softer and more frequents stools in young children (Moro *et al.*, 2003; Ziegler *et al.*, 2007).

4. Fussiness, gassiness accompanied by crying

Although many infants are distressed because of fussiness and gassiness, almost all of these infants also cry a lot, and therefore caregivers are more focused on the crying than the other signs and symptoms. Therefore, in these cases, a good medical history is critical. Infants usually communicate and express themselves by crying (Vandenplas *et al.*, 2013). Healthy infants cry between 20 min and 3.5 h/day (Baildam *et al.*, 1995). By the time parents present to a doctor with their crying child, they are often anxious, frustrated, and sleep-deprived. These emotions contribute to the difficulty of making an evaluation of the nonverbal crying infant, aggravated by insufficient caretaker knowledge and information (St. James-Roberts and Peachey, 2011). Overall crying can be substantially reduced when parents adopt methods of care involving more physical contact and greater responsiveness (St. James-Roberts, 2008). In a very small number of cases, prolonged crying and fussiness in the first three months may be due to food intolerance and other organic disturbances (St. James-Roberts, 2008).

Diagnosis

Symptoms such as fussiness or excessive gas are in the great majority of cases not associated with any medical condition. A fussy infant is one that is easily upset and given to bouts of ill temper (Vandenplas *et al.*, 2013). The presence of a certain amount of air in the digestive tract is normal; however, when there is an excess, symptoms/signs such as abdominal distension, and even pain can be present. Improper feeding techniques are an important cause of aerophagia. Some findings may alert doctors to the potential presence of an organic condition (in decreasing order of evidence): (1) positive physical exam; (2) frequent regurgitation, vomiting, diarrhoea, blood in stools, weight loss/failure to thrive; (3) lack of a diurnal rhythm, (4) positive family history of migraine, asthma, atopy, eczema; (5) maternal drug ingestion (Figure 3; Vanderplas *et al.*, 2013). Low lactase activity and/or secondary lactose malabsorption in fussy babies can be associated with excessive gas and soft stools with/without presence of diaper rash (Gormally, 2001). The clinical history and physical exam are the cornerstones for evaluating young infants whose chief complaints include crying, irritability, screaming, or fussiness.

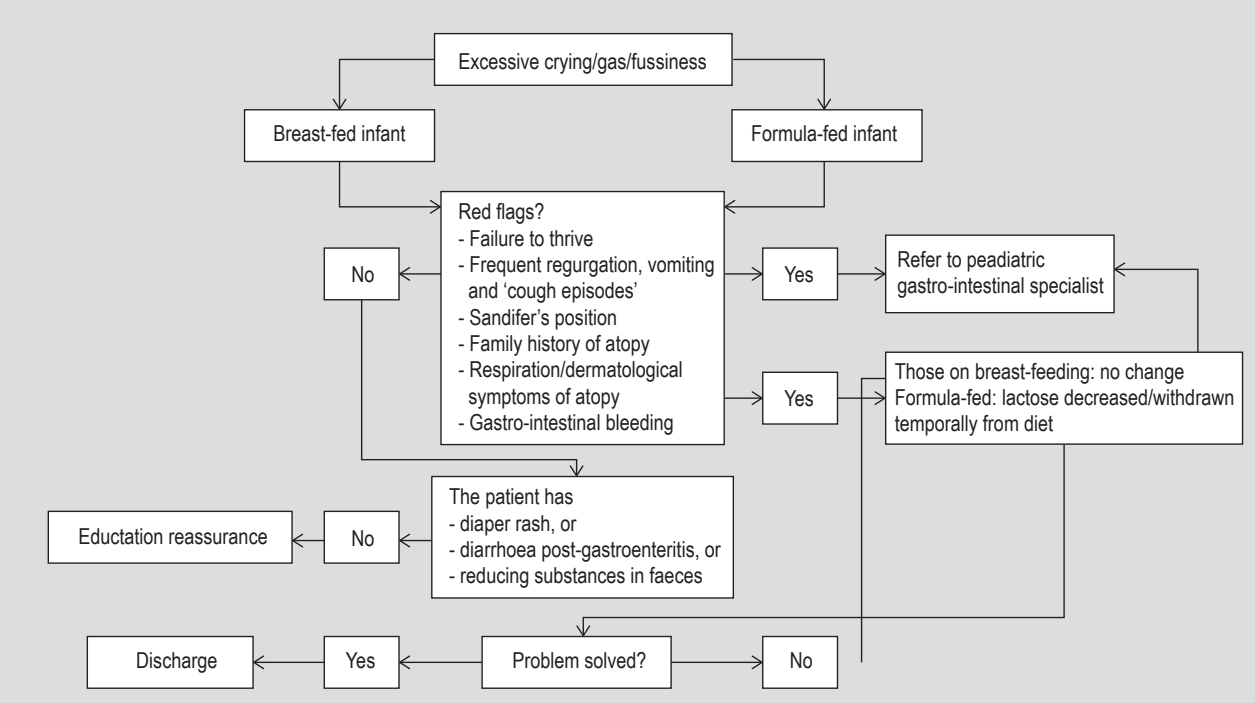

Figure 3. Algorithm for the management of gassiness in formula-fed infants.

Management

Fussiness, crying, and excessive gas production may be normal. There is strong evidence that the introduction of structured parenting based on behavioural principles from about six weeks of age is likely to help prevent night waking and signalling after 12 weeks (St James-Roberts and Peachey, 2011). Where no organic disturbances are found, the available evidence provides no basis for advising parents in general that changes in their care are likely to resolve crying problems in one-to-three-month-old infants (Vandenplas *et al.*, 2013). Once organic disturbance has been considered and the infant's healthy growth and development are confirmed, the focus of intervention should be on containing the crying and providing parents with information and support (Vandenplas *et al.*, 2013). Important elements advocated by an expert group are: (1) examining the notion that crying means there is something 'wrong' with a baby at this age; introducing alternatives, e.g. that it signals a reactive or vigorous baby; (2) viewing the first three months of infancy as a developmental transition, which all babies go through more or less smoothly; (3) reassuring parents that it is normal to find crying aversive and discussing the dangers of 'shaken baby syndrome'; (4) discussing ways of containing/minimising the crying, and highlighting positive features of the baby; (5) considering the availability of support and the development of coping strategies which allow individual parents to take time out and 'recharge their batteries'; (6) empowering parents and reframing the first three months as a challenge which they can overcome, with positive consequences for themselves and their relationships with their babies; (7) continuing to monitor infant and parents. In formula fed infants, when low lactase activity is suspected and the child has gassiness, diarrhoea, and in some cases diaper rash, and parents really focus on this, lactose may be withdrawn from the diet temporarily (Barr *et al.*, 2001; Vandenplas *et al.*, 2013). No randomised clinical trials have been published on partial whey hydrolysate formulas in infants with colicky symptoms (Vandenplas *et al.*, 2014c). In some individual cases GERD may cause crying and fussiness. However, all placebo controlled studies evaluating the efficacy of proton pump inhibitors (PPI) in fussy infants failed to show benefits (Vandenplas, 2014).

5. Infantile colic

The original definition of infantile colic (IC) dates back from 1954: crying lasting three or more hours a day, at least three days a week for at least three weeks (Wessel *et al.*, 1954). 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' (Hyman *et al.*, 2006). The incidence varies between 5 and 30% (Savino and Oggero, 1996; Shergill-Bonner, 2010). IC occurs equally in breast- and bottle-fed infants, and in both sexes. The aetiology is unknown and multiple hypotheses have been proposed, including altered GI function, food intolerance, transient low lactase activity, CMPA, GER, intestinal microflora imbalance, etc. (Miranda, 2009). Parental coping is of major importance for colic, more than any other functional GI manifestation.

Diagnosis

The cardinal symptom is excessive and persistent loud crying, which mostly occurs late in the afternoon. During each episode the child appears distressed, irritable and fussy and contracts the legs, becomes red-faced, and frequently experiences episodes of borborygmi. CMPA and GER-disease should be considered in patients with severe IC. According to limited literature, a transient low lactase activity could cause also excessive crying (Cohen-Silver and Ratnapalan, 2009). But attention should also always focus on parental coping (parental anxiety, depression, absence of mother-child reciprocity, risk for child abuse, etc.) (Figure 4).

Management

There are no uniform criteria for a specific therapeutic regimen. The first recommended step is to look for potential 'red flags' to exclude organic disease (see algorithm). If these 'red flags' are not present, the feeding technique should be evaluated, the caregivers should be reassured and supported. General advice emphasising the self-limiting nature of the condition is of importance. For breast-fed infants, clinicians should advise mothers to continue breast feeding, but can sometimes recommend that the mothers avoid intake of cow's milk proteins for a minimum of two weeks. In formula-fed infants, the elimination of cow's milk proteins and dietary treatment with an extensively hydrolysed protein formula has been reported as an effective treatment (Shergill-Bonner, 2010). When CMPA is a not a potential cause of the IC, experience, but not evidence, has shown that partially hydrolysed formulas can be an useful alternative or in cases where an extensive hydrolysate would be too expensive or not available (Shergill-Bonner, 2010; Vandenplas *et al.*, 2014c). In some cases, these formulas are lactose-reduced or lactose-free and have added prebiotics showing, with varying levels of evidence, a reduction in the number of crying episodes per week and total crying time (Vandenplas *et al.*, 2014c). However, a beneficial role of lactose-free formulas or soy based formulas has not been consistently demonstrated in patients with IC (Critch, 2011). Nevertheless, selection of patients is likely to be a major bias in these studies.

The efficacy of medications such as dicyclomine, dicycloverine or cimetropium has been evaluated. The latter has shown a high rate of lethargy, motion sickness and/

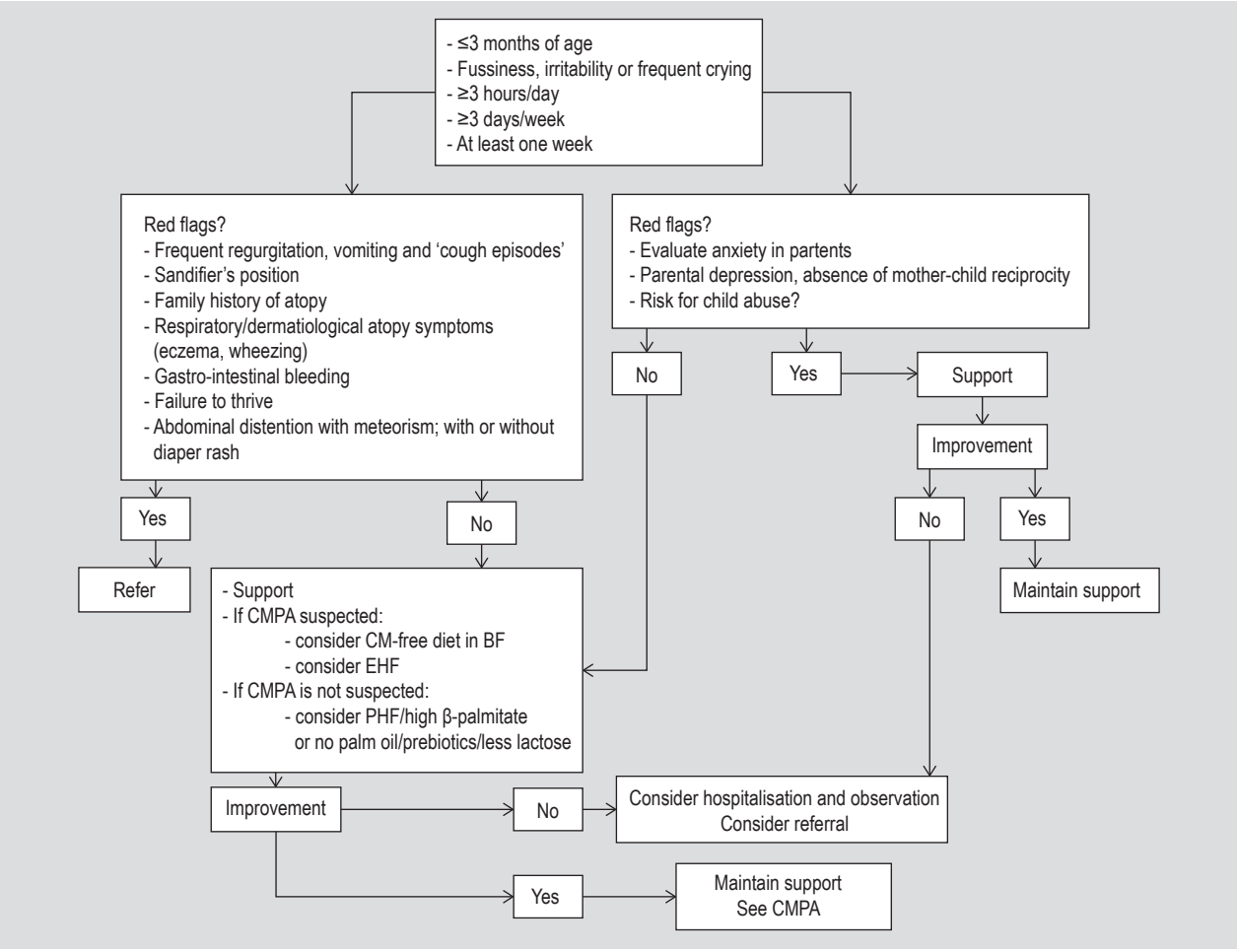

Figure 4. Algorithm for the management of colic in formula-fed infants. AR = anti-regurgitation; BF = breast-feeding; CMPA = cow's milk protein allergy; EHF = extensive hydrolysate formula; PHF = partial hydrolysate formula.

or somnolence (Savino *et al.*, 2002). Simethicone showed no difference versus placebo (Metcalf *et al.*, 1994). Other RCTs have studied glucose or saccharose solutions, with varying effects on crying time (Akçam and Yilmaz, 2006). One clinical trial showed safety and efficacy of *L. reuteri* in prevention of IC (Indrio *et al.*, 2014). Two randomised double blind trials showed that *L. reuteri* effectively reduces crying time in breastfed infants (Savino *et al.*, 2010; Szajewska *et al.*, 2013). A recent Australian study with the same probiotic strain *L. reuteri* in a community sample of breastfed infants and formula fed infants with IC failed to show any benefits (Sung *et al.*, 2014). At 1 month, the probiotic group even cried or fussed 49 min more than the placebo group (95% confidence interval: 8 to 90 minutes, P=0.02) (Sung *et al.*, 2014). In a prospective randomised controlled study a partial hydrolysate, with high β-palmitate, and a prebiotics mixture of GOS/FOS resulted in a significant reduction of crying episodes in infants with colic within one week of intervention (Savino *et al.*, 2006). Several studies have been performed with PPI in distressed infants; they all failed to show any benefits (Chen *et al.*, 2012; Orenstein *et al.*, 2009; Smith *et al.*, 2013; Winter *et al.*, 2012). Studies have evaluated the role of additional familial caregivers' support, counselling therapies, car rides during colic episodes, reduction of stimulating actions (such as changing diapers), chiropractic, spinal massages or even the use of herbal options. Unfortunately, none of these trials has been of sufficient methodological quality to allow a recommendation (Hall *et al.*, 2013; Savino *et al.*, 2005).

IC is a multi-factorial condition. This multifactorial aspect makes it unlikely that a single intervention will be found that is associated with significant improvement in an unselected patient population. The effect/benefit of probiotics need further evaluation. Also, the data with prebiotic oligosaccharides are too limited to recommend their routine use at this time. So far, there is limited evidence for a beneficial effect of partial hydrolysates. Actually, partially hydrolysed milk has also been shown to be helpful and can be a useful option in the community when a cow's milk allergy is not considered to be an underlining cause of the colic (Critch, 2011; Shergill-Bonner, 2010). In many centres, infants presenting with colic are treated with extensively hydrolysed formulas. However, the evidence for

this recommendation comes from a few studies performed in reference centres. There are no data on the efficacy of extensive hydrolysates in unselected infants with colic, when there is absence of arguments for a diagnosis of CMPA. Nevertheless, the elimination of cow's milk protein and using extensively hydrolysed protein formula have been shown to be effective treatments for a subset of babies with infantile colic (Critsch, 2011; Shergill-Bonner, 2010).

6. Conclusions

Healthy infants presenting with common functional GI-problems often go through a series of unnecessary investigations and medical treatments. These practical algorithms will help general practitioners and paediatricians in the diagnosis and management of these frequent functional GI disorders, focusing on reassurance and dietary intervention. Depending on the GI symptom/condition our proposed algorithms offer dietary alternatives for a practical nutritional management. Overall, medication has failed to bring significant improvement in these conditions. Although there is some evidence that many functional GI disorders are accompanied by a dysbiosis, the efficacy of therapeutic intervention with prebiotics and probiotics is promising but still limited. However, since these interventions are very safe, they are a worthwhile therapeutic option even if the evidence of benefit is limited.

Conflict of interest

Y. Vandenplas is consultant for Biocodex and United Pharmaceuticals. The other author has no conflicts of interest relevant to this article to disclose.

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