Abstract
Over 50% of all infants present with one or more functional gastrointestinal disorders (FGIDs) during the first months of life. The literature on the effect of partially hydrolyzed formula (pHF) in the management of FGIDs was reviewed. There is insufficient evidence to recommend pHFs in regurgitation, although one study suggests that a thickened pHF may be more effective than antiregurgitation formulas with intact protein. No randomized clinical trials on pHFs in infants with colicky symptoms have been published. pHFs, fortified with pre- and/or probiotics, with high levels of sn-2 palmitate in the fat blend or without palm oil provide some benefit in functional constipation. However, there are no studies evaluating the efficacy of pHF as single intervention in constipated infants. Conclusion: Overall, pHF may offer some useful alternative to intact protein in the dietary management of common FGIDs, although the evidence is very scarce. Well-designed, randomized trials are needed to allow to recommend the use of pHF in infants with FGIDs.

Introduction
Many publications focus on the role of partially hydrolyzed formulas (pHFs) in allergy prevention. In this chapter, the role of pHFs in the management of functional gastrointestinal disorders (FGIDs) in infants presenting with regurgitation, infantile colic (IC) and functional constipation (FC) is reviewed. In many countries, pHFs are marketed as having a better ‘digestibility’ and ‘being
effective in the dietary management of common GI symptoms’. These symptoms can be considered as part of the normal developmental process during infancy and are often not the manifestation of underlying (GI) disease. FGIDs are considered to be benign conditions, but they are often frustrating problems for parents and caregivers. These FGIDs occur in up to 50% of all infants, each accounting for 15–25% [1]. Since these GI manifestations are self-limiting transient conditions, ‘time is the cure’. Limited data suggest that FGIDs such as IC may be associated with recurrent abdominal pain, migraine, allergic disorders, sleep disturbances and maladaptive behavior such as aggressiveness in later life [2]. Many infants present with a combination of GI symptoms [2].

**Definition of Partially Hydrolyzed Formulas**

Hydrolyzed formulas are manufactured through enzymatic processes which break native proteins into smaller pieces. Based on the degree of enzymatic hydrolysis, ultraheating and ultrafiltration, protein hydrolysates are differentiated into pHFs or extensively hydrolyzed formulas (eHFs) [3]. There is no general agreement on the criteria to define pHF and eHF, and protein size is generally used to identify each one. The degree of protein hydrolysis are characterized by biochemical techniques, such as the spectrum of peptide molecular weights or the ratio of α-amino nitrogen to total nitrogen [4]. A wide range of proteins, including cow’s milk, soy and rice, are common ingredients of pHFs. Regarding cow’s milk, major protein fractions (i.e. whey, casein or both) are used rather than whole cow’s milk protein. Cow’s-milk-based formulas with intact proteins contain proteins in the range of 14 kDa (α-lactalbumin) to 67 kDa (bovine serum albumin). pHFs contain oligopeptides that have a molecular weight generally <5 kDa (range 3–10 kDa) while >90% of peptides in eHFs have a molecular weight of <3 kDa [5]. Both pHFs and eHFs consist of a wide range of peptide sizes. In commercially available whey pHF, 18% of peptides have a molecular weight >6 kDa. Peptides need to be in the range of 10–70 kDa (predominantly 10–40 kDa) to be able to act as an allergen [6].

**Partially Hydrolyzed Formulas and Regurgitation**

Thirteen studies reported that the prevalence of regurgitation varies widely (range 3–87%) in infants younger than 12 months (table 1) [1]. Of these, 8 studies were prospective and 5 were cross-sectional trials. The criteria used to define regurgitation showed a large range of variation. Two studies using the Rome III
criteria (‘two or more episodes a day for at least 3 weeks’) reported a prevalence of 17.3 and 26% [1]. Other studies used definitions ranging from at least one episode a day to at least four episodes a day. In studies reporting on infants at different ages, prevalence was highest in the first few months of life and declined after about 6 months.

Daily regurgitation occurs in more than two thirds of otherwise healthy infants and represents a topic of discussion with pediatricians at one quarter to one fifth of all routine 6-month infant checkups [1]. Poor weight gain, failure to thrive, dysphagia, abdominal or substernal/retrosternal pain, cough, laryngitis, sinusitis and wheezing in infancy may raise the suspicion of gastroesophageal reflux disease and suggest the need to conduct further diagnostic or therapeutic interventions [7]. From the diagnostic point of view, detailed history taking and careful physical examination are sufficient to reliably diagnose uncomplicated gastroesophageal reflux [7].

From the therapeutic point of view, no intervention is required for uncomplicated gastroesophageal reflux. The management of regurgitation starts with reassuring parents by providing information on the natural history of regurgitation, correct formula preparation if the infant is not breastfed and how to avoid overfeeding that may exacerbate the symptoms [2, 7]. Regurgitation is not a reason to stop breastfeeding. Further education of parents may involve positioning and avoidance of environmental smoke exposure.

Thickened or ‘antiregurgitation formulas’ decrease regurgitation [2, 7]. Proton pump inhibitors do not decrease infant regurgitation, crying, distress and irritability [8]. There is no indication for drug treatment in ‘happy spitters’ or even in troublesome regurgitation [2]. Commercially available antiregurgitation formulas contain different thickening agents: processed rice, corn or potato starch, guar gum or locust bean gum. Locust bean gum does not increase the caloric density but may cause bloating [7].

Table 1. Prevalence of infant regurgitation, IC and constipation

<table>
<thead>
<tr>
<th></th>
<th>Regurgitation, %</th>
<th>IC, %</th>
<th>Constipation, %</th>
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<tbody>
<tr>
<td>Lower limit</td>
<td>6.1</td>
<td>4.0</td>
<td>2.0</td>
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<tr>
<td>P25</td>
<td>14.9</td>
<td>10.5</td>
<td>3.8</td>
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<tr>
<td>Median</td>
<td>26.7</td>
<td>17.7</td>
<td>7.8</td>
</tr>
<tr>
<td>P75</td>
<td>40.9</td>
<td>21.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Upper limit</td>
<td>61.5</td>
<td>64.5</td>
<td>61.5</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>27.0</td>
<td>21.0</td>
<td>21.5</td>
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Questionnaire: estimated prevalence by a group of key opinion leaders [adapted from ref. 1]; medical, P25 and P75, and extremes reported in the literature.
eHFs empty the stomach significantly faster than standard infant formula and pHF (medians 46 vs. 55 and 53 min, respectively) [2]. pHFs fortified with prebiotics and low levels of lactose were associated with a reduction in the number of regurgitation episodes (95% CI 1.57–2.16; p < 0.05) [2]. A prospective, double-blind, randomized crossover trial, which was performed for a 1-month period in 115 formula-fed infants (aged 2 weeks to 5 months), comparing an antiregurgitation formula with intact protein to a thickened pHF showed that the number and volume of regurgitation episodes decreased significantly in both groups, but that the reduction was statistically greater with the pHF [9]. The thickened pHF was also found to decrease crying time and to improve quality of life of the parents and the baby [9].

In an infant with persistent and recurrent regurgitation, especially when associated with other manifestations of allergic disease such as atopic dermatitis and/or wheezing, cow’s milk protein allergy (CMPA) should be suspected.

In summary, a thickened formula reduces infant regurgitation. One study indicates that a thickened pHF may be of additional benefit, although the data are too limited to result in a recommendation.

**Partially Hydrolyzed Formulas and Infantile Colic**

The Rome III criteria define IC as ‘episodes of irritability, fussing or crying that begin and end for no apparent reason and last at least 3 h a day, at least 3 days a week for at least 1 week’. The original Wessel criteria stated that the duration of symptoms had to be at least 3 weeks. IC occurs equally in breast- and formula-fed infants and in both sexes. Symptoms include excessive crying in otherwise normal thriving infants, which often occurs in the evenings. Crying episodes often start in the first weeks of life, decrease thereafter and resolve at the age of 4–5 months. Young infants with long crying bouts, hard-to-soothe behavior and fussiness that do not match the Rome III criteria are also frequently labeled as ‘colicky’ babies.

According to the data from 30 studies, a prevalence of IC or crying/fussing problems was reported in 2–73% of infants <12 months (table 1) [1]. Of these, 18 were prospective studies; the rest were cross-sectional or retrospective surveys. Only 2 studies used the Rome III criteria. One of these was prospective and reported a prevalence of IC of 19%, while the other was cross sectional and reported a prevalence of 6% [1]. Another 6 studies using the Wessel criteria reported a prevalence of 9–22% [1]. The other studies used a variety of definitions. One study reported a prevalence ranging from 9 to 16% depending on the definition used. The study reporting the highest prevalence was based on parental
report of paroxysmal irritability [1]. A systematic review from 2001 of 15 community-based surveys of the occurrence of IC found rates in the first 3 months of life ranging from 3 to 28% in prospective studies and from 8 to 40% in retrospective studies [1].

Despite its relatively benign nature, this condition can be extremely distressing for parents, especially when they are dealing with their first child. Mothers of infants that cry excessively often believe that their child is not healthy [1, 2]. Although the etiology of IC is not known, there is limited evidence linking persistent crying in the young infant to food allergy. Early studies have demonstrated a high prevalence of IC in infants with CMPA. In a sequential cohort of 100 patients with challenge-proven CMPA, 44% of the infants displayed irritability and colicky behavior during the challenge procedure [2]. This led to the hypothesis that IC may represent a subgroup of a clinical presentation of CMPA. However, there is no agreement on what proportion of infants with IC suffers from CMPA. Indeed, somehow the epidemiologic data on IC are contradictory. While it is said that the incidence of IC in breastfed and formula-fed infants is comparable, it has to be acknowledged that the incidence of CMPA is much higher in formula-fed infants than in breastfed infants. Further epidemiologic and intervention trials have to clarify these aspects.

Regarding the management of IC in breastfed infants, clinicians should advise mothers to continue breastfeeding. Eliminating cow’s milk from the maternal diet may be recommended in a subgroup in order to assess for possible CMPA. In highly selected formula-fed infants with IC, the use of eHFs has been shown to be an effective treatment.

It is beneficial to empower parents and ask them to consider the first 3 months of life as a test that they can overcome with positive consequences for the baby and family [2]. Regarding feeding, there is no justification to discontinue breastfeeding in these infants. In formula-fed infants, when low lactase activity is suspected and the child has gassiness, diarrhea and, in some cases, diaper rash due to the evacuation of acidic stools, lactose may be decreased or withdrawn temporarily from the diet [2]. Lactose malabsorption in young infants is mainly a load phenomenon. The presence or absence of lactose in infant feeding is an area of debate: while the advantage of lactose-reduced or lactose-free infant feeding is not evidence based, low intake of lactose is also not related to major negative effects. Lactose-free infant feeding does not adversely affect growth in term infants.

No randomized clinical trials have been published demonstrating the efficacy of partially hydrolyzed protein as the single change in IC. Nevertheless, reviews suggest that pHF can be beneficial if CMPA is not a potential cause of IC.
Various randomized controlled trials have been published demonstrating the efficacy of pHF. However, in many cases, these formulas are lactose reduced or free of lactose, and have added prebiotics showing, with varying levels of evidence, a reduction in the number of crying episodes per week and total crying time. There is no scientific support for the use of soy formula in these patients. However, in a study of 1,803 infants with common digestive symptoms, 19.8% reported colicky symptoms and received a soy-based infant formula recommended by medical personnel [10]. Unfortunately, this study provides no data on the efficacy of soy. A meta-analysis of various treatments for IC showed that substituting soy- for cow’s-milk-based infant formula was effective, but this benefit disappeared when the analysis was limited to studies of good methodological quality [2].

In summary, there are insufficient data to recommend pHF as single dietary intervention in colicky infants since most studies included other dietary changes as well. However, there is a clear trend showing that industry prefers pHF for the management of IC. Since pHF are likely to be nutritionally adequate and safe, their use can be debated given the nonsignificant trend of improvement in the absence of adverse effects.

Partially Hydrolyzed Formula and Constipation

Eight studies were found reporting a prevalence of FC ranging from 0.05 to 39.3% in infants <12 months (table 1) [1]. Only 2 of the 8 studies were prospective, 5 were cross-sectional studies and 1 a retrospective study. Three of the studies used the Rome III criteria of passage of large-diameter stools at intervals of less than twice a week, with retentive posturing and avoiding defecation by purposefully contracting the pelvic floor. Of these, 1 prospective study found that FC was present in 12% of the 465 infants at 3 months, 14% at 6 months and 11% at 12 months after birth. The other 2 studies were cross sectional with a prevalence of 0.05 and 5%. Several studies of populations outside the age range for this review reported a prevalence of FC ranging from 5.2 to 27.3% in children aged <24 months, and a small study in Brazil found a prevalence of 11–19% using various criteria in 57 children aged 6–41 months. A recent study in China found a prevalence of constipation of 5.6% (55/972) in children <4 years [1].

Hard stools are only noted in 1.1% of exclusively breastfed infants versus 9.2% of standard-formula-fed infants, and firm or hard stools are often seen with the change from breast milk to infant formula or after the introduction of solids [2].
Regarding the management of FC, the first step is parental education [11]. Pediatricians should discuss the myths and worries about FC and point out that it is one of the most frequent, nondangerous conditions in pediatrics and that it usually has a benign long-term outcome. Infants who have constipation and have not yet begun solid foods can be treated with the addition of indigestible, osmotically active carbohydrates to the formula, titrating the dose to induce a daily bowel movement. Glycerin suppositories or rectal stimulation with a lubricated rectal thermometer or catheter can be used occasionally if there is a need for urgent, rapid relief, such as when there is a very hard stool in the rectum, but should not be used frequently. Mineral oil (which has the risk of lipoid pneumonia if aspirated) or enemas (e.g. phosphate) are not indicated and may be harmful in infants.

Regarding dietary management, if an infant with FC is receiving breast milk, is growing and feeding normally, and has no signs or symptoms of obstruction or enterocolitis, reassurance and close follow-up should be sufficient. Infants fed standard formula are more prone to have hard stools due to differences in fat digestion and absorption, and in carbohydrate and protein composition compared to breast milk. If the infant is receiving a standard infant formula, it is recommended to verify that formula preparation is correct. However, in practice, a change in the formula is often suggested. Studies have shown that the type of macronutrients in the formula play a role in the stool pattern. For example, harder stools are frequent in infants fed formula containing palm olein oil or palm oil as the main source of fat. Palm oil has a reduced content of fatty acids esterified to glycerol in the sn-2 position and an increase in those esterified in the sn-1 and sn-3 positions. Fatty acid in positions sn-1 and sn-3 undergoes hydrolysis in the intestine, releasing palmitic acid, which is poorly absorbed and forms calcium soaps responsible for firmer stools [2]. Thus, a formula rich in fatty acids in position sn-2 is likely to soften the stools.

Regarding carbohydrates, it was found that lactose-free formula had a significantly higher percentage of softer stools and lower percentage of hard stools compared to the lactose group at 14 and 28 days of age [2]. However, the authors did not explain the mechanism underlying these findings. These findings are relevant since many pHFs do have a reduced lactose content.

Constipation is more frequent in casein- than in whey-predominant formula [1]. Hydrolyzed formulas produce more frequent and softer stools. A pHF containing an ultrafiltrated mixture of hydrolyzed whey and hydrolyzed casein (75% with a molecular weight <1.5 kDa) and 15% free amino acids has a much shorter GI transit time than standard preterm formula (9.8 vs. 19 h, respectively) [2]. Significantly more stools are passed by breastfed and eHF-
fed infants versus infants given standard or soy-based formulas. Infants receiving breast milk or eHF had twice as many stools as other formula groups [2].

pHFs, fortified with pre- and/or probiotics, with high sn-2 palmitate in the fat blend or without palm oil as the main source of fat in the oil blend offer a good alternative for managing FC in infancy [2]. There are no studies evaluating the efficacy of pHFs as single intervention in constipated infants. There is some evidence that pHFs induce softer stools than standard infant formula in nonconstipated infants.

**Discussion**

FGIDs such as constipation, fussiness, colic or spitting are very common at an early age. Both exclusively breastfed and formula-fed infants can suffer from these symptoms. The incidence of regurgitation and IC is reported to be similar in breastfed and formula-fed infants, while the incidence of constipation is higher in formula- than in breastfed infants.

Evaluation of the feeding technique, effective reassurance of the caregivers and careful education is recommended to alleviate parental anxiety. When the child is formula fed, these mild digestive feeding issues generally cause parents and health care practitioners to switch to a different infant formula based on the belief that the symptoms may be a reflection of formula intolerance.

In the last few years, new formulas, intended to help these children, have been launched worldwide. One of the main characteristics of these formulas is that the proteins are partially hydrolyzed. Many of these formulas also contain other bioactive ingredients like prebiotics, probiotics or special types of fats in their oil blends and, in general, they contain low levels of lactose or are lactose free.

Overall, pHF may offer some benefit over intact protein in the dietary management of common functional GI symptoms. However, the literature is too scarce to actively recommend pHF in the treatment of FGIDs.

**Disclosure Statement**

There is no potential conflict of interest related to this paper.
References


