

Infantile Colic and Food Allergy

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KEY CONCEPTS

- The term “infantile colic” describes episodes of paroxysmal unexplained crying and fussing (for more than 3 hours per day) in otherwise healthy infants less than 3 months of age.
- Although the etiology of colic is multi-factorial, there is increasing evidence linking this condition to gastrointestinal food protein allergies (non-IgE-mediated).
- In breast-fed infants, hypersensitivity reactions may be caused by ingestion of intact food proteins contained in breast milk.
- In formula-fed infants, extensively hydrolyzed (casein- or whey-predominant) or amino-acid-based formulas have been shown to improve colic symptoms, whereas soy, partially hydrolyzed or lactose-free cow’s milk formulas offered no therapeutic benefit.
- Maternal elimination diets have been shown to significantly reduce the crying duration in breast-fed infants with colic presenting before 6 weeks of age.

Introduction

Persistent crying is a common pediatric problem that affects up to 28% of young infants [1]. In the majority, the distressed behavior commences at 2 weeks of age, peaks at about 6 weeks, and gradually improves toward 3–4 months of age [2,3]. However, a recent Canadian study showed that 6.4% of infants still had colic at 3 months of age [4]. Although the etiology of infantile colic is multi-factorial, there is increasing evidence linking persistent crying and distress in the young infant to food allergy [5–7]. Interactive factors and behavior patterning also influence the clinical course of infantile colic [8].

Crying and fussing, especially in the evening, are normal developmental phenomena in the first months of life [2]. Unexplained paroxysms of irritability, fussing, or crying that persist for more than 3 hours per day, for more than 3 days per week, and for at least 3 weeks, are considered a separate clinical condition termed “colic” [3,9]. During such episodes the legs may be drawn up to the abdomen and the infant may become flushed. Abdominal distension and increased passage of flatus are often noted. Parents may attribute these episodes to pain. However, the infant appears generally well,

and it has been suggested that in less than 5% of infants an underlying medical etiology can be identified [8].

Epidemiology of colic

Prevalence figures for infantile colic vary greatly, depending on the definition of colic and recruitment method used in epidemiological studies [1,10]. No population-based prevalence study, using generally accepted diagnostic criteria for colic, has to date been performed. Many studies are biased toward severe colic or families presenting in crisis [1]. For example, mothers with depressive symptoms may be more likely to seek help for their crying infant [11,12]. In addition, parents perceive persistent crying as more worrisome if there are associated symptoms such as regurgitation [13] or feeding difficulties [14] which may lead to an overestimate of underlying medical conditions. Table 14.1 shows the varying prevalence of colic reported from several Western countries.

Clinical classification of crying syndromes

The etiology of infantile colic is multi-factorial. Our understanding of the mechanisms leading to distressed behavior in early infancy is incomplete. The term “colic” implies that the infants’ distress is related to visceral pain or spasm, although such a mechanism has never been conclusively demonstrated. For this reason, alternative terms such as “persistent crying” or “distressed behavior” have been used.

In the following discussion, the term “colic” will be used interchangeably with each of these terms while not implying a particular pathological mechanism.

Barr has suggested four main crying syndromes in infancy [8]. These syndromes are difficult to define and may overlap clinically:

- Infantile colic.
- Persistent mother–infant-distress syndrome.
- The temperamentally “difficult” infant.
- The dysregulated infant.

According to this model, infantile colic is considered part of normal emotional development, in which an infant displays diminished capacity to regulate crying duration [8]. If colic is unresolved for several weeks, this may lead to disturbances in the mother–infant relationship, that is the persistent mother–infant-distress syndrome; this group often presents with associated organic manifestations. These may include feeding difficulties [14,18], gastroesophageal reflux (GER) [18–21], esophagitis [22], lactose malabsorption [23,24], or gastrointestinal motility disturbance [25–27]. Many of these manifestations have been linked to food protein allergy [28]. The temperamentally “difficult” infant may be predisposed to negative affect and have an increased tendency for persistent crying. The last category, the “dysregulated” infant, is thought to have a central dysregulation leading to poor self-calming, poor tolerance to change, and hyper-alert arousal.

Infantile and parental factors associated with infantile colic

Infantile factors

Brazelton [2] used parental recording on cry charts to document the natural history of distressed behavior in infancy. Figure 14.1 summarizes the pattern of crying and fussing in a group of 80 non-colicky infants studied in the first 12 weeks of life. Distressed behavior frequently deteriorated until infants were about 6 weeks of age, and then gradually improved. In the majority of infants, fussing behavior

occurred during the late afternoon and evening [2,9]. Barr *et al.* [28] developed 24-hour cry charts which they validated against voice-activated audiotape recordings (VAR) of crying infants. Using these validated cry charts, Hunziker and Barr [37] confirmed Brazelton’s [2] findings.

Studies by our group compared the pattern and duration of distressed behavior in 30 colicky and non-colicky infants [38]. Figure 14.2 shows the higher levels of distressed behavior in the colicky infants compared to non-colicky infants. The evaluation of distressed behavior on an hour-by-hour basis found a predominance of nocturnal symptoms, but prolonged episodes of crying also occurred during other periods of the day. These prolonged and inconsolable episodes of crying appear to be features that are specific for infantile colic in the first weeks of life [39].

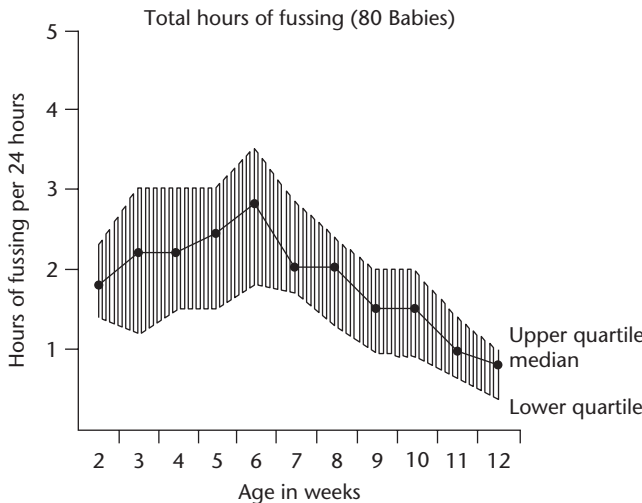


Figure 14.1 Total crying duration per 24 hours in 80 infants during the first 12 weeks of life (Reproduced from Brazelton TB [2], with permission.)

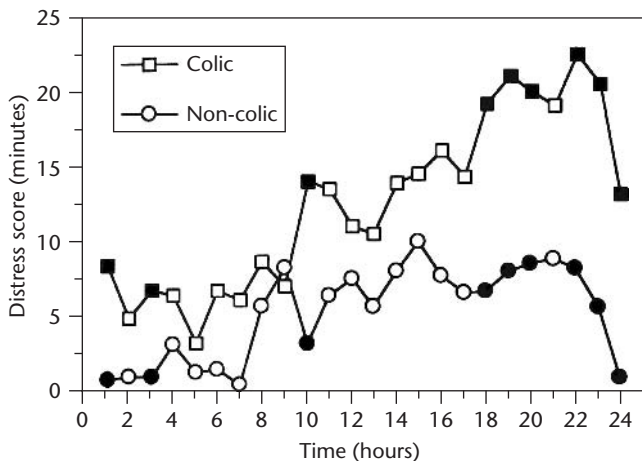


Figure 14.2 Comparison of diurnal variation in distress scores for infants with and without colic; hourly mean duration of crying and fussing time, recorded over 24 hours. Filled symbols mark periods with a significant difference in crying and fussing between groups ($p < 0.05$) [38].

Table 14.1 Prevalence of infantile colic

Author	Country	Year	Prevalence (%)
Hide and Guyer [29]	England	1982	16
Rubin and Prendergast [30]	England	1984	26
Carey [31]	USA	1984	10
Lothe [32]	Sweden	1989	17
Michelsson <i>et al.</i> [33]	Finland	1990	14
Hogdall <i>et al.</i> [34]	Denmark	1991	19
Rautava <i>et al.</i> [12]	Finland	1993	28
Lehtonen and Korvenranta [35]	Finland	1995	13
Canivet <i>et al.</i> [15]	Sweden	1996	11
Canivet <i>et al.</i> [16]	Sweden	2002	9.4
Clifford <i>et al.</i> [17]	Canada	2002	24
Wake <i>et al.</i> [36]	Australia	2006	19.1

Children with a past history of colic are at increased risk of experiencing negative emotions, negative moods, during meals and more likely to report abdominal pain in early childhood, suggesting that infant temperament may be a factor contributing to infantile colic [40]. However, the majority of colicky infants will develop normal parent–child interactions and relationships, and only a small number will progress to a more generalized “persistent mother–infant-distress syndrome” [41]. A recent Australian study of distressed infants found that persistent crying and sleep problems in the first 2 years of life are usually transient [36]. A 10-year follow-up study of 96 infants with a history of infantile colic showed a high prevalence of recurrent abdominal pain, allergic disorders, and psychological abnormalities [42]. Unremitting, severe persistent crying beyond 3 months of age may also be a marker of cognitive deficits in later childhood [43].

Maternal factors

The unpredictable, prolonged, and unexplained nature of crying in colicky infants is a source of great concern and anxiety for parents [44,45]. Maternal anxiety during late pregnancy has been shown to be a risk factor for infantile colic [46]. Studies by Rautava *et al.* in Finnish infants suggested an association between colic and maternal distress during pregnancy and childbirth or unsatisfactory sexual relationships, but not between colic and socio-demographic factors [47]. Mothers who report excessive infant crying are also more likely to perceive a lack of positive reinforcement from their infant [48].

Maternal report of a sleep problem in their infant was significantly associated with depressive symptoms [10]. This may indicate that maternal depressive symptoms during the early infant period are caused by, or compounded by, sleep deprivation. A recent study reported that persistent, rather than transient, infant distress was associated with maternal depression and parent stress [36].

Behavior interventions and parental support

Several studies have assessed the importance of behavioral and interactive factors in infantile colic. The results of these studies are summarized in Table 14.2. Taubman [49] compared parental counseling and dietary interventions in a study of 21 colicky infants. He found that increasing parental responsiveness had a similar effect on persistent crying as the introduction of a cow’s milk-free diet. Interestingly, the distressed behavior of diet-responsive colicky infants decreased further with parental counseling.

Barr *et al.* [50] studied the effect of supplemental carrying on 66 colicky infants. In 6-week-old colicky infants, a significant treatment benefit of supplemental carrying could not be demonstrated. Wolke *et al.* [51] examined the effect of different supportive strategies in 92 mothers of infants with colic. After 3 months, infant distress had improved in

all patients. Infants of mothers who had received advice on behavior modification improved their distress by 51%, compared with 37% in infants of mothers who were receiving empathic support, and 35% in the control group.

Colic as a manifestation of food protein allergy

Several trials have demonstrated a treatment benefit for soy and extensively hydrolyzed formulas in infants with colic, even when no other symptoms of food protein allergies were evident (Table 14.3). Irritability is a common finding in infants with allergy to cow’s milk and other food proteins [5,28]. Some infants may also react to soy formula or

Table 14.2 Studies investigating disturbed family interaction as a cause of colic

Author	Study details	Outcome: change in distress (hours per 24-hour period)
Hunziker and Barr [37] ^a	Carrying (<i>n</i> = 49) Control (<i>n</i> = 50)	1.2 2.2 (<i>p</i> < 0.001)
Barr <i>et al.</i> [50]	Carrying (<i>n</i> = 31) Control (<i>n</i> = 35)	3.3 3.4 (<i>p</i> > 0.05)
Taubman [49]	Counseling (<i>n</i> = 10) Diet (<i>n</i> = 10)	3.2 versus 1.06 (<i>p</i> = 0.001) 3.2 versus 2.03 (<i>p</i> = 0.01)
Wolke <i>et al.</i> [51]	Empathy (<i>n</i> = 27) Behavior modification (<i>n</i> = 21) Control (<i>n</i> = 44)	6.3 versus 3.7 (<i>p</i> < 0.001) 5.8 versus 2.8 (<i>p</i> < 0.001) ^b 5.7 versus 3.7 (<i>p</i> < 0.001)

^aStudy of non-colic infants.

^bBehavior modification superior to empathy and control (*p* < 0.02).

Table 14.3 Studies supporting the role of diet as a cause of infantile colic

Author	Study details	Outcome
Jakobsson and Lindberg [52]	Breast (<i>n</i> = 10)	Conditional probability of 95% that intact when protein is implicated in colic
Evans <i>et al.</i> [53]	Breast (<i>n</i> = 20)	Range of maternal diet significant (<i>p</i> < 0.05)
Lothe and Lindberg [54]	Formula (<i>n</i> = 24)	Casein hydrolysate 1.0 hours versus intact whey protein 3.2 hours (<i>p</i> < 0.001)
Forsyth [55]	Formula (<i>n</i> = 17)	Cow’s milk distress > casein hydrolysate distress (<i>p</i> < 0.01)
Lucassen <i>et al.</i> [56]	Formula (<i>n</i> = 43)	Difference in decrease of crying by 63 minutes/day for extensively hydrolyzed whey formula compared to standard formula (<i>p</i> < 0.05)

extensively hydrolyzed formula preparations [57,58]. In a sequential cohort of 100 patients with challenge-proven cow's milk allergy (CMA), 44% of infants displayed irritable and colicky behavior during the cow's milk challenge procedure [59].

Cow's milk allergy and colic

Cow's milk challenge in young children suspected of having CMA elicited a range of diverse manifestations [59–62]. Three clinical groups of CMA were identified based on the timing of reactions (immediate, intermediate, and late onset) [59]. Children who developed immediate reactions reacted to small volumes of cow's milk within 1 hour of commencing the challenge. Infants with intermediate reactions tolerated 60–200ml of cow's milk, before vomiting and diarrhea developed after several hours. The third group with late-onset reactions usually tolerated greater volumes of cow's milk before gastrointestinal, cutaneous, or respiratory symptoms of CMA developed after 24–72 hours. Interestingly, the prevalence of distressed behavior after cow's milk challenge was similar in the three groups, suggesting that distressed behavior in infants with CMA may be due to several immunological mechanisms.

Food allergy in breast-fed infants

There is increasing evidence that maternal ingested food antigens are secreted into human milk and elicit clinical adverse reactions in the breast-fed infant [63–66]. Sensitization to multiple food antigens has been described in breast-fed infants [67]. Several intact dietary antigens have been demonstrated in breast milk, including β -lactoglobulin [65], ovalbumin [66], peanut [68], and gliadin [69].

Allergic IgE sensitization may occur as early as during the fetal period [70,71]. Immunological host factors appear to mediate the sensitization to food allergens in breast milk. TGF- β is considered an important immunoregulator in promoting development of oral tolerance. During early infancy, breast milk is the main source of TGF- β . Kalliomäki *et al.* found that TGF- β promotes specific IgA production in human colostrum [72]. IgA antibodies in human milk have a protective effect on sensitization to food allergens as they may prevent antigen entry at the intestinal surface of infants [73]. Other factors that may mediate the immune response to ingested food antigens include regulatory lymphokines, such as TNF- α and IFN- γ . TNF- α is produced by activated macrophages and T-lymphocytes in human milk and upregulates HLA class II expression. Defective TNF- α production may be a factor impeding the development of oral tolerance to ingested food antigens in breast-fed infants [74].

Differences between breast- and formula-fed infants

In contrast to breast-fed infants, formula-fed infants often develop infantile colic before 6 weeks of age [2,75]. There

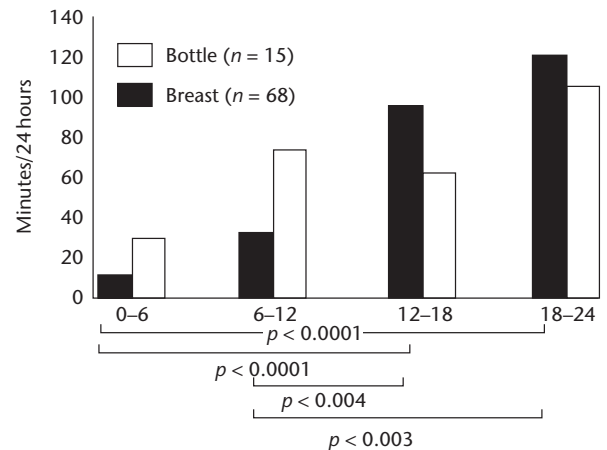


Figure 14.3 Bottle-fed infants show more distress before midday, whereas breast-fed infants have significantly more distress in the afternoon and evening [5].

are significant differences in the diurnal variation of distressed behavior between breast- and formula-fed infants. In our studies on colicky infants, we found that while the total distress levels were similar over a 24-hour period, formula-fed infants showed significantly more distress in the morning hours than breast-fed infants, whereas breast-fed infants were more distressed in the afternoon [5,38] (Fig. 14.3). Axelsson *et al.* [76] noted that about 4 hours after maternal cow's milk ingestion, β -lactoglobulin appeared in breast milk, and the highest concentrations of β -lactoglobulin in breast milk were found 8–12 hours after ingestion. Paganelli *et al.* demonstrated that cow's milk antigen appeared in serum within 1 hour of ingestion [77]. Thus, formula feeding with a large dose of ingested antigens may elicit a more rapid distress response than prolonged low-dose antigen exposure through breast milk. These observations may explain the differences in age of onset and diurnal variation of distressed behavior between breast- and formula-fed infants with colic.

Intestinal microbiota in infants with colic

There are significant differences in the composition of intestinal microbiota in infants with and without colic. Typically, bifidobacteria and lactobacilli are the predominant gut bacteria in breast-fed infants. Savino *et al.* [78] found that breast-fed infants with colic were less frequently colonized with lactobacilli and carried more Gram-negative gut bacteria. Also the type of lactobacilli appeared to vary between infants with and without colic. While *L. lactis* and *L. brevis* were only found in infants with colic, *L. acidophilus* was only found in healthy infants [69]. It remains unclear how these different bacterial microbiota are involved in the pathogenesis of infantile colic.

Development of food allergy in children with previous infantile colic

The absence of atopic manifestations in the majority of infants with colic infants suggests that non-IgE-mediated mechanisms predominate in the pathogenesis of infantile colic. However, a study from Finland suggested that infants with a history of colic are at increased risk of atopy, as compared to non-colicky infants [80]. In that study, of 116 infants with atopy at 2 years of age, 44 (38%) had presented with infantile colic. By contrast, a prospective study of 983 infants found no evidence of an increased risk for asthma and other atopic manifestations in infants with colic [81].

Infantile colic may respond to cow's milk protein elimination even in the absence of other clinical manifestations of CMA. In a study of 70 infants with severe colic, Iacono *et al.* [82] treated 70 cow's milk formula-fed infants with severe colic with soy formula. Fifty infants had improvement of colic after a change to soy formula, and their distress relapsed within 24 hours after cow's milk was reintroduced into the infants' diet [82]. Within 3 weeks, 8 of 50 infants developed soy allergy; and at the age of 9 months, 18 of 50 patients developed other symptoms of CMA at challenge. Lothe *et al.* [83] noted a similar phenomenon. Of 43 infants with colic who responded to exclusion of cow's milk, 18% showed other features of CMA by the age of 6 months, and 13% retained these features to at least 12 months of age [83]. These observations suggest that infantile colic represents an early manifestation of food allergy.

Infantile colic and gastrointestinal disorders

Gastroesophageal reflux, esophagitis, and infantile colic

Persistent distress and feeding refusal in the early infant period are frequently attributed to GER [19,20,84]. This is based on the assumption that acid reflux, even in the absence of esophagitis, may be associated with pain and feeding resistance. Crying itself does not appear to increase GER [85]. Distressed infants are often treated with anti-reflux medications on an empirical basis [18,86]. However, a causal relationship between GER and distress has never been conclusively demonstrated [19,22].

GER is considered pathological if it is associated with acid-peptic complications (esophagitis, esophageal strictures, etc.), failure to thrive, or respiratory complications (aspiration, persistent wheeze, stridor, apneic episodes). In three retrospective series of infants with severe persistent distress, abnormally frequent acid reflux was demonstrated by esophageal 24-hour pH monitoring in 15–25% of infants studied [18,22,86]. This exceeds the expected prevalence of 5–10% in young infants [87] and may in part be explained by selection bias in infants referred for gastroenterological investigation. Abnormally frequent or prolonged GER on pH monitoring usually presented with

overt regurgitation and non-regurgitant "silent" GER was uncommon [18,22]. The duration of crying and fussing per day did not correlate with the severity of GER [18]. In a randomized clinical trial of infants with colic or persistent crying, treatment with ranitidine and cisapride was no better than placebo [88]. In a similar subsequent randomized trial, omeprazole, a proton pump inhibitor, was not effective in treating crying infants [89]. In that study, effective acid suppression was achieved in the infants on active medication but not on placebo. Both studies make a direct causal relationship between GER and colic unlikely [88,89].

Esophageal 24-hour pH monitoring is the definitive diagnostic test for GER. In a study of 125 distressed infants and symptoms of GER, one quarter of infants had an abnormal pH study, and one quarter had histological esophagitis. However, we found poor diagnostic agreement between abnormal pH monitoring and histological evidence of esophagitis [22]. This may indicate a non-acid-peptic etiology of the esophagitis in these infants. Esophagitis was frequently associated with gastritis or duodenitis, suggesting the presence of a more generalized upper gastrointestinal inflammatory process in infants with persistent distress [2,90].

There is evidence supporting the hypothesis that GER and esophagitis in infancy are caused by food hypersensitivity. Previous studies have provided clinical evidence of gastric dysrhythmias in infants with CMA, presenting with reflex vomiting and GER [91]. Iacono *et al.* demonstrated that in more than 42% of infants with histological esophagitis, reflux symptoms improved on hydrolyzed formula and relapsed on subsequent blinded formula challenges [92]. We have previously described a group of infants with intolerance to soy and extensively hydrolyzed formula and persistent distress attributed to reflux esophagitis, who responded to a hypoallergenic amino-acid-based formula diet (AAF) [90]. Older children with idiopathic eosinophilic esophagitis have also successfully been treated with an AAF [93]. These findings support the hypothesis of an immunologically mediated esophagitis. Recently, the infiltrate in idiopathic eosinophilic esophagitis in adult patients has been characterized as a T-helper 2-type allergic inflammatory response [94].

Colic and intestinal spasm

In a systematic review of treatments for infantile colic, dicyclomine, an anticholinergic agent, was found to be effective [6]. It is no longer used in the treatment of colic because of its potentially serious side effects in infancy [95]. The therapeutic effect in colicky infants was poorly understood but may have been due to antispasmodic properties on intestinal smooth muscle. Another anticholinergic agent, cimetropium bromide, has been shown to significantly shorten the duration of crying episodes in infants with infantile colic

[96]. This drug, a synthetic scopolamine derivative, appears to have fewer serious side effects than dicyclomine. About three quarters of infants responded to treatment with cimetropium bromide. The mean duration of crying episodes was 17.3 minutes for active medication and 47.5 minutes for placebo ($p < 0.005$). Although not conclusive, these findings may add further weight to the hypothesis that infantile colic is associated with spasmodic visceral pain that is relieved by these medications.

Animal models of food hypersensitivity have provided direct evidence of gastrointestinal spasm and motility disturbance in response to dietary antigen challenge [25]. In sensitized rats, mucosal exposure to food protein antigens resulted in gastric [97] or intestinal smooth muscle contraction [26,98]. The potential importance of disturbed gut motility in colic is further supported by the finding of increased levels of the hormone motilin, a prokinetic gastrointestinal hormone, both postnatally and at the age of onset of colicky behavior [27,99]. Maternal smoking during pregnancy and lactation has been linked to an increased risk of infantile colic and elevated serum motilin levels [100]. Serum motilin levels are higher in infants with colic, and among those infants, formula-fed infants had higher motilin levels than breast-fed infants [101]. Another gastrointestinal hormone, ghrelin, was also found to be significantly increased in infantile colic, as compared to healthy control infants [101]. These findings provide some clues to the etiology of distress in young infants and should stimulate further research into the role of abnormal gut motility in the etiology of colic in young infants.

Lactose intolerance

The role of lactose intolerance in infants with colic has remained unclear [6,7]. Lactose intolerance may occur as a result of small intestinal mucosal damage and disaccharidase depression. It is therefore possible that lactose intolerance may occur as a result of a food protein-induced enteropathy. Moore *et al.* examined the effect of lactose-containing formula on breath hydrogen production in colicky and non-colicky infants [23]. This study found that breath hydrogen concentrations, after intake of human milk or lactose-containing formula, were higher in colicky than in non-colicky infants. However, two subsequent randomized controlled trials found no significant benefit for lactase treatment of human milk or cow's milk formula [24]. A recent double-blind placebo-controlled study in 53 colicky infants has found a modest benefit of pre-incubation of feeds with lactase on colic symptoms [102]. The response to lactase treatment, however, appeared variable and the trial remained inconclusive. Low-lactose formula or pre-treatment of feeds with lactase are therefore generally not recommended as treatments for infantile colic [6,7].

Dietary treatment of colic

The self-limiting course of infantile colic makes the assessment of therapeutic interventions difficult, and no firm conclusions can be drawn unless proper double-blind placebo-controlled randomized trials are performed. However, only a few well-designed randomized trials on the treatment of colic have been conducted, and many previous studies had some shortfalls in methodology or study design. This review will focus predominantly on the role of hypoallergenic diets in the treatment of infantile colic.

Hypoallergenic formulas

Several studies have assessed the effect of dietary interventions on persistent crying, including treatment with soy- [42,103], partially hydrolyzed whey- [104], extensively hydrolyzed whey- [56], extensively hydrolyzed casein- [105], and AAFs [106,107]. Following a preliminary study, Jakobsson and Lindberg [52] noted that one-third of breast-fed infants with colic improved on maternal dietary cow's milk elimination, and relapsed on reintroduction of cow's milk into the diet. Evans *et al.* [53], however, were unable to confirm these findings. Lothe *et al.* [83] reported that 11 of 60 colic infants on cow's milk formula responded to soy formula; another 32 improved following administration of a casein hydrolysate formula. These preliminary studies have been criticized because of some methodological limitations [64,53,108].

Other more recent investigations have addressed some of these shortcomings. Lothe and Lindberg [54] implemented a 5-day cow's milk-free diet using casein hydrolysate. A marked reduction of distressed symptoms occurred in 24 of 27 colicky infants. In these infants, the total crying time decreased from 5.6 to 0.7 hours ($p < 0.001$). The 24 responding infants then entered into a randomized, double-blind, crossover trial of intact whey protein formula. Of the 24 infants challenged, 18 (two thirds of the original study population) demonstrated increased distress on whey protein challenge.

In a blinded crossover study of 17 colicky infants, casein hydrolysate alone or casein hydrolysate plus cow's milk formula were fed in sequence for four 4-day-periods [55]. Significant decreases in distressed behavior were noted after the first two formula change periods only. Over the four formula challenge periods, only 2 (11.8%) of the infants showed a reproducible effect of formula change on colic behavior. Forsyth concluded that diet was likely to be only one factor in the causation of colic [55]. He drew attention to the feelings of helplessness, frustration, and decreased confidence in parenting ability that parents of infants with colic may experience.

A recent randomized trial assessed the effect of a partially hydrolyzed whey-based formula in 199 infants with colic [104]. The formula was supplemented with prebiotic

fructo- and galacto-oligosaccharides, as well as β -palmitic acid. The control group was randomized to receive either standard cow's milk formula or simethicone. Infants in the active treatment group had a significantly greater reduction in the number of crying episodes at 1 and 2 weeks than the untreated infants [104]. Further studies are required to assess the role of partially hydrolyzed formula in the prevention and treatment of colic.

The incomplete response to treatment with hypoallergenic formulas may be due to the residual allergenicity of extensively hydrolyzed whey- or casein formula [109,110]. An estimated 10–15% of infants with CMA are also intolerant of extensively hydrolyzed formula [111]. In these infants, treatment with AAF has proved effective and safe [112,113]. Recently, several groups have assessed the effect of AAF on persistent crying [58,90,106,107,114]. These preliminary studies provided evidence that AAF is effective in reducing persistent crying. However, further prospective randomized trials are required to assess the efficacy and cost-effectiveness of this approach in the community.

Maternal elimination diets

Allergen avoidance is one of the key principles in the treatment of food allergies [53]. The Melbourne Colic Study examined the role of a hypoallergenic diet on crying and fussing in a cohort of 115 colicky infants [115]. Infants were referred from community-based pediatric facilities. Mothers assigned to the active low-allergen diet excluded cow's milk and other common food allergens, such as egg, wheat, peanut, nuts, fish, and shellfish, from their diet. Formula-fed infants were randomly assigned to a casein hydrolysate preparation (low-allergen diet) or cow's milk-based formula. The response to diet was assessed on the previously validated infant-distress charts at baseline and after 1 week [28].

Clinical response to diet was defined as a reduction in distress of 25% or more. Infants on the active diet had a significantly higher response rate than those on the control diet (odds ratio 2.32; 95% confidence interval (CI) 1.07–5.0; $p = 0.03$). The treatment effect was greatest in breast-fed infants aged less than 6 weeks. These findings were confirmed in a subsequent randomized trial of a low-allergen maternal elimination diet among breast-fed infants less than 6 weeks of age with colic [116]. Again, mothers were randomly allocated to a low-allergen diet (avoiding cow's milk, soy, wheat, fish, egg, peanut, nuts, and chocolate), and a control diet. After 1 week, the clinical response rate in the low-allergen group was 74%, compared to 37% in the control group – a risk reduction of 37% in favor of the maternal elimination diet. This corresponds with a reduction in crying duration by 274 minutes/48 hours in the low-allergen group, compared to 102 minutes/48 hours in the control group; $p = 0.028$ (Fig. 14.4). This group difference demonstrates that maternally ingested food proteins

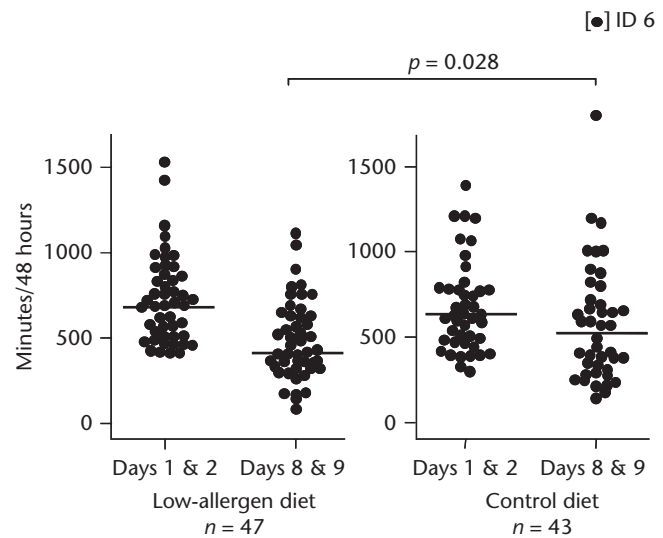


Figure 14.4 Effect of a maternal elimination diet in 90 breast-fed infants less than 6 weeks of age. There was a significantly greater reduction in cry/fuss duration for infants on the low-allergen diet, compared to infants of mothers on the unrestricted control diet [110].

are likely to be implicated in breast-fed infants with colic. However, the exact mechanisms remain to be elucidated.

Conclusion

Infantile colic is a common pediatric problem in the first months of life. No general consensus has emerged about its most likely multi-factorial etiology. Behavioral and interactional factors strongly influence the natural history of infantile colic. Infants with colic appear generally well, and in less than 5% of distressed infants a medical explanation for the distress can be found [7]. GER, esophagitis, or lactose intolerance, although sometimes present in infants with colic, are not likely to be the cause of the persistent distress, and empirical treatment with gastric acid suppressing medications or lactose-free formula is ineffective. Several trials have demonstrated a treatment benefit for hypoallergenic formulas or maternal elimination diets. Based on our community-based observations, at least 37% of young breast-fed infants with colic adversely reacted to one or several food proteins and responded to a maternal elimination diet. This may be associated with gastrointestinal inflammation and motility disturbances. The exact mechanisms by which food proteins cause persistent crying are still unclear.

In formula-fed infants with moderate to severe unremitting colic, a trial of a hypoallergenic formula should be attempted. Breast-fed infants may respond to a maternal low-allergen diet by reducing the antigen load in breast milk. The therapeutic effect of elimination diets appears to be greatest in young infants less than 6 weeks of age. After remission of symptoms, the diet can be gradually normalized and food proteins introduced into the diet, as tolerated.

Elimination diets should be closely supervised by an experienced dietician in order to prevent insufficient macro- or micronutrient intakes for both mother and infant, and growth parameters of the infant should be monitored [117]. In addition to any dietary interventions, successful management of infants with colic and their families should address the adverse effects of prolonged parental stress and maternal depression.

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