

“THE GRIPE”: AN INTEGRATIVE APPROACH TO INFANT COLIC

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Babies cry. In fact, crying is considered part of normal infant development. Noted psychologist Gwen Gustafson offers this scientific explanation: “Neonatal crying is a species-specific behavior which achieves its likely evolutionary function (infant survival) by reliably eliciting responses from caregivers.”¹ The great behavioral observer Charles Darwin described his own baby’s distress in superb biological detail: “With one of my own infants, from his eighth day and for some time afterwards, I often observed that the first sign of a screaming-fit, when it could be observed coming on gradually, was a little frown, owing to the contraction of the corrugators of the brows; the capillaries of the naked head and face becoming at the same time reddened with blood.”² Harvard developmentalist T. Berry Brazelton observed that the typical baby cries up to 2.25 hours daily,³ supporting current speculation that crying, like most things, exists along a spectrum. Yet, there are those babies (and their families) that seem to suffer more than most; these infants in Darwin’s England were said to have “the gripe.” Today we call it colic. We have widely accepted the “Rule of 3s” definition first offered by pediatrician Morris Wessel in 1954.⁴ Dr Wessel, who studied infant crying behavior as part of the Yale Rooming-In Project, defined *colic* as paroxysmal fussing in infancy for more than three hours per day, at least three days per week, for at least three weeks duration. Surveys indicate that up to 26% of infants are diagnosed with colic,⁵ making the condition one of the most common reasons for infant visits to primary care practitioners today.

We know colic when we see it, but we still do not know what causes it. The most popular conventional medical theory is that colic is an extreme variant of infant irritability, perhaps related to neural regulation differences. Pediatrician Harvey

Karp speculates that some babies have a more difficult time adjusting to what he terms the “fourth trimester,” a three-month period of time in which infants must cope with potentially overwhelming sensory stimuli.⁶ Just like adults, babies vary in how well they integrate these external stimuli, and colic may well represent an adjustment disorder—the far end of an infant irritability syndrome. Most parents claim that their colicky babies seem to suffer abdominal pain, and interestingly, there is now mounting evidence that the gastrointestinal tract may be involved in colic via neuroimmune connections. In fact, babies with food allergy and other atopic disorders are more likely to be diagnosed with colic.⁷ Exposure to cigarette smoking, a known link to colic for quite some time, is thought to exacerbate distress by a connection to gastroesophageal reflux.⁸ A recently published 10-year prospective study challenges a commonly held view that there are no long-term health-related issues in children who had colic in infancy.⁹ Approximately 100 infants were evaluated at one to three months of age, and then again at the age of 10 years. There was an association noted between infantile colic and later recurrent abdominal pain, atopic disease, and sleep disorders. This association does not, of course, prove causation, but suggests that whatever processes are involved in the development of colic may also predispose children to subsequent health concerns. We need to evaluate these potential links closely, as any connection would support actively working with families to prevent and treat excessive infant irritability.

RATIONALE FOR AN INTEGRATIVE APPROACH

There is no widely accepted conventional treatment for colic. Practitioners will offer families psychological support, with the hope that with time—as is often the case—

colic will fade by the time newborns are 12 to 16 weeks of age. There is encouraging evidence that parenting intervention can reduce crying time in colicky babies.^{10,11} Many families, though, seeking a more active role in reducing infants’ distress, turn to complementary and alternative medical (CAM) therapies. Surveys of CAM use in culturally diverse populations indicate that colic is a common reason for use of herbal and nutritional therapies in early childhood.^{12,13} Even in the 1950s, Wessel noted that among the most prevalent treatments used by parents were dietary modifications and various soothing regimens,⁴ sometimes today termed as CAM. But are these therapies actually alternative? In the case of colic, it is difficult to distinguish conventional from unconventional approaches, as culture and geography play such a large role in what is commonly used.

The largest systematic review to date of treatments for colic found little evidence to support many conventional therapies, including the widely used simethicone, while noting that several nutritional and botanically based approaches were indeed evidence based.¹⁴ An integrative approach, combining the best conventional and CAM prevention and treatment strategies, is a wonderful paradigm for the management of infantile colic. Integrative medicine, with its focus on family-centered and culturally sensitive holistic care, provides practitioners and families with the best opportunities for successful outcomes.

SPECIFIC THERAPIES

The integrative management of colic demands consideration of every tool in the practitioner’s toolbox. Individualization of treatment, as is typical in integrative practice, is crucial in these cases. Some approaches work quite well for some families and not at all for others. An integrative

primary care practitioner will openly dialogue with families and collaborate with various CAM therapists as warranted. The most commonly used therapies, including mind-body medicine, infant massage, botanical and homeopathic remedies, nutritional modulation, and probiotics, will all be discussed in the following sections.

Mind-Body Medicine

Perhaps no period of relative wellness in a family's life is more stressful than the first few months of infancy. Even typical infant crying and sleep patterning is disruptive and unsettling. The entire family dynamic is shifted, and caregivers may experience severe mood lability and tension. Wessel believed it was this family tension that was responsible for colic symptoms in infants⁴; we now understand that stress can indeed modulate neurological responses, therefore supporting the need to promote parental stress-coping mechanisms. There are clear links between maternal mood states, including postpartum depression, and the development of colic in infants.¹⁵ Screening for postpartum psychological disorders is feasible in pediatric offices¹⁶ and should be standard practice. Reducing parenting stress is a proven method of helping families cope with irritable infants,¹⁷ and there are many strategies to do so. Despite the lack of randomized controlled trials proving efficacy or cost-effectiveness in colic management, practices such as guided imagery, self-hypnosis, mindfulness-based stress reduction, yoga, or energy healing techniques like Reiki may be helpful in reducing parental distress. Modulating infant stimulation may also prove effective, as demonstrated in one randomized controlled trial.¹⁸ Dr Karp advocates a system of "five Ss" (sucking, shushing sounds, side/stomach positioning, swinging, and swaddling),⁶ which many parents find useful to enhance their infants' calming reflexes. Karp advises side/stomach positioning only while holding the baby, not for sleep positioning; one must be careful to promote the back-sleeping position for sudden infant death syndrome prevention.

Infant Massage

Therapeutic infant massage is one of the most widely studied CAM therapies in pediatrics. It is also a terrific way to improve the parent-child bond in stressful times.

The power of touch is quite apparent and remarkable in colicky infants. A recent *Cochrane Database Systematic Review* of massage intervention in infants acknowledges that there is "evidence of benefits on mother-infant interaction, sleeping and crying, and on hormones influencing stress levels."¹⁹ Infant massage is effective in reducing excessive crying in even the most vulnerable of infants, including premature babies and cocaine-exposed neonates.^{20,21} Families can be taught to use simple and safe massage techniques, and they appreciate the power of this self-care approach. This effect seems to be superior to simple vibration devices²² and may be enhanced by the use of essential oils.²³ Whether this latter effect is related to the oil as aromatherapy or simply adds to the physical massage technique, or both, is unknown. For safety reasons, caution should be taken with the application of essential oils in children; they should not generally be used directly on the skin, but mixed first in a carrier oil (eg, sesame, almond, or grape seed). One must be careful about allergies and skin sensitivity as well with these products.

Botanically Based Therapies

Many cultures have used botanical remedies for fussy babies for thousands of years. There are as many herbs used for colic as there are babies with the condition. One of the more widely known therapies, gripe water, dates back to the 1850s, when it was developed by William Woodward, a British pharmacy apprentice.²⁴ Woodward borrowed the formula—a combination of dill seed oil, sodium bicarbonate and alcohol, among other substances—from physicians who were using solution in the 1840s to treat babies with "fen fever," a form of malarial illness. It seemed that these babies were soothed by the concoction and reportedly found relief from gastrointestinal troubles (known at that time as "watery gripes"). Woodward subsequently sold his formula, and over the years, gripe water has become not one standard recipe but a recipe that contains any number of purportedly soothing herbs and substances. The large amount of alcohol in the original formulation has been removed from most contemporary commercially available preparations, but some families will make their own versions, which can contain significant

amounts of alcohol. This practice should be discouraged. It is important to ask families specifically about the use of gripe water and other herbal blends, and to figure out which substances are being ingested by the baby. The Natural Medicines Comprehensive Database lists five separate products labeled as "gripe water," and all have different constituents.²⁵

Other available botanical products are marketed as gastrointestinal soothers and used by parents for colic symptom relief. Some of these carry the same name, are made by different companies, but have radically different ingredients. For example, Chinese star anise (*Illicium verum*) is a spice used in many cultures for infantile colic. Although this specific herb is generally recognized as safe, its close relative, Japanese star anise (*Illicium anisatum*), absolutely is not. It contains constituents with the potential for neurologic and gastrointestinal toxicity, as noted in a case report of seven infants significantly affected by this herb.²⁶ Of great concern, these babies were given a Chinese star anise product adulterated with Japanese star anise. In another report, a case of pseudomonas bacterial sepsis in an infant was linked to the use of an imported Indian gripe water preparation.²⁷ As with all herbal supplements, one must be aware of regulatory and quality control issues.

Herbs commonly found in today's gripe water preparations include dill, fennel, ginger, and chamomile. The first three herbs contain volatile oils that produce smooth muscle relaxation and an antispasmodic effect.²⁵ Dill (*Anethum graveolens*), from the Norwegian word meaning to lull, has seeds containing volatile oils rich in carvone. Fennel (*Foeniculum vulgare*) seeds hold another volatile oil, anethole, and ginger's oil contains sesquiterpenes. Ginger (*Zingiber officinale*) contains active constituents known as gingerol, gingerdione, and shogaol, responsible for a myriad of effects, including antipyretic, analgesic, antitussive, anti-inflammatory, sedative, antibiotic, weak antifungal, and other properties. German chamomile (*Matricaria recutita*) contains multiple active constituents, including quercetin, apigenin, and coumarins, and the essential oils matricin, chamazulene, alpha bisaboloid, and bisaboloid oxides. Some of these components may have anti-inflammatory and antispasmodic activity.

There have been several published studies of herbal remedies for colic. A group from Israel evaluated an Italian herbal tea preparation (Calma-Bebi) containing chamomile, vervain, licorice, fennel, and lemon balm.²⁸ In the trial, 68 colicky infants aged two to eight weeks were randomized to receive either tea or placebo for seven days. Colic diagnosis was based on the Wessel definition according to parent description of behavior. Infants were allowed to have the liquid up to three times per day at a volume of up to 150 mL (five ounces). The average intake during the study was actually far less, at two servings per day, for a cumulative total of about three ounces per day. Infants who received the tea were much more likely to improve than those receiving placebo (a powdered mixture of glucose and unspecified natural flavorings); 57% of babies in the treatment group versus 26% of those in the placebo group. Although this difference was statistically and clinically significant, it is worthwhile noting the marked placebo effect. No significant adverse effects were reported. Unfortunately, this study is hampered by so many unknowns that it is impossible to generalize advice based on its results. The amounts and types of each herb, the volume each infant received, and the exact nature of the placebo are all unspecified variables that may have had an impact on colic resolution.

A second study, from a group in Russia, was much more specific. Alexandrovich et al²⁹ compared the effect on colic of a 0.1% water emulsion of fennel seed oil and 0.4% polysorbate-80 with that of a polysorbate-only placebo. One hundred twenty-five infants aged from 2 to 12 weeks were diagnosed with colic according to the Wessel definition and randomized to one of the two groups. The groups were allowed 5 to 20 mL of solution up to four times per day, but actually ingested an average of two to three doses per day, for a total of less than two ounces per day. After the one-week trial, colic was eliminated in 65% of the treatment group versus 23.7% of the placebo group. Again, this is a statistically and clinically significant finding, but with a notable placebo effect.

Finally, a third trial, from Savino et al,³⁰ compared a standardized extract (ColiMil) of three herbs (chamomile, fennel, and lemon balm) with a placebo in 93 breast-fed colicky infants. This study was quite

specific in extraction and delivery methods. Each dose of ColiMil consisted of the following standardized extracts: sweet fennel fruit powdered extract standardized to 0.05% to 0.1% essential oil, chamomile flower powdered extract standardized to 0.3% apigenin, lemon balm essential oil standardized to 2% rosmarinic acid, 0.85 mg of vitamin B₁, 3.24 mg of calcium pantothenate, and 1.20 mg of vitamin B₆. Placebo consisted of reverse osmosis filtered water, fructose, pineapple flavoring, citric acid, and potassium sorbate. Diagnosis of colic was according to Wessel criteria, and infants were enrolled at age three to nine weeks. Each infant received an exact standardized dose of 2 mL/kg per day twice daily before breast feeding for seven days. At the end of the trial, a statistically and clinically significant reduction of crying time was observed in 85.4% of patients receiving ColiMil and in 48.9% of infants receiving the placebo. Average daily crying time was reduced from about 200 minutes/day to 76.9 minutes/day in the treatment group, and from 200 minutes/day to only 169.9 minutes/day in the placebo group. Notably, crying was still reduced at 2 weeks after the end of the trial in the ColiMil treatment group. Neither group reported adverse side effects. It seems that individual fennel seed oil or blends of the aforementioned herbs may be quite effective and safe in treating colic in infants. Interestingly, there is a consistent placebo effect and a reassuring lack of reported adverse effects. As long as parents are instructed how to use herbal teas and solutions wisely, including limiting beverage temperature and avoiding potentially harmful botanicals and contaminants, these products offer potential therapeutic benefit.

Another botanically based colic therapy is aromatherapy. Many of the same herbs listed above, along with lavender and other soothing scents, are used by families to cope with infant distress. Aromatherapy is often delivered by the use of essential oil extracts, either aerosolized or by incorporation into a massage-oil base. Although historical use suggests a positive effect of aromatherapy on infant and parent stress, and therefore colic, there are no published trials to date evaluating such claims. Still, as long as essential oil safety guidelines are observed (eg, keep out of reach of children to avoid ingestion), aro-

matherapy may be a useful tool to help families cope with colicky babies.

Homeopathy is also widely used by many Western European and American parents for colic treatment. These consist of both single remedies and blends of various highly diluted herbs, including chamomila (chamomile), colocynthis (bitter apple), dioscorea (wild yam), fennel, ginger, caraway, peppermint, aloe, and lemon balm. If one buys a commercially available blend, note that just as in the case of gripe water, there are products with the same name but containing different constituents. Some families like to use homeopathy as a self-care regimen, whereas others prefer to consult with a classical homeopath. Given its very low risk for adverse reactions, homeopathy is generally considered safe for treatment of colic.

One of the most intriguing potential natural health products for colic therapy is the neurohormone, melatonin, or 5-methoxy-N-acetyltryptamine. In humans, melatonin is produced by pinealocytes in the pineal gland and also by the retina and gastrointestinal tract. In fact, there is at least 400 times more melatonin in the gastrointestinal tract than in the pineal gland.³¹ Furthermore, melatonin receptors are abundant throughout the gastrointestinal tract, and many biological effects of melatonin are produced through activation of these receptors. It has been hypothesized that because endogenous melatonin production does not mature until infants are 12 weeks old, when colic generally resolves, that abnormal circadian melatonin rhythms may be implicated in colic development.³² Why some infants are excessively irritable may have to do with differences in melatonin or receptor physiology, and perhaps administration of exogenous melatonin would be an effective colic treatment. Of course, both safety and efficacy studies need to be done before general recommendations can be made. Of note, most commercially available melatonin is synthesized in the laboratory, based on the endogenous pineal gland substance, but in rare cases, it is derived from animal pineal gland extracts, which should be avoided due to the possibility of contamination.

Nutritional Modulation

Nutritional modulation is one of the few preventive and therapeutic options for infants with colic. It does not appear that breast feeding exclusively prevents colic,³³

but it has been historically observed that certain foods either ingested by breast-feeding mothers or by formula-fed infants lead to fussy periods in infancy. We can therefore speculate that avoiding highly allergenic or irritating foods may prevent colic in at-risk infants (eg, those with family histories of atopy) or treat colic in excessively fussy babies. Although there is no clear consensus on avoidance of these foods for allergy prevention despite extensive study,³⁴ there does seem to be mounting evidence in support of food avoidance for babies with colic.

The most recently published trial by Hill et al³⁵ from Australia found that exclusion of certain allergenic foods (cow's milk, soy, wheat, eggs, peanuts, tree nuts, and fish) was positively associated with a reduction in colic in breast-fed infants.³⁵ One hundred seven infants presenting with excessive irritability (average crying time over 300 minutes per day) aged under six weeks were randomized to a one week trial of maternal low-allergen diet versus control (nonelimination) diet. At the completion of the trial, 74% of treated infants versus 37% of control infants experienced significant reduction in crying time (about 200 minutes per day less compared with 100 minutes less per day on average, respectively). These differences are both statistically and clinically significant; just ask any parents of a colicky infant. Still, there is a notable placebo effect. Which of these foods was primarily responsible (if any in isolation was responsible for the change) is unknown. In practice, it may be more feasible to advise single food group elimination trials (for one week per food), or if avoidance of all foods is initially advised, one can add back one food group per week at a time to evaluate clinical effect. It is important to maintain appropriate maternal and infant intake of essential vitamins and minerals (eg, calcium, vitamin D, and iron) during this period. Additionally, some researchers have found that other food types may contribute to colic in breast-fed babies, including cruciferous vegetables and chocolate.^{36,37} New research indicates that maternal essential fatty acid status also may be linked to infant distress and sleep patterning.³⁸ Babies of mothers with higher docosahexaenoic acid concentrations at birth had a significantly higher quiet sleep to active sleep ratio on day two of life. The implications

of this finding are unknown at present, but one can speculate that docosahexaenoic acid supplementation both prenatally and postnatally may prevent or lessen colic.

In infants who are partially or fully formula fed, the choice of formula may play a role in colic development. There have been no prospective studies of colic prevention in formula-fed babies, but if one extrapolates from allergy research, avoiding cow's milk or soy formulas in infants at high risk of atopy is warranted. These infants seem to have fewer atopic symptoms when fed with hydrolyzed formulas³⁹; gastroesophageal reflux and perhaps colic may also be prevented with this same approach in these select infants. There is evidence, however, supporting the use of hydrolyzed formulas for reducing colic symptoms in those infants already exhibiting excessive irritability. Both extensive casein hydrolysates (eg, Alimentum, Nutramigen, both more prevalent in the United States) and whey hydrolysates (eg, Nutrilon Pepti, available predominantly in Western Europe) have been demonstrated to be more effective than nonhydrolyzed cow's milk formulas in reducing crying times in colicky babies.^{40,41} Though some families and practitioners will consider soy and partially hydrolyzed formulas as alternatives for colic treatment, there is no evidence to support this practice.^{42,43} If an infant with colic presents with additional atopic symptoms (eczema, wheezing, allergic rhinitis, and gastroesophageal reflux), one must consider avoiding food allergens in formula or in breast milk as a treatment priority.

Probiotics

Probiotics have been defined as "a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host."⁴⁴ These microorganisms colonize the intestinal tracts of infants during the birth process and shortly thereafter, and they have been implicated in promoting immunological balance and digestive health. Savino et al,⁴⁵ in Italy, have published several fascinating papers on the nature of probiotic balance in infants and the relationship to colic. They initially described quantitative differences in lactobacillus species, find-

ing fewer overall lactobacilli in breast-fed colicky infants versus noncolicky infants. A follow-up study found that one type of lactobacillus species (*Lactobacillus acidophilus*) was less prevalent, and two other types (*Lactobacillus brevis* and *Lactobacillus lactis*) were more prevalent in infants with colic.⁴⁶ It is likely that some strains of lactobacilli confer protection against gastrointestinal neuroimmune disruption and subsequent pain, whereas others contribute to disorder and disease. Most recently, the Italian group published results of a trial of *Lactobacillus reuteri* in comparison with simethicone in the treatment of infantile colic.⁴⁷ Simethicone, while a commonly used antigas agent used by families for infants with colic, has been found previously to be ineffective in this regard.¹⁴ In this trial, 90 exclusively breast-fed colicky infants between ages 21 and 90 days were randomized to one of two groups: they either received *L reuteri* once daily at a dose of 10⁸ CFU, or simethicone 30 mg/dose twice daily, for 28 days. Mothers were instructed to avoid all sources of cow's milk during the trial. At the start of the study, both groups of infants were reportedly crying for approximately 200 minutes per day. The probiotic treatment group had a significantly reduced crying time (minutes/day) by only seven days into the trial (159 vs 177 in the simethicone group), a disparity that widened at weeks two, three, and four (51 vs 145). At the endpoint of the study, 95% of the probiotic treatment group were responders (did not meet Wessel criteria) versus only 7% of the simethicone group. Of note, both infants with and without a family history of atopy demonstrated equally significant benefits. Is there something unique about *L reuteri* as opposed to other probiotics in this regard? We can't yet say, but it is likely that supplementation with other strains (*Lactobacillus acidophilus*, L. GG) could achieve similar results. How best to deliver the probiotics is another question. Some researchers have investigated whether infant formulas can safely and effectively be supplemented with probiotics or prebiotics (nutrients that support probiotic growth). Two such trials have looked at colic reduction in this regard. Saavedra et al⁴⁸ from Johns Hopkins University led a randomized controlled trial of a cow's milk formula containing two probiotics (*Bifidobacterium lactis* and *Streptococcus ther-*

mophilus). This was not technically a study of colic, as the infants were older (3-24 months), but the findings were notable in that consumption of the formula supplemented with *B lactis* and *S thermophilus* was well tolerated and resulted in reduced reporting of colic or irritability. In the second study, Savino et al⁴⁹ randomized infants with colic to a controlled trial of a partially hydrolyzed whey protein formula supplemented with prebiotic oligosaccharides. Prebiotics are biological substances that increase the growth and activity of probiotic organisms. The control group received a standard cow's milk formula and simethicone treatment. There was a significant reduction in crying episodes between the two groups, favoring the prebiotic supplemented formula. Although clearly more research is needed to determine optimal probiotic and prebiotic types and dosing regimens, these therapies seem quite promising for both prevention and treatment of colic.

CONCLUSION

Infantile colic is one of the most frequently cited reasons for visits to child healthcare practitioners, as well as for use of CAM therapies in babies. It is also one of the first crises in a young family's life. An integrative approach, taking into account mind, body, and spirit considerations in a culturally sensitive manner, can help practitioners and family both navigate through this extraordinarily stressful three- to four-month period. The conventional wisdom of providing emotional support to families is an important component of colic management, but there are many complementary therapies that may provide additional relief. The most promising, reviewed here, include mind-body methods, infant massage, specific botanical remedies, nutritional modulation, and probiotics. Practitioners caring for infants should familiarize themselves with these methods and initiate an open-minded dialogue with their patients' families. Furthermore, if colic is indeed a precursor to later pain, behavioral, or atopic syndromes, we would do well to heed the warning signs and do what we can to modulate the process.

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