Probiotics for Colic—Is the Gut Responsible for Infant Crying After All?

"Colic" is a term coined by the ancient Greeks centuries ago, derived from "kolikos," meaning crampy pain, sharing its root with the word colon. For more than one-half of a century, researchers have tried to prove the condition to be related to the gut, and have failed to do so. That is, perhaps, until this last decade, with a sudden explosion of studies indicating gut microbiota, inflammation, and the gut-brain axis may play a part. The role of the probiotic *Lactobacillus reuteri* DSM17938 in infant colic has recently come under intense scrutiny. The study by Fatheree et al[1] in this volume of *The Journal* adds to this increasing and fascinating pool of evidence.

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Since 1994, there have been at least a dozen case-control studies that have indicated differences in the gut microbiota between infants with and without colic. Some studies have indicated infants with colic to be less frequently colonized or have different colonization patterns of *Lactobacillus* species than those without colic.[2-5] At least 4 teams have indicated infants with colic to have more gram-negative organisms like *Escherichia* than those without colic.[3,5-9] One cross-sectional and 2 case-control studies indicated *Bifidobacterium* to be protective against crying.[3,10,11] *Helicobacter pylori* and *Clostridium difficile* have also been found in higher proportions in infants with colic than those without.[12-14] The underlying mechanisms of altered gut microbiota in infant crying are yet to be proven, but a possible pathway is through gut inflammation. Calprotectin is a gut inflammatory marker that has been shown to be increased in inflammatory bowel disease, cow's milk protein allergy, celiac disease, necrotizing enterocolitis, and intestinal cystic fibrosis.[15-18] Rhoads et al[7] demonstrated that infants with colic had double the fecal calprotectin levels than those without colic, although another larger study did not find any difference in fecal calprotectin levels between infants with and without colic.[19] Partty et al[20] even suggested infants with colic to have low-grade systemic inflammation, indicated by increased levels of cytokines (interleukin-8 [IL-8]), chemokines monocyte chemotactic protein and macrophage inflammatory protein 1beta in cases compared with controls.

One hypothesis is that probiotics may play a role in infant colic by altering gut microbiota, reducing gut inflammation and thereby reduce crying. *L reuteri* DSM17938 is the best studied strain, with 3 double-blind, placebo-controlled randomized trials in Italy, Poland, and Canada,[21-23] 1 single-blind trial in China,[24] and 1 open-label trial in Pakistan[25] concluding it to be effective at the dose of 1×10^8 colony forming units in breastfed infants with colic. Sample sizes for these positive trials ranged from 42 to 80 infants. In contrast, the largest and only double-blind, randomized trial that included both breastfed and formula-fed infants with colic (n = 167) in Australia was ineffective.[26] Interestingly, the US study by Fatheree et al, although very small in comparison, adds to this literature, being the second double-blind, randomized, placebo-controlled trial of *L reuteri* DSM17938 shown to be ineffective in breastfed infants with colic. The study's strengths include recruitment of a well-phenotyped group of infants with colic, use of a validated measure of infant crying and fussing, and detailed laboratory measures including blood and fecal samples. Unfortunately, the final sample size was small (n = 20), significantly below the target sample size of 45 to detect group differences in adverse effects of sepsis and fever, and well below the sample size required to detect group differences in infant crying. Therefore, its conclusions must be interpreted with caution.

Nevertheless, the study reignites the hypothesis that gut inflammation may underlie infant colic. It is the first study to document neutropenia and thrombocytosis in infants with colic, and also the first to document increased fecal calprotectin levels that decrease with reduced crying. Interestingly, the study did not find evidence of systemic inflammation in these infants, unlike the study by Partty et al,[20] indicating that infants with colic have increased laboratory indicators of mild systemic inflammation compared with controls. It is possible that the documented levels of low neutrophil count, high platelet count, and high fecal calprotectin levels may be reflections of normal levels in healthy young infants, which change over time. Platelet and fecal calprotectin levels are higher in neonates as compared with older children, and there is no consensus for "normal cutpoint" levels for fecal calprotectin in infants.[27-31] Direct comparison of neutrophil, platelet, and fecal calprotectin levels in this cohort of infants with colic with healthy controls would be able to clarify this issue.

Like so many previous studies, *Escherichia* was the most frequently identified family of gut organisms in this study's infants with colic, adding to the evidence that the presence of gram-negative organisms in the gut may contribute to crying. However, the proportion of gut *Escherichia* did not correlate with crying time, and in fact increased with resolution of colic in the majority of infants. Interestingly, the proportion of gut *Bacteriodes* increased with reduction in crying, a finding that is similar to the *L reuteri* trial by Savino et al, where responders were found to be more frequently colonized by *Bacteroides* species.[32]

Although underpowered, this is the second negative *L reuteri* DSM17938 trial for infant colic treatment. Interestingly, like

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the negative Australian trial, it included a significant proportion of infants on antireflux medications. It is possible that these medications may alter the gut microbiota composition or dampen the way the gut responds to the administration of *L reuteri* DSM17938. However, it is to be noted that, in the Australian trial, both the probiotic and placebo groups had an equal proportion of infants on antireflux medications,[26] and moreover, antireflux medications have been demonstrated to be ineffective in reducing crying.[33-37]

Despite the limitation of its small sample size, the study by Fatheree et al sheds further light on the possible role of the gut microbiota, gut inflammation and the gut-brain-axis in infant colic. Whether these findings represent the cause or consequence of infant colic is difficult to untangle. Perhaps, it is true that infant colic is related to the gut after all and the ancient Greeks seem to have had the correct "gut feeling" all along. ■

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Epilepsy by Any Other Name Would (Not!) Smell as Sweet

Shakespeare, in *Romeo and Juliet* (Act II, Scene II), implies that what something is called does not detract from its fundamental meaning or worth: "A rose by any other name would smell as sweet." Juliet was expressing her love for Romeo, irrespective of his name (alas, he was a Montague!). But in medicine, the importance of linguistic precision cannot be underestimated.[1] Although names (for diseases, conditions, symptoms, signs, etc) differ in various contexts, optimal medical care requires accurate communication between health care providers, patients, and families, and this accuracy begins with consistency in the use of words to communicate medical information. This challenge is nowhere more poignant than in epilepsy, a disorder still fraught with stigma worldwide[2] and with dismal public awareness,[3] in part owing to the way that we professionals use (and misuse) terminology. The recent evolution of nomenclature to define and classify seizures and epilepsy,[4-6] driven by rapid advances in our understanding of the pathophysiology, genetics, and imaging correlates of seizure generation and epileptogenesis, is making it hard enough for specialists to keep up, let alone patients and families!

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How can a parent or other primary caregiver of a child with epilepsy be expected to understand the definition of the term if medical professionals lack a common language? Even some epilepsy experts are hesitant to use the word epilepsy, instead couching the disorder as a nonspecific phrase such as seizure disorder or some other euphemism.[7] Calling epilepsy a seizure disorder is akin to calling asthma a breathing disorder or Ewing sarcoma a cancer disorder—those terms lack specificity and provide no clinical detail, rendering them almost useless. Yet, the moniker seizure disorder continues to be used widely among physicians and even neurologists. Epilepsy is currently defined as: (1) at least 2 unprovoked (or reflex) seizures occurring more than 24 hours apart, or (2) 1 unprovoked (or reflex) seizure with at least a 60% chance of recurrence, or (3) a diagnosis of an epilepsy syndrome.[4]

Therefore, epilepsy certainly entails seizures, but it is so much more, especially in pediatric epilepsy, where syndromes often comprise a specific age range of onset, etiology, medication responsiveness, genetic background, and natural history. There is an oft-told story of parents who expressed surprise and chagrin when it was mentioned that their child had epilepsy, whereas for years they had been told the child only had a seizure disorder; although apocryphal, this story exemplifies the need to communicate in the most accurate fashion from the outset. Otherwise, we are committing a disservice to patients and families who deserve an accurate diagnostic label to facilitate their own understanding of their child's disorder as they navigate the medical system, seek support from disease advocacy organizations, and communicate with friends, relatives, friends, and the wider community.

How well do caregivers of children with epilepsy understand the terms used to describe this condition? The report by Nagan et al in this volume of *The Journal* is a valiant attempt to characterize and quantify parental understanding of the term epilepsy.[8] They hypothesize that parents have a poor understanding of the term. Through a carefully designed telephone survey, the investigators surveyed 45 caregivers whose children had been diagnosed with epilepsy. They inquired how well caregivers understood the definition of epilepsy in 3 ways. First, they asked whether their child had a seizure disorder, epilepsy, or both. Second, they asked the caregiver to define epilepsy, in an open-ended manner. Third, using a multiple-choice format, they asked parents to choose among 4 possible definitions of epilepsy. In addition, they obtained a sense of the caregivers' own self-perceived understanding of epilepsy.

The results were discouraging, but not surprising. Their hypothesis was verified—very few caregivers correctly identified their children as having epilepsy or provided an accurate definition. A full one-third of respondents had no correct

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