Eosinophilic Gastrointestinal Disorders Affect More Than Just the Esophagus

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See ''Prevalence of Eosinophilic Gastritis, Gastroenteritis, and Colitis: Estimates From a National Administrative Database'' by Dellon et al on page 36.

In 1937, Dr R. Kaisjer provided the first description of eosinophilic gastroenteritis after reviewing surgical resections taken from various parts of the gastrointestinal (GI) tract (1). During the next few decades, other descriptions, again derived from whole tissue surgical specimens, followed. With the advent of flexible endoscopy in the 1960s, physicians were provided the necessary tools to procure mucosal biopsy samples from patients, escorting in a new era of defining the resident and pathological inflammatory cells of the intestinal mucosae. In the early 1980s, 2 publications identified eosinophils as markers of gastroesophageal reflux disease (2,3). The association of esophageal eosinophilia with gastroesophageal reflux disease held firm until the early 1990s when 3 publications provided the first descriptions of eosinophilic esophagitis (EoE) as a distinct disease entity (4,5,5a). Since then, 3 consensus recommendations and a European guideline have been published identifying and refining the diagnostic criteria for EoE (6–9).

The emergence of EoE as an increasingly recognized distinct clinicopathological entity rekindled interest and raised questions about the role of the eosinophil in GI health and disease; for example, do eosinophils play a role in innate host defense and increase as a compensatory mechanism or is their increased presence a manifestation of a pathological inflammatory or allergic condition? (10,11). The latter explanation has certainly garnered more attention, and when tissue eosinophilia is seen in the context of organ-specific symptoms, with peripheral eosinophilia, without evidence of infection, and with resolution after steroid treatment, the diagnosis of an eosinophilic GI disease (EGIDs) is strongly considered.

This interest in EGID has recently extended beyond the esophagus, to encompass the remainder of the GI tract ''south'' of the diaphragm (12,13). Unlike the esophagus, which is normally devoid of eosinophils, the stomach, intestine, and colon are populated by eosinophils under normal healthy conditions. When these levels are elevated in these tissues and other etiologies for eosinophilia are ruled out, patients are diagnosed as having EGID. The critical question that leads to the complexity of the study of these disorders is what number of eosinophils is considered abnormal or elevated. Unlike EoE, no universally accepted thresholds for abnormal tissue eosinophilia in the rest of the GI tract exist.

Although EoE has clearly emerged as a distinct and well-defined entity with a prevalence of 4 in 10,000, epidemiological features of the less common EGIDs, including eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC), remain less defined (12,14–19). The literature to date is limited to case series from isolated center's experiences that may not accurately reflect those of larger patient populations with EGID. Adding to the heterogeneous nature of these conditions is that symptoms vary based on the location and layer of organ involvement. For instance, patients with EG and EGE may present with abdominal pain, nausea, vomiting, diarrhea, and possibly hematemesis secondary to ulceration and bowel obstruction secondary to stricturing disease. Patients may also present with signs of anemia, malabsorption, hypoalbunimenia, ascites, and edema. The presentation of EC can also be varied and include symptoms of diarrhea, constipation, hematochezia, and abdominal pain. Endoscopic findings include edema, ulceration, polyps, and friability, but in some cases the mucosa can appear relatively normal. Elimination diets may bring clinicopathological remission, but patients often require treatment with systemic or topical steroids.

To date, clinical experiences suggest that EG, EGE, and EC are uncommon diseases, but with the increasing accrual of mucosal samples, each is becoming increasingly recognized. Documenting and defining the epidemiology, risk factors and natural history of these EGIDs is of critical importance to allow for accurate diagnosis, understanding the pathophysiology, and identifying novel therapeutic targets. In this regard, Jensen et al's (20) publication brings new and important insights. Similar to their previous works with EoE, they examined large databases to provide initial prevalence estimates for EG, EGE, and EC (21–24). They probed a 2-year span of databases representing more than 75 million US individuals ranging in age from 0 to 64 years with commercial insurance. They captured individuals in whom an *International Classification of Diseases-9* code specific for EG, EGE, or EC was used more than once in the database and extrapolated the findings to estimate the US prevalence of these diseases. Consistent with clinical experiences, their finding revealed that each is rare with an estimated prevalence of EG at 6.3, EGE at 8.4, and EC at 3.3 per 100,000. In this population, EGE was most common in children younger than 5 years. Allergic diseases occurred in approximately 40% of affected individuals and were more common in children. In contrast to EoE, females were more often affected by these EGIDs. This important work provides the first prevalence estimates for EGIDs beyond the esophagus detected in a large population, thus identifying trends that are difficult to recognize in single-center studies involving smaller numbers of individuals.

Because the results rely on an insurance database without a validated administrative case definition, these involve the use of diagnosis codes without thorough examination of medical records, and because diagnostic guidelines are less well defined for EG, EGE, and EC than for EoE, the prevalence numbers should be considered estimates and may not precisely reflect the general population. Potential confounders capable of altering the normal numbers of GI eosinophils are numerous and include age, environment, antibiotic use, and diet, among others. Clinical experiences

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suggest that the interpretation of what constitutes a normal versus abnormal number of eosinophils in GI tissues varies by interpreter. In fact, in some cases, patients may have received an initial diagnosis of EGID but upon review of their pathology and following their clinical course, indeed are found to have irritable bowel syndrome. Alternatively, some patients have increased numbers of mucosal eosinophils with features of chronicity and indeed have an inflammatory bowel disease. Because a diagnosis of EGID carries therapeutic and long-term consequences, more research from well-characterized large patient populations with access to medical records is urgently needed to help define normal and abnormal GI eosinophilia, identify associated clinical features, etiology, determine the natural history, and identify novel therapeutic targets for each of these EGIDs.

To address the issues associated with the characterization of these less common EGIDs, the recently funded NIH U54-funded Consortium for Eosinophilic GastroIntestinal Disease Research (CEGIR—*https://www.rarediseasesnetwork.org/cms/CEGIR*) seeks to identify phenotypic and genotypic features of EGIDs. In a prospective longitudinal study, a variety of clinical outcome measures, histology, and molecular markers will be collected from children and adults with EoE, EG, and EC. Results from these studies will help clarify the diagnostic features of these diseases and provide an improved framework for the present *International Classification of Diseases* codes. Outcomes from this work will also include the development of diagnostic guidelines for the remaining EGIDs and provide a deeper understanding of commonly shared and distinct features of each EGID. Patients with EGID are urged to register on the Contact Registry at *https://www.rarediseasesnetwork.org/cms/CEGIR*.

Clinical experiences and the intriguing data provided by Jensen et al suggest that EG, EGE, and EC are unlikely to affect as many people as EoE. Regardless, the future rewards of studying these diseases will be significant in regards to establishing well-defined diagnostic criteria, identifying novel therapeutic targets, understanding pathogenetic mechanisms, and better defining the role of the eosinophil in GI health and disease.

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Need for Infant Formula

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See ''An Opinion on ''Staging'' of Infant Formula: A Developmental Perspective on Infant Feeding'' by Lönnerdal and Hernell on page 9.

There will always be a need for infant formula, no matter how successful we are in promoting breast-feeding. Some mothers will not be able to breast-feed because of illness or separation from their babies. Some mothers will choose not to breast-feed.

Approximately 5% of mothers do not produce enough milk to completely support their babies (1). When a baby is not breast-fed, the best possible nutrition should be available. Because breast-feeding is the acknowledged gold standard, choosing alternative nutrition will always be less than optimal. The questions then become: how much of a compromise is acceptable and how to minimize the compromise. Elsewhere in this issue Lönnerdal and Hernell (2) propose to reduce the compromise by introducing 3-staged formulas for infants <1 year of age: stage 1, from birth to 3 months; stage 2, 3 to 6 months; and, stage 3, to cover the second 6 months of life. This contribution raises the question: are the present infant formulas acceptable?

Breast milk is a dynamic fluid: it changes with gestational age, stage of lactation, within the same feeding and from one mother to another. These features will never be duplicated by formula-feeding. Changes in infant formula have brought the performance of formula progressively closer to breast milk and have increased formula safety. Formula manufacturers have compiled an impressive but not perfect record of safety and efficacy. When infant formula is the sole source of nutrition for the first 4 to 6 months of life it supplies all the nutrient and energy needs of healthy full-term infants (3,4). The past decades have served as a ''natural experiment'' to demonstrate the adequacy of formula feeding. In the early 1970s, 75% of infants in the United States were exclusively formula-fed and 90% were formula fed after 3 months of age (4). We have seen no dire health consequences that can be directly related to formula feeding. This was a time of decreasing cardiovascular disease (5); the obesity epidemic came later (6), when breast-feeding rates were increasing (7).

The rationale for the proposal of Lönnerdal and Hernell is essentially 3-fold: growth curves of formula-fed infants and breast-fed infants do not exactly overlap; the iron requirement of early infancy is much less than during the second 6 months of life, but the iron content of formula is targeted to cover the requirements for the entire first year; the protein content of infant formula may be greater than required.

When comparing the World Health Organization (WHO) growth curves (derived from exclusively breast-fed infants) and the Centers for Diseases Control and Prevention (CDC) curves compiled from a combination of formula-fed and breast-fed infants) breast-fed infants tend to gain more rapidly during the first 3 to 4 months and then more slowly later in the first year. Given the vastly different methods used to construct the WHO and the CDC growth curves, it would be surprising if the curves were superimposable. WHO curves were intended to be ''prescriptive.'' They demonstrate how infants grow under ideal conditions, whereas the CDC curves are ''descriptive'' compiling data from several national surveys from varying times. CDC curves represent growth in real life. Given these methodological differences, the curves are in fact similar (8).

It is true that the average infant needs little iron during the first several months of life. There are exceptions. In some circumstances, infants' needs may exceed stores. Iron requirements during the second 6 months increase and become substantial. The iron content of complimentary foods tends to be low (thus the American Academy of Pediatrics recommends that meats, which contain bioavailable iron, be introduced early). Present formulas provide iron not needed by most infants up to 6 months, to cover the iron needs of all infants after 6 months. Significant harm has not been substantiated from iron supplied to infants <6 months (9–11).

Infant formula provides more protein than breast milk. The reason for the higher protein in formula was to compensate for differences in protein quality and to provide sufficient protein for the majority of infants, not the average infant. Fomon et al (12) investigated formula with low protein content and concluded that formula containing 1.7 g/100 kcal was adequate but not safe. In a systematic review of studies of formulas with decreased protein, Abrams et al (13) suggested that lower protein may provide for adequate growth but that further testing is necessary. More important, this article points out that testing of all groups that are likely to be affected need to be performed. These groups would include near-term infants, small-for-gestational-age infants, and younger and older healthy, full-term infants.

The basis for Lönnerdal and Hernell proposal are the shortcomings of our present infant formula. There have, however, been no trials of the proposed staged formulas. In fact, a detailed description of the contents of the staged formulas is not included. Before this proposal can be considered as even a feasible alternative, prospective formulas need to be devised and testing must be conducted. As pointed out in the proposal by Lönnerdal and Hernell, in Europe, the present recommendation is for 2 formulas: one formula for the first 6 months life and the other, different, formula for the second 6 months of life. There is no readily available population-based study demonstrating that this 2-stage plan is superior to the single-stage plan used in the United States, nor is there evidence on how well parents adhere to this recommendation. Therefore, there is no concrete evidence that the staged formulas would be superior to the present formulas.

We suggest that it is reasonable to keep it simple. At the present time there are 143 infant formulas listed on a commercial Web site and this number is conceded to be incomplete (*http://www.goodguide.com/categories/255741-baby-formula-reviews-and-ratings*). Studies have documented the misuse of infant formula by parents (14). Other studies attest to the incomplete knowledge of practicing pediatricians (15). Available on the shelves of supermarkets are formulas for colicky babies, for babies with reflux, for babies with constipation, and formulas for any number of other conditions. How would parents deal with choosing a formula, if this number were multiplied by 3?

Infant feeding, whether it be human milk or formula, is vitally important from birth until complementary feeding is started. From the point of the first introduction of complementary feeding until weaning is complete at approximately a year of life, the infant should derive more and more nutrients from food. Breast milk/formula should become progressively less important. This period of ''weaning'' has not received the attention that it deserves. There is evidence, at least in animal models, that weaning itself may trigger developmentally important physiologic changes (16). Perhaps we should be focusing our research on what is given to infants in addition to breast milk or formula.

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