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Eosinophilic Gastroenteritis and Colitis – Not Yet Ready For the Big Leagues

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Eosinophilic gastrointestinal diseases (EGID) are a heterogeneous group of conditions characterized by common gastrointestinal (GI) symptoms and an eosinophil predominant infiltrate in the involved tissues. Over the course of the last several decades, eosinophilic esophagitis (EoE) has emerged as the most recognized EGID. In order to advance the care of EoE patients, a succession of meetings and discussions were held during the last two decades to develop and publish a series of consensus guidelines[1–5]. In 2007, the initial EoE guidelines were based more on expert opinion and experience than the limited experimental evidence available at the time. These guidelines allowed researchers from around the world to perform studies with relatively uniform disease criteria, producing a robust number of studies and large amounts of higher quality data. Subsequent guidelines incorporated this experimental evidence and guided future studies. This work was simplified by the fact that the healthy esophageal epithelium does not contain any eosinophils and thus defining the histological criteria for EoE was relatively straightforward.

For unknown reasons, recent clinical experiences and reports are identifying an increasing number of patients with eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC)[6]. With this emergence, a similar need has developed to identify consensus guidelines for diagnosis and monitoring disease activity of these newer EGIDs. Hopefully, this development will follow the same process as those developed for EoE. In contrast to EoE, where the void of eosinophils allowed for an easier diagnostic threshold, the distal gut has a resident population of eosinophils that varies widely. In addition, eosinophils may play a role in the innate immune system and thus increase in some circumstances.[7,8]

In this issue of JPGN, Kiss et al.[9] have attempted to bring us one step closer to identifying a diagnostic threshold in children. They conducted a literature search and meta-analysis of

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studies reporting eosinophil counts in the small intestine and colon of children without apparent GI diseases. In this process, they identified 8 studies that provided comprehensive data to analyze, and only 3-6 relevant studies for any particular sampling site, thus emphasizing the difficulties in standardizing assessments of resident mucosal eosinophils. As part of their rigor, only studies for which eosinophil counts could be converted to standardized eosinophil/mm^2 counts were included. Kiss et al[9] found that mean eosinophil count per standardized $0.2mm^2$ high power field (HPF) in the duodenum was 8.26 (95% CI 4.71-11.8) and in the terminal ileum was 11.52 (95% CI 7.21-15.8). In the colon, a decreasing gradient was found from proximal to distal colon. Cecal counts were higher, with 14.12 (95% CI 9.05-19.19) while the in the rectum the counts dropped to 7.39 (95% CI 4.2-10.59). One of the strengths of this study is that in addition to providing means and confidence intervals for each of the sites examined, the authors recognized the limitations of the few available studies, and also report the much broader prediction intervals. The prediction intervals estimate the intervals in which future observations will fall within a specified probability. Thus, while the confidence interval for eosinophil counts in the duodenum was approximately 4.7-11.8, the prediction interval was wider, 0-20.6, reflecting the scant quality data available.

Adding to the difficulty in assessing normal eosinophil numbers, significant complexities arise when attempting to calculate mucosal eosinophilia in EGIDs. In their highly active state, eosinophils degranulate, releasing active mediators into the extracellular matrix. Gauging only intact eosinophils may therefore underestimate the eosinophil burden in the tissue. Furthermore, while the prevailing descriptive unit for tissue eosinophils has been Eos/HPF, there is no uniform definition of the area of a high power field. As Kiss et al and others have shown, small differences in microscope lenses, may lead to significant differences in the eos/HPF counts[9,10]. In the current publication, they report all counts as both eos/HPF standardized to a $0.2mm^2$ area, as well as a more recently published metric, eos/mm^2. When assessing eosinophils in EGID, the location of eosinophils within the tissue may make sampling and assessing even more problematic because the relevant cells may be deeper than the reach of mucosal biopsy forceps in the submucosal, muscular or serosal sites or beyond the reach of the endoscope in the more distal small bowel[11].

In order to improve care of patients potentially affected by these diseases and advance current research platforms, a number of approaches can be taken. First, retrospective studies of well-defined healthy patients can potentially provide more and better data needed to characterize normal tissue eosinophilia. Sources of tissues from healthy subjects may include prospective studies in healthy populations undergoing screening. Currently, screening endoscopies (colonoscopy for colon carcinoma and upper endoscopy for gastric carcinoma in high risk populations) are only performed in the adults. In addition, archived data from previous randomized population studies or cohorts from prospective studies involving conditions not associated with gastric or intestinal eosinophilia may be sources. In contrast to adults, obtaining pediatric tissue samples from healthy children is ethically problematic, however autopsy samples of those who died without GI symptoms may be considered, as was reported by Lowichik et al.[12] In their analysis, Kiss et al included samples taken from children with GI symptoms in whom no apparent diseases were identified[9]. While such samples are the best source currently available, recent data

suggesting a role for eosinophils in functional GI diseases both in children and adults, should be recognized, as it further blurs the border between “apparently normal” children and those with mild pathology[11]. Second, prospective studies will be important to pursue to validate numbers of normal mucosal eosinophils. This will help to determine the impact of co-morbid diseases, medications, age, gender and geographic influences on this metric. Third, as these metrics are developed, therapeutic trials will need to use this information as a part of the biomarker panel readout and endpoints for novel treatments. As the pathogenesis of EGIDs are still uncertain, and the associated cells are not well identified in the tissue space, eosinophils will remain a central cell to enumerate and assess as a metric of therapeutic success.

The time is ripe for international consensus groups to convene and decide on preliminary EGID disease definitions including consensus for the initial cut-off limits for abnormal eosinophil counts at each intestinal locus. Despite the fact that it is likely that these definitions will change in the future as more evidence becomes available, they will enable higher quality research to be initiated with more uniformity. The current study by Kiss et al is an important step in the right direction towards consensus, however their study highlights the sparsity of the available evidence and emphasizes the need for more collaborative studies in EGID research. Current work within the National Institutes of Health U54 funded Consortium for Eosinophilic Gastrointestinal International Researchers (CEGIR - https://www.rarediseasesnetwork.org/cms/CEGIR) is beginning to address this in a multi-site study.

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