Peripheral Eosinophils and Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease associated with mucosal infiltration of the esophagus. EoE incidence appears to be increasing, especially in children, and repeat esophagogastroduodenoscopy (EGD) often is needed to confirm therapeutic response to EoE (typically topical mucosal steroid therapy or dietary changes directed at preventing allergic disease). Since clinical symptoms of EoE are not a good indicator of clinical response to therapy, one of the current goals in EoE research is to find non-invasive biomarkers to monitor disease activity. In that regard, the blood eosinophil count has the potential to be such a marker.

The authors of this study performed a retrospective chart review of all pediatric patients (less than 18 years of age) diagnosed with EoE over a 7-year period. Patients with coexisting GI disease were excluded, and EoE was defined as an eosinophil count greater than or equal to 15 eosinophils per high-power field (HPF) in biopsies in any of 3 regions of the esophagus (lower, mid, upper). All patients in this group had been on a proton pump inhibitor for at least 4 weeks prior to EGD. The primary study endpoint was determination of a possible correlation between absolute peripheral eosinophil count and esophageal eosinophilic infiltration. The secondary study endpoint was to see if esophageal eosinophils correlated with biopsy findings of basilar hyperplasia, spongiosis, and the presence of neutrophils and lymphocytes.

A total of 57 patients with EoE, 91 EGDs, and 279 biopsy specimens were included in the study. The oldest patient in the study was 17.9 years while the youngest patient was 1.6 years. The age of participants ranged from 1.6 years to 17.9 years of age, and white study subjects comprised 80% of the study population. A total of 66 procedures (71%) had biopsies consistent with EoE while the other 29% had less than 15 eosinophils per HPF or had no disease noted on biopsies. A significant correlation was seen between absolute eosinophil counts in blood samples and highest esophageal counts in biopsy specimens (P=0.0009). There was a significant correlation between absolute eosinophil counts in patients with active EoE compared to patients with biopsies showing less than 15 eosinophils per HPF or no eosinophilic infiltration. An absolute eosinophil count less than 500 correlated well with patients with inactive disease although an absolute eosinophil count greater than 500 did not correlate well with active EoE. However, when using a logistic regression model for race, sex, weight, height, and body mass index (BMI), none of these factors correlated with absolute eosinophil counts in relation to EoE activity.

It was noted that 58.1% of patients with EoE had allergic rhinitis, 50.5% of patients had food allergies, 38% had asthma, 29 % had eczema, and 14% had all of these conditions together. The most common symptoms included odynophagia (6.5%), food impaction (7.5%), chest pain (11.8%), nausea (23.7%), gastroesophageal reflux symptoms (24.7%), emesis (24.7%), dysphagia (25.8%), and abdominal pain (33.3%). The most common endoscopic finding in patients with EoE included esophageal furrowing (43%). Basilar hyperplasia, spongiosis, and microabscesses were significantly more common in patients with EoE compared to patients with no EoE although the presence of lymphocytes and neutrophils in biopsies did not differ between groups.

Although absolute eosinophil count may be a marker for inactive EoE which has the potential to be used for disease response, this study showed that it was difficult to correlate such findings with worsening EoE. Basilar hyperplasia, spongiosis, and microabscesses (potential early markers of the development of fibrosis) did seem to correlate with EoE although infiltration of other cell types (neutrophils, lymphocytes) did not. The authors state that the patients with EoE in this study were all treated with swallowed budesonide, and we have no data on other interventions such as swallowed fluticasone or dietary therapy. It appears that absolute eosinophil count is not a good marker for following EoE activity over time.

Choudhury S., Kozielski R., Hua J., Wilding G., Baker S. Do histological features of eosinophilic esophagitis in children correlate with peripheral eosinophils? Journal of Pediatric Gastroenterology and Nutrition 2020; 70: 604-607.

Collagenous Colitis Shares Genetic Risk with Other Immune-Mediated Diseases

An array-based, genetic association study was carried out in a cohort of patients with collagenous colitis (CC) and the common genetic basis was investigated

between that and Crohn's disease (CD), ulcerative colitis (UC), and celiac disease.

DNA from 804 CC formalin-fixed, paraffin-embedded tissue samples were genotyped with Illumina Immunochip. Matching genotype data was carried out on control samples and CD, UC, and celiac cases were provided by the respective consortia.

A discovery association study followed by meta-analysis with an independent cohort, polygenic risk score calculation and cross-phenotype analyses were performed. Enrichment of regulatory expression, quantitative trait loci among the CC variants was assessed in hemopoietic and intestinal cells.

Three HLA alleles (HLA-B*08:01, HLA-DRB1*03:01 and HLA-DQB1*02:01), related to the ancestral haplotype 8.1, were significantly associated with increased CC risk. An independent protective effect on HLADRB04; 01 was noted on CC risk. Polygenic risk score quantifying the risk across multiple susceptibility loci was strongly associated with CCI risk.

An enrichment of expression quantitative trait loci was detected among the CC susceptibility variants in various cell types. The cross-phenotype analysis identified a complex pattern of polygenic pleiotropy between CC and other immune-mediated diseases.

It was concluded in this largest genetic study of CC to date, with histologically confirmed diagnosis, this strongly implicated the HLA locus and proposed potential non-HLA mechanisms in disease pathogenesis. A shared genetic risk was also detected between CC, celiac disease, CD and UC, supporting clinical observations of comorbidity.

Stahl, E., Roda, G., Dobbyn, A., et al. "Collagenous Colitis is Associated with HLA Signature and Shares Genetic Risks with Other Immune-Mediated Diseases." Gastroenterology 2020; Vol. 159, pp. 549-561.

Necrotizing Enterocoliltis: Is Care Getting Better?

Necrotizing enterocolitis (NEC) is a devastating intestinal condition typically associated with premature infants in neonatal intensive care units (NICUs). NEC is associated with both a high mortality rate as well as a high rate of neurodevelopmental disability (NDD). As survival of premature infants increases, the risk of NEC also has increased, and the authors of this study looked at current outcomes of NEC in the medical literature. In particular, a review of the literature occurred using the PRISMA Statement (http://www.prisma-statement.org/PRISMAStatement/PRISMAStatement). PubMed also was searched for the following terms: "NEC," "mortality," "morbidity," "neurodevelopmental outcome," "outcomes", and "intestinal failure." Included articles had to be in English and had to be published after January 2010 with reported NEC outcomes (mortality) from international/national/regional/multi-center studies from high-income countries.

Initially, 1371 articles were included, but only 31 articles met the criteria of studying mortality that could be included in a meta-analysis. Mortality from NEC (Bell stage 2A or higher) was 23.5% (95% confidence interval 18.5% to 28.8%) with low birthweight and history of NEC surgery being risk factors. In particular, the mortality of infants less than 1000 grams who underwent surgery for NEC was 50.9% (95% confidence interval 38.1% to 63.5%). The meta-analysis demonstrated that mortality from NEC in premature infants ranged from 10% to 21%. Five studies meeting criteria for evaluating NDD in the setting of NEC, and severe NDD ranged between 24.8% and 59.5% although the definition of "severe" varied between studies. Finally, only three studies described the association between intestinal failure (defined as intestine loss preventing normal intestinal absorption and growth) and NEC with intestinal failure rates of 15.2% in all infants with NEC and 35.4% in infants with NEC requiring surgery.

This meta-analysis provides convincing evidence that NEC still is extremely problematic in NICUs, and further research is necessary to decrease associated morbidity and mortality. Further research should be aimed towards understanding potential associated genetic mechanisms involved in NEC as well as considering the possibility of new types of pre-/pro-/symbiotic strains to reduce the complications of this devastating disease.

Jones I. and Hall N. Contemporary outcomes for infants with necrotizing enterocolitis – a systemic review. Journal of Pediatrics 2020; 220: 86-92.

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