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### An allergist's perspective to the evaluation of Eosinophilic Esophagitis



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Eosinophilic Esophagitis (EoE) is a classic atopic disease as it shares features with other atopic disease on all levels including pathogenesis, genetics, epidemiology, and treatment options. EoE has elements of Th2 pathogenesis with increase levels of Th2 cytokines (IL4, 5, and 13). In addition, it shares atopic genetic risk factors including thymic stromal lymphopoietin (TSLP) loci as a risk factor in genome wide association studies. EoE patients have a higher rate of other atopic disease (asthma, allergic rhinitis and food allergy) compared to the general population indicating their atopic phenotype. Like asthma, atopic dermatitis or food allergy, EoE has increased in the last 20 years. Treatment options include the basic principle of other atopic diseases include using topical steroids or avoidance of the triggers (food or pollen). An allergist provides a critical role as they are experts in the treatment of atopic disease including avoidance strategies.

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Eosinophilic Esophagitis (EoE) is a chronic immune and antigen mediated clinicopathological disease, which is characterized by eosinophil infiltration into the esophageal epithelium and results in esophageal fibrosis and dysfunction [1]. EoE is emerging as an increasingly common cause of esophagitis in children and adults and requires intensive monitoring and treatment to prevent complications including poor growth, nutritional deficiencies, food impaction, stricture formation, and spontaneous

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esophageal perforation. In this review, we will briefly review why EoE is considered an atopic disease from a mechanistic, epidemiological, treatment standpoint and the role of allergist in the disease management.

### **Mechanistic viewpoint-Why EoE is an atopic disease?**

Overall, there is a chronic inflammatory infiltrate in EoE, which includes eosinophils, mast cells, basophils and T-cells that produce Th2 cytokines (i.e. IL-4 and IL-13) and promote additional inflammation and dysfunction. Similar to other atopic diseases, EoE is triggered by environmental irritants/allergens and food allergens, culminating in esophageal fibrosis or tissue remodeling [2,3]. Like atopic dermatitis, there is an altered epithelial barrier dysfunction. Indeed, both gene expression profiling [4] and immunolocalization studies [5] have demonstrated a down-regulation in the expression of the cell adhesion protein desmoglein-1 (DSG-1) in the esophageal epithelium in actively inflamed EoE, which partially normalizes after clinical treatment.

Classic atopic cytokines and chemokines play an essential role in the inflammation associated with EoE, resulting in increased Th2 response, eosinophil survival, and fibrotic changes. For example, IL-4 promotes Th2-lymphocyte survival, eosinophil migration via induction of eotaxin-3 (CCL-26), and profibrotic changes by inducing periostin, collagen and  $\beta$ -actin. There are likely redundancies in cytokine function as anti-IL-5 leads to only partial reduction of esophageal eosinophilia in human trials [6,7]. Thymic stromal lymphopoietin (TSLP) is an IL-7 like cytokine that is a master regulator of Th-2 type allergic inflammation. It is primarily secreted by cells of non-hematopoietic lineage such as epithelial cells, fibroblasts, and smooth muscle cells in response to atopic cytokines (IL-4, IL-13, TNF $\alpha$ ) and environmental allergens. TSLP is increased in the esophageal biopsies of EoE subjects compared to non-EoE subjects [8–10] and is overexpressed within epithelial barriers including the epidermis in atopic dermatitis [11,12]. Polymorphisms in TSLP are linked to EoE, and deletion of TSLP in a murine model of EoE completely eliminates esophageal eosinophilia. In EoE, expression of TSLP may be induced by tissue injury or stimulation of the esophageal epithelium starting the Th2 cascade. TSLP has also shown to be pivot in the pathogenesis of asthma, allergic rhinitis and atopic dermatitis [13–15]. The same animal models that develop asthma or atopic dermatitis [16] can develop EoE [10,17] showing the link between atopic disease. Like most atopic diseases, T cells play a critical role as following eosinophils, intraepithelial T-lymphocytes are the most prominent infiltrating cell type in EoE. EoE patients have activated Th2 cells secreting IL-4, IL-5 and IL-13 in both the peripheral blood and active esophageal biopsies [18,19]. These diverse evidence (animal, cytokine, histology) all indicate that EoE is an atopic disease.

### **Epidemiological viewpoint: Why EoE is an atopic disease?**

EoE has not only an atopic mechanism for disease progression. Like other atopic disease, the incidence and prevalence of EoE has increased dramatically in the last decade. The rise in EoE mirrors the increased prevalence of allergic diseases (asthma, allergic rhinitis, atopic dermatitis, and food allergy) over the last few decades [20–22]. In our cohort at The Children's Hospital of Philadelphia, we have seen a 70-fold increase, from 1994 to 2011 [23]. This rise has also been observed in the adult population with increased prevalence from 2/100,000 in 1989 to 23/100,000 in 2004 in Olten Country, Switzerland [24]. In addition, the patients are highly atopic with much high rate of asthma, allergic rhinitis and IgE-mediated food allergy compared to general population. Approximately 30–50% of individuals with EoE have asthma compared to 10% in the normal population [25,26]. Similar, 50–75% have allergic rhinitis compared to 30% in healthy children. In addition, 10–20% of children with EoE have IgE-mediated food allergy (urticaria and anaphylaxis) compared to 1–5% in normal children [25–27]. These rates of atopy (asthma, allergic rhinitis and atopic dermatitis) are approximately three times higher than what is expected in the general population. Other studies of pediatric and adult patients with EoE have confirmed the higher prevalence of environmental and/or food allergies, approximately fifty percent higher than the general population [28–30]. These data suggests EoE is a super-atopic phenotype.

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