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Pediatric and adult eosinophilic esophagitis (EoE): similarities and differences

History and epidemiology of adult and pediatric EoE

The esophagus is frequently affected by disturbances mainly because of the dysfunction of the lower esophageal sphincter, which is responsible for maintaining a large pH gradient. The history of adult and pediatric esophageal diseases is therefore strongly dominated by dysfunction of the esophago-gastric junction leading to gastroesophageal reflux disease (GERD) and its sequela.

In the early 1990s, two case series described *adult patients* suffering from *dysphagia* associated histologically with an eosinophil-predominant infiltration. Kelly and colleagues reported on a series of allergic children suffering from severe GERD like symptoms refractory to medical or surgery therapy.

Clinical characteristics of adult and pediatric EoE

While EoE may affect individuals at any age, clinical presentation is highly dependent on the patient's abilities to report symptoms associated with esophageal dysfunction. Recognition of clinical signs, along with laboratory and endoscopic findings, is critical for the identification of new patients with EoE and those with established disease and uncontrolled inflammation.

Medical history

Both children and adults with EoE are typically individuals in a good general condition. They present with unspecific symptoms, a variety of compensatory behavior strategies, or episodes of food impaction. Therefore, in adults and adolescents, it usually lasts 4–5 years before the EoE diagnosis is made. Important clues to the diagnosis of EoE can be obtained by taking a careful patient's history that focuses on esophageal and upper abdominal symptoms.

Table 1 Symptoms reported by pediatric and adult patients with eosinophilic esophagitis

Children	Abdominal pain Chest pain or heartburn Coughing Decreased appetite Dysphagia (food sticking – especially meat, bread, pasta, and pills; 'toy car' in throat; 'furball' in throat; sticky saliva; throat makes a clunking sound; food wads up; holds food in mouth for 15 min before swallowing; chews food finely; needs a much water to wash food down; and last one to leave the table)
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Adults	Food refusal (spits out food; throws food away; self-limits food; fear of choking; and picky eater) Choking/gagging Nausea Regurgitation Sleeping difficulty Throat pain (itchy, scratchy spicy, and hot spit) Dysphagia Food impaction Retrosternal pain
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Adapted from Newton et al.

Physical examination

In part, owing to the anatomic location of the esophagus hidden deep within the chest cavity, the physical examination of children and adults with EoE is typically normal. In some children, failure to thrive may be obvious. Features of concomitant allergic diseases (asthma, eczema, allergic rhinitis etc.) are frequently found.

Laboratory analyses

Mild peripheral eosinophilia occurs in 5–50% of children and adults with EoE. Approximately 70% of patients with EoE have elevated total IgE values.

Endoscopic features

Upper endoscopy is the first diagnostic step in the work-up of individuals with dysphagia. Although there is neither a pathognomonic endoscopic sign nor a typical pattern of abnormalities, a considerable number of endoscopic features may be observed. These signs usually appear in random combination and represent evidence of active inflammation with mucosal edema (furrows, exudates, etc.) or chronic inflammation with tissue remodeling (crepe-paper mucosa, corrugated rings, stricture). To date, no systematic studies have compared endoscopic features of EoE in children and adults. But according to our clinical experience, signs of active inflammation occur mainly in children, whereas manifestations of chronic inflammation are observed more frequently in adults. The suspected diagnosis of EoE requires histologic confirmation with a mucosal biopsy.

Eosinophils

Eosinophils are not normally found in the esophageal epithelium and the quantity of intraepithelial eosinophils is a crucial component in the diagnosis of EoE. The consensus recommendations, based on extensive

literature review, endorse using the same minimum threshold level of esophageal epithelial eosinophilic inflammation for both children and adults. Over time, in adults, intraepithelial eosinophils may diminish but in children may increase.

This apparent contradiction may be due to differing therapies, as well as to more skillful accommodation to disease (e.g., prolonged chewing) in adults compared with children.

Immunopathogenesis

The striking eosinophil infiltration of the esophageal tissue suggested that an immunologic mechanism contributed to the pathogenesis of EoE. The recognition that EoE represents a Th2-type inflammatory disease was a large step forward in our understanding of the disease. This landmark study showed that the esophageal epithelium of patients with EoE contains not only eosinophils, but also IL-5-expressing T cells, B cells, and IgE-bearing mast cells, pointing to the possibility that EoE is an allergic entity.

Allergic profile in adults and children with EoE

It has become increasingly clear that there is a significant allergic predisposition in the EoE population, with the majority of patients having concurrent allergic rhinitis, asthma, eczema, and/or a history of atopy. Based on its pathogenesis, it is likely that EoE represents a new manifestation of atopy. In children, EoE seems to be primarily a food antigen-driven disease with the majority of children responding to the elimination of common dietary antigens and having disease recrudescence upon reintroduction of the instigating food antigens. Also adult EoE may be driven by food antigens in many patients. Interestingly, in adolescents and adults with EoE aeroallergen sensitization has mainly been observed. However, these patterns of sensitization do not necessarily prove a shift in EoE triggers, but rather a shift in the known pattern of allergic sensitization in allergic subjects, consistent with a sensitization pattern that follows the atopic march.

Aeroallergen and food sensitization in adult EoE

In adult patients, EoE is often associated with elevated serum IgE levels. Initial EoE reports mention elevated total IgE levels and concomitant allergic diseases in 70% and 77%, respectively. A prospective study on 31 adult patients with EoE revealed specific IgE to aeroallergens, food allergens or both in 80%, and positive skin prick test (SPT) in 84%. In 63% of patients sensitized to food allergens, cross-reactive aeroallergens were identified, in particular, to grass pollen, wheat, and rye. However, elimination diet of wheat and rye failed to improve EoE symptoms in sensitized patients. Recent studies demonstrated sensitization to environmental allergens in 86–93% and to food allergens in 50–82% of adult patients with EoE. Peanut, soybean, egg white, cow's milk, and

tree nuts as well as wheat, tomato, carrots, and onions were identified as common food allergens in adult patients with EoE. Pan allergens present in pollen as well as in fruits and vegetables, for example, profilin, have been identified as relevant allergens in EoE. Because an elemental diet does not seem practical in adults, specific elimination diet can be tried.

Aeroallergen and food sensitization in pediatric EoE

Similar to the adult data, pediatric patients commonly have aeroallergen sensitization and >70% have elevated total IgE. While a lack of elevated total IgE may indicate a subset of EoE children who do not have elevations in specific IgE to food or aeroallergens, the overall data do not support a need to follow or analyze total IgE levels in patients with EoE. Children are sensitized to both outdoor and indoor allergens, with reports of 26% and 37% of patients allergic to grass and *Alternaria*, respectively, and 16–19% sensitized to cockroach and house dust mite allergens. Similar to adults, there can be seasonal variations in the diagnosis and severity of EoE in children. Despite these clinical observations, a definitive instigating link between pollen and human pediatric EoE remains unclear. Therefore, further studies that clearly document the pattern of aeroallergen sensitization with the season of EoE onset and/or exacerbation are required.

Genetics

Numerous studies have suggested EoE's strong genetic inheritability. Indeed, 6.8% of patients with EoE have at least 1 family member suffering from the same disease, about three of four patients with EoE present with a family history of atopic disorders, three of four patients are men, 9 of 10 are Caucasian and the sibling recurrence risk ratio is 80 in EoE, while it is approximately 2 for asthma. The two EoE subtypes, sporadic EoE and familial EoE, have been compared for clinical, endoscopic, pathological features, and global esophageal transcript expression profiles and were found to be very similar.

Treatment for EoE in adult and pediatric patients

Indications and modalities for EoE treatment

Currently, the treatment modalities for EoE include the 3Ds, drugs (topical corticosteroids, immunosuppressants, and biologic agents), hypo-allergic diets, and finally esophageal dilation. We hereby provide further insights into the different treatment modalities for adult and for pediatric patients with EoE.

- **Proton pump inhibitors**
- **Systemic and topical corticosteroids**
- **Leukotriene inhibitors**
- **Elimination diets**
- **Esophageal dilation**

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Introduction

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose. It was defined in 1929: 'The three cardinal symptoms in nasal reactions occurring in allergy are sneezing, nasal obstruction and mucous discharge.'

Allergic rhinitis is a global health problem that causes major illness and disability worldwide. Patients from all countries, all ethnic groups and of all ages suffer from allergic rhinitis. It affects social life, sleep, school and work. The economic impact of allergic rhinitis is often underestimated because the disease does not induce elevated direct costs.

Definition and classification of allergic rhinitis

- Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation.
- Allergic rhinitis is subdivided into IAR or PER disease.
- The severity of allergic rhinitis can be classified as 'mild' or moderate/severe'.
- Allergic rhinitis impairs QOL, sleep, school and work.
- Many nonallergic triggers induce nasal symptoms which mimic allergic rhinitis. They include drugs (aspirin and other nonsteroidal anti-inflammatory agents), occupational agents, foods, physical, emotional and chemical factors and viral infections.

Definition and classification of rhinosinusitis

- Sinusitis and rhinitis usually coexist and are concurrent in most individuals; thus, the correct terminology for sinusitis is rhinosinusitis.
- Depending on its duration, rhinosinusitis is classified as acute or chronic (over 12 weeks).
- Symptoms and signs overlap with those of allergic rhinitis.
- For the diagnosis of CRS (including nasal polyps, NP), an ENT examination is required.
- Sinus X-rays are not useful for the diagnosis of CRS.
- Computerized tomography scans may be useful for the diagnosis and management of CRS.

Risk factors for allergic rhinitis

Allergic rhinitis is a multifactorial disease induced by gene-environment interactions.

- Indoor and outdoor inhalant allergens cause allergic rhinitis.
- Major outdoor allergens include pollens and molds.
- Major indoor allergens include mites, animal danders, insects and molds.

- Food allergens are rarely the cause of isolated nasal symptoms.
- Occupational agents can cause rhinitis by allergic and nonallergic mechanisms.
- The role of indoor and outdoor air pollutants is probably of importance, but more data are needed to assess their effect.
- Socioeconomic differences are reported in allergic diseases, but more data are required before producing specific recommendations.

Mechanisms

Allergic inflammation

Allergic rhinitis is classically considered to result from an IgE-mediated allergy associated with a nasal inflammation of variable intensity. Cells, mediators, cytokines, chemokines, neuropeptides, as well as adhesion molecules and cells all cooperate in a complex network provoking specific symptoms and nonspecific nasal hyperreactivity.

The understanding of the mechanisms of disease generation provides a framework for rational therapy in this disorder, based on the complex inflammatory reaction rather than on the symptoms alone.

IgE-dependent mechanisms.

Allergic rhinitis is characterized by an inflammatory infiltrate and the release of mediators responsible for the symptoms. Moreover, neurogenic mechanisms including a naso-nasal reflex play a role which is still not fully appreciated.

Burden of allergic rhinitis

- Allergic rhinitis is a global health problem that causes major illness and disability worldwide.
- Patients from all countries, all ethnic groups, all socioeconomic conditions and of all ages suffer from allergic rhinitis.
- In many countries, the prevalence of allergic sensitization is often higher than 50% of the population in some age groups.
- Using a conservative estimate, allergic rhinitis occurs in over 500 million people around the world.
- Allergic rhinitis is increasing in prevalence in areas with low or medium levels of prevalence. It may be plateauing or even decreasing in high prevalence areas.
- Allergic rhinitis affects social life, sleep, school and work.
- The economic impact of allergic rhinitis is often underestimated because direct costs for the disease are not elevated. The indirect costs are substantial.

Diagnosis of allergic rhinitis

- The diagnosis of allergic rhinitis is based upon the concordance between a typical history of allergic symptoms and diagnostic tests.
- Typical symptoms of allergic rhinitis include rhinorrhoea, sneezing, nasal obstruction and pruritus.
- Ocular symptoms are common, in particular in patients allergic to outdoor allergens.
- Diagnostic tests are based on the demonstration of allergen-specific IgE in the skin (skin tests) or the blood (specific IgE).
- The measurement of total IgE is not useful in the diagnosis of allergic rhinitis.
- Many asymptomatic subjects can have positive skin tests and/or detectable serum-specific IgE.
- Many patients have positive tests which are clinically irrelevant.
- In some countries, the suspicion of allergic rhinitis may be addressed in the pharmacy.
- Patients with PER and/or moderate/severe symptoms of rhinitis should be referred to a doctor.
- Most patients with rhinitis are seen in primary care and, in developed countries, allergy tests are available to screen for allergy.
- Patients with PER and/or moderate/severe symptoms of rhinitis need a detailed allergy diagnosis.

Environmental control

- The majority of single preventive measures of indoor allergen control fail to achieve a clinically relevant improvement of asthma and rhinitis.
- Standard procedures for the control of indoor allergens in the tertiary prevention of rhinitis or asthma are not advisable for public health.
- In patients allergic to animals with fur who have symptoms on contact with the allergen, animal avoidance is recommended.
- In low-income settings with a high load of pollutants (and allergens), a multifaceted intervention may be useful.
- Total avoidance of occupational agents is recommended in sensitized subjects.
- Occupational agent control may be useful when total avoidance is not possible.

Drug treatment

Pharmacotherapy of allergic rhinitis and conjunctivitis

- Second-generation oral or intranasal H1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children.
- First-generation oral H1-antihistamines are not

recommended when second-generation ones are available, due to safety concerns.

- Topical H1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis.
- Intranasal glucocorticosteroids are recommended for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for the treatment of allergic rhinitis.
- Intramuscular glucocorticosteroids and the longterm use of oral glucocorticosteroids are not recommended due to safety concerns.
- Topical cromones are recommended in the treatment of allergic rhinitis and conjunctivitis, but they are only modestly effective.
- Montelukast is recommended in the treatment of seasonal allergic rhinitis in patients over 6 years of age.
- Intranasal ipratropium is recommended for the treatment of rhinorrhoea associated with allergic rhinitis.
- Intranasal decongestants may be used for a short period of time in patients with severe nasal obstruction.
- Oral decongestants (and their combination with oral H1-antihistamines) may be used in the treatment of allergic rhinitis in adults, but side effects are common.
- The treatment of allergic rhinitis should consider the severity and duration of the disease, the patients preference, as well as the efficacy, availability and cost of medications.
- A stepwise approach depending on the severity and duration of rhinitis is proposed.
- A tailored approach is needed for each individual patient.
- Not all patients with moderate/severe allergic rhinitis are controlled despite optimal pharmacotherapy.

Complementary and alternative medicine

- Many patients who use complementary and alternative medicine appear to be satisfied.
- Evidence-based recommendations are difficult to propose for most complementary and alternative medicine interventions because of methodological problems.
- There is no evidence for the efficacy of most complementary and alternative medicines on allergic rhinitis and asthma.
- The safety of phytotherapy raises concerns.

Surgical treatment of rhinitis

As surgery cannot contribute to the treatment of allergic disease itself, it may only be used in certain precise conditions such as turbinate hypertrophy, cartilaginous or bony obstruction of the nasal airways or secondary and independent sinus disease.

Indications for a surgical intervention are:

- drug-resistant inferior turbinate hypertrophy;
- anatomical variations of the septum with functional relevance;
- anatomical variations of the bony pyramid with functional/aesthetic relevance;
- secondary or independently developing chronic sinusitis;
- different forms of nasal unilateral polyposis (choanal polyp, solitary polyp and allergic fungal sinusitis) or therapy-resistant bilateral NP and • fungal sinus disease (mycetoma, invasive forms) or other pathologies unrelated to allergy (cerebrospinal fluid leak, inverted papilloma, benign and malignant tumors, Wegeners disease, etc.).

Links between rhinitis and asthma

The nasal airways and their closely-associated paranasal sinuses are an integral part of the respiratory tract. The nasal and bronchial mucosa present similarities and one of the most important concepts regarding nose–lung interactions is the functional complementarity. Most patients with asthma have rhinitis suggesting the concept of one airway one disease. The presence of allergic rhinitis commonly exacerbates asthma, increasing the risk of asthma attacks, emergency visits and hospitalizations for asthma. However, not all patients with rhinitis have asthma and there are differences between rhinitis and asthma.

Common risk factors

Asthma and allergic rhinitis share common risk factors. Nonetheless, many studies have provided evidence of some differences in environmental or genetic risks among these related conditions, suggesting a certain degree of specificity of phenotypes. Among the causative agents inducing asthma and rhinitis, some [e.g. allergens and aspirin] are well known to affect both the nose and the bronchi.

Commonalities and differences in mechanisms between rhinitis and asthma

- Most asthmatics have rhinosinusitis as demonstrated by CT scans.
- Severe asthmatics have more severe rhinosinusitis than mild asthmatics.
- Eosinophilic inflammation is present in the nasal and bronchial mucosa of asthmatics.
- Epithelium and basement membrane differ in the nasal and bronchial mucosa of asthmatics.
- The bronchial and nasal mucosa of COPD patients appear to be similar.
- Endobronchial challenge in rhinitis patients induce a bronchial reaction.

- Bronchial challenge induces nasal inflammation.
- Nasal challenge induces bronchial inflammation.
- Allergic inflammation has a systemic component.

Therapeutic consequences

Treatment of rhinitis and asthma using a single approach

- Oral H1-antihistamines are not recommended, but not contraindicated in the treatment of asthma.
- Intranasal glucocorticosteroids are at best moderately effective in asthma.
- Intranasal glucocorticosteroids may be effective in reducing asthma exacerbations and hospitalizations.
- The role of intrabronchial glucocorticosteroids in rhinitis is unknown.
- Montelukast is effective in the treatment of allergic rhinitis and asthma in patients over 6 years of age.
- Subcutaneous immunotherapy is recommended in both rhinitis and asthma in adults, but it is burdened by side effects, in particular in asthmatics.
- Anti-IgE monoclonal antibody is effective for both rhinitis and asthma.

Rhinitis and asthma: a continuum of disease?

There are similarities and differences between the nasal and bronchial mucosa in rhinitis and asthma. It appears that most asthmatics experience rhinitis, whereas only a fraction of rhinitis patients have clinically demonstrable asthma even though a greater number of patients have nonspecific bronchial hyperreactivity. It seems that the epithelial–mesenchymal trophic unit exists from the nose to the bronchiolar–alveolar junction and that the same inflammatory cells are present throughout the airways suggesting a continuum of disease. Some mediators such as NO can exert action in the entire airways.

Management of asthma and rhinitis in athletes

Elite athletes commonly use drugs to treat asthma, exercise-induced bronchial symptoms and rhinitis. Only a few controlled studies have been conducted on the effects of antiasthma drugs on asthma symptoms, bronchial hyperresponsiveness and airway inflammation in elite athletes. Inhaled β_2 -agonists and leukotriene receptor antagonists are effective against exercise-induced bronchoconstriction.

Other co-morbidities and complications

Allergic conjunctivitis is a common co-morbidity of allergic rhinitis.

- The other forms of conjunctivitis are not associated with an IgE-mediated allergic reaction.
- Although the sinus may be involved during an allergic reaction, the role of allergy as a risk factor for CRS is still unknown.

- Allergy does not appear to be a risk factor for NP.
- The role of allergy as a risk factor of otitis media with effusion (OME) is unknown.
- Chronic cough can be caused by several etiologies including allergic rhinitis and CRS.

Rhinitis in children

Allergic rhinitis is the most prevalent chronic allergic disease in children. Although it is not life-threatening, it can have a significantly detrimental effect on a child's QOL, and it may exacerbate a number of common co-morbidities, including asthma and sinusitis. There are

many different causes of rhinitis in children and approximately 50% are induced by allergy. Allergic and nonallergic rhinitis are often difficult to differentiate based on symptoms.

Allergen-specific subcutaneous immunotherapy is not usually recommended before the age of 5 y due to safety concerns as well as difficulties in performing serial injections of allergens over months or years. There are some preliminary studies on SLIT in preschool children. It has been found to be safe but its efficacy needs to be tested further. Moreover, SLIT in young children with allergic rhinitis may possibly prevent a later development of asthma.

Ref: Allergy 2008; 63 (Suppl. 86): 8–160

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Dear Doctor

We are happy to present you the "Allergy News Letter" Vol. 02 No. 02. In this issue, we have concentrated on " Pediatric and adult eosinophilic esophagitis (EoE): similarities and differences" and "Allergic Rhinitis and its Impact on Asthma (ARIA)". We hope you will enjoy reading the publication.

We appreciate your comments and queries.

Please participate in Quiz competition & win prizes.